Drug Delivery® Technology

October 2007 Vol 7 No 9 www.drugdeliverytech.com

Reviewing Next-Generation DPIs

The science & business of specialty pharma, biotechnology, and drug delivery

Mr. Scott Fuson
Dow Corning: Going Beyond the Silicone Molecule

James C. DiNunzio, MS
Development & Design Technology for Next-Generation DPIs

Qiuxi Fan, PhD
The Issues & Challenges Involved in IVRT for Semi-Solid Formulations

IN THIS ISSUE

INTERVIEW WITH CATALENT PHARMA SOLUTIONS' SENIOR VP, GLOBAL SALES

MR. DAVID HEYENS

FEATURING

SPECIALTY PHARMA Strategies For Business Development

Which Dow Corning do you need today?

Since that first drop of silicone, Dow Corning has expanded our local presence throughout the world with a range of performance-enhancing solutions and materials. In China, Dow Corning used our local facilities and formulation expertise to help a leading manufacturer develop a premium skin moisturizer that was smooth, easy-spreading, and lightweight. And our insight into regional market trends helped them expand their brand into promising new markets. Learn more at www.dowcorningnow.com.

DOW CORNING

We help you invent the future.™

THE ADVANTAGES

OF MULTI-PHASE, MULTI-COMPARTMENT CAPSULES ARE CLEAR

Deliver Incompatible Compounds
Deliver incompatible compounds in a single dosage form with different release profiles.

Multiple Release Profiles
Incorporate one or more release profiles into a single dosage form such as immediate, enteric, targeted, chronotherapy and pulsatile.

Higher Perceived Value
Consumers view multi-phase, multi-compartment capsules as having a higher perceived value than ordinary tablets, capsules and soft gels.

Choice of HPMC or Gelatin Capsules
With multi-phase, multi-compartment capsules you are not limited to just gelatin (animal-based product) but have the option of natural HPMC (hydroxypropyl methyl- cellulose) and alternative capsule materials.

Better Visual Appeal
Multi-phase, multi-compartment capsules have none of the dust and residue associated with powder capsules. Better visual product appearance translates to higher perceived value.

Increased Absorption and Bioavailability
Liquids naturally offer faster and increased absorption and availability of active ingredients.

Increased Profit Potential
Add up all the advantages. Expect higher sales…and high margins!

Multi-Phase System
Compounds can be delivered with the most advantageous pharmacokinetic profile such as liquids and solids

Faster Development
Multi-phase, multi-compartment capsules reduce the development time compared to bi-layer tablets to get a new product into clinical trials faster.

Smaller Capsules
Hard-shell capsules have thinner wall construction, allowing them to contain more ingredient in a smaller capsule versus thicker-shelled soft gel capsules. Hard shells have faster and more complete dissolution than soft gels.

Less Odor and Less Irritation
Reduces unpleasant ingredient taste and odor commonly found with tablets and traditional capsules. And, liquids provide less irritation than traditional delivery methods.

Tamper Proof Sealing
Band sealing reduces tampering and provides a non-permeable barrier to retard oxidation and increase shelf-life.

Unique Appearance
This new delivery system stands apart from look-alike products that crowd retail shelves.

Compounds
Deliver Pharmaceutical, bio-pharmaceutical and nutraceuticals in a single dosage form.

InnerCap™ Technologies, Inc

Patent Pending US-2005-0008690-A1

9745 International Court • St. Petersburg, FL 33716 USA • (813) 837-0796 • www.innercap.com • fmiller@innercap.com

Drug Delivery Technology

October 2007 Vol 7 No 9

Corporate/Editorial Office
219 Changebridge Road, Montville, NJ 07045
Tel: (973)299-1200
Fax: (973) 299-7937
www.drugdeliverytech.com

3M Drug Delivery Systems
Enabling your success

We've made our experience count

"Wonderful" "Outstanding" "Brilliant" – patient research says it all

For precise dose by dose counting and display, patients praise the new 3M™ Integrated Dose by Dose Counter. Partners appreciate our capability to integrate the dose counter into their product development, provide necessary regulatory documentation and help bring better products to market faster.

When you need drug delivery results, experience matters.

For further information contact:

US: 1-800-643-8086 ext 710
UK: +44 (0) 1509 614000
Japan: (81) 3-3709-9671
Email: ddsinfo@mmm.com
www.3M.com/DDS/dosecounter

3M

Table Of Contents

Next-Generation DPIs

"The proper design of clinical trials to study the effectiveness of delivery devices is complicated and can be confounded by a number of different issues, including differences in drugs used, inappropriate dose administered, formulation variations between test groups, number of test subjects, and the duration of the study. In addition to functionality, patient compliance and proper usage are critical for effective therapy."

p.22

SPEED PRODUCT DEVELOPMENT WITH SCOLR

Conquer Delivery Barriers

With Our Self Correcting Oral Systems

Our suite of patented self-correcting oral delivery systems can handle your most challenging drug or nutritional ingredient. CDT®'s simple but elegant technology provides partners with rapid product development and the highest possible success in clinical trials.

- Our "**Dual Polymer**" platform allows production of novel Matrix tablets and capsules regardless of their initial flow properties.
- Our "**Electrolyte**" platform is capable of custom tailored release profiles, including zero order, that can emulate complex delivery systems. (i.e. osmotic pumps, bead systems, layered tablets)
- Our "**Amino Acid**" platform can enhance solubility to allow precision controlled delivery in simple monolithic dosage forms.

SCOLR Pharma, Inc.
Self Correcting Oral Delivery Systems

3625 132nd Ave S. E. • Suite 400
Bellevue, WA 98006
425.373.0171
www.scolr.com

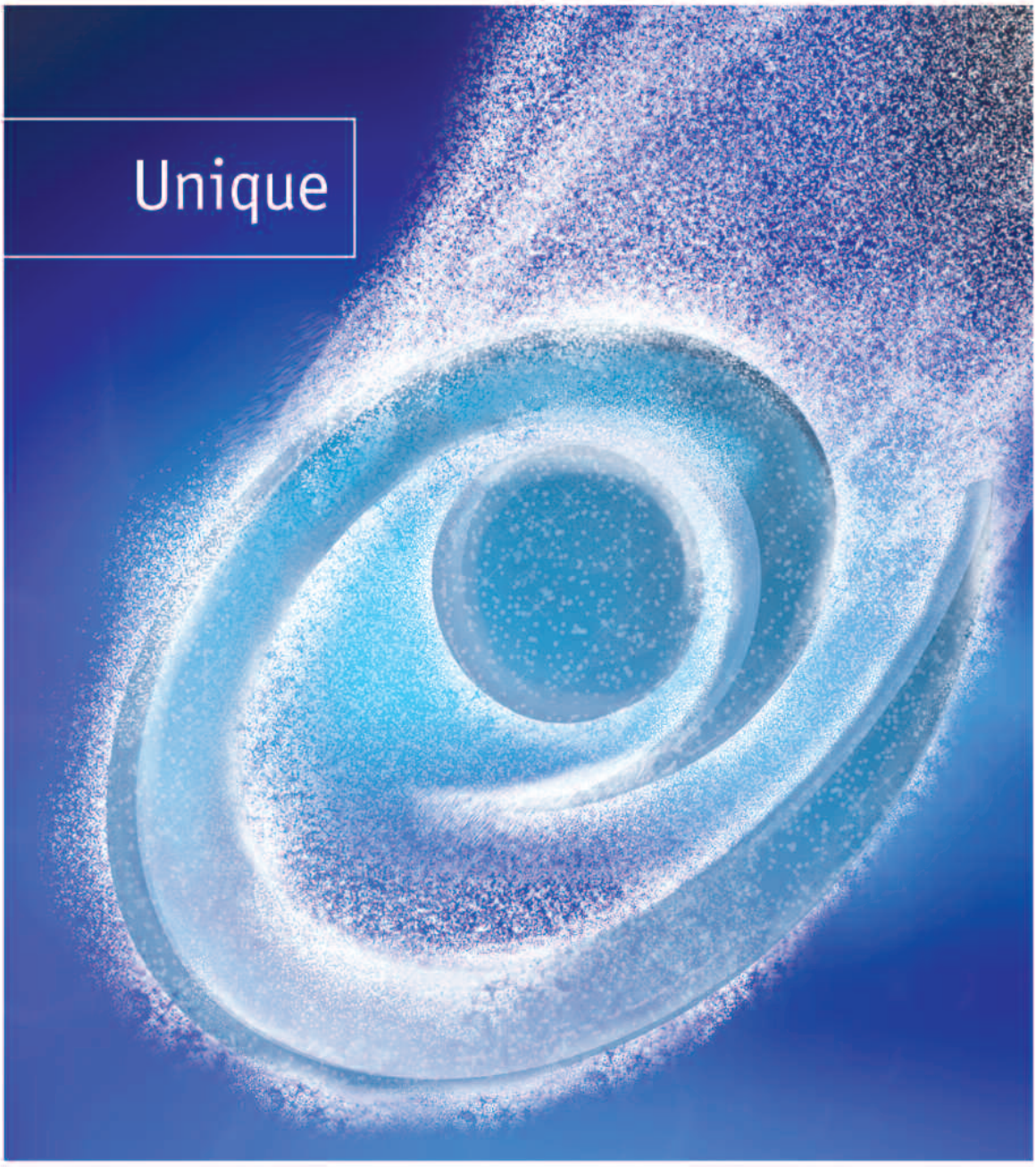
Intranasal Insulin

"For more than 2 decades, the medical community has been searching for a less-invasive and patient-friendly method for treating diabetes. Intranasal delivery of insulin has the potential for significantly better patient compliance than a routine of insulin injections and may facilitate earlier entry into therapeutic regimens for patients reluctant to administer insulin by injection, potentially resulting in delayed onset of diabetes complications."

p.86

Table Of Contents

Departments



Unparalleled taste Flexible dose Versatile release Robust tablet

AdvaTab® The next generation ODT

Eurand's AdvaTab is an orally disintegrating tablet (ODT) technology that combines superior taste and mouth feel properties in a robust tablet. AdvaTab is unique, offering both high dose capacity and modified drug release making it the most broadly applicable ODT available. Utilization of standard tabletting processes allows for cost-efficient manufacturing and conventional packaging. The next generation ODT is here!

EURAND

www.eurand.com

USA +01-937-898-9669
EU +39-02-95428-309

ODT CUSTOMIZED RELEASE TASTE MASKING ENHANCED BIOAVAILABILITY

The EDITORIAL Advisory Board

WE DON'T JUST PROVIDE SOLUTIONS, WE CREATE SUCCESSFUL PARTNERSHIPS.

PharmaForm has an international reputation for developing novel solutions to challenging problems in pharmaceutical product development, manufacturing, and analytical testing. We specialize in working side-by-side with our clients, to deliver customized solutions to product development challenges. **Our Expertise. Your Advantage.**

Our Services:

- Formulation and Product Development
- Analytical Services
- GMP/GLP Manufacturing
- Method Development
- Validation Services
- Quality Control Testing and Stability Storage
- Reverse Engineering
- Patent Litigation Support
- Product and Platform Licensing Opportunities

GMP/GLP Compliant
FDA Registered/Inspected
DEA Licensed/Inspected

PharmaForm® L.L.C.
Excellence & Innovation in the Pharmaceutical Sciences

North America:
Michael M. Crowley, Ph.D., (512) 834-0449 ext. 202

International:
Josef Bossart, Ph.D., (512) 834-0449 ext. 278

Market News and Trends

Bristol-Myers Squibb to Buy Partner Adnexus Therapeutics for $430 Million

Bristol-Myers Squibb Company and Adnexus Therapeutics recently announced the companies have signed a definitive agreement under which Bristol-Myers Squibb will acquire privately held Adnexus Therapeutics, developer of a new therapeutic class of biologics called Adnectins. The acquisition of Adnexus will help advance Bristol-Myers Squibb's biologics strategy across multiple therapeutic areas and includes a Phase I oncology biologic, Angiocept. Adnexus Therapeutics will become a subsidiary of Bristol-Myers Squibb and remain based in Waltham, MA.

Under the terms of the agreement Bristol-Myers Squibb will acquire all of Adnexus' issued and outstanding shares of capital stock and stock equivalents in an all-cash transaction for a gross purchase price of $430 million, with the net purchase price being $415 million after deducting Adnexus' net cash balance at closing. In addition, there is an earn-out structure that could result in Bristol-Myers Squibb paying an additional amount of approximately $75 million, in three increments of approximately $25 million each, in the event certain development and regulatory milestones are achieved. The closing of the transaction is subject to customary regulatory approvals.

Adnectins are a proprietary class of targeted biologics developed by Adnexus. PROfusion is Adnexus' proprietary protein design engine, with which trillions of protein variations can be engineered at one time. Angiocept is an Adnectin designed to be an anti-angiogenic drug and is currently in Phase I development.

"Bringing Adnexus into the Bristol-Myers Squibb family builds upon a successful and productive collaboration between the two companies in oncology and is an important step in accelerating the strategic transformation of our pharmaceutical business to a biopharma business model," said Jim Cornelius, CEO, Bristol-Myers Squibb. "Biologics are one cornerstone of our growth strategy. This investment in biologics discovery complements our continued investment in a growing biologics pipeline and portfolio, and will benefit from our expanding biologics manufacturing capabilities, both at our existing site in Syracuse, NY, and our future large-scale bulk biologics facility in Devens, MA."

"Adnectins and the PROfusion technology are among the most exciting next-generation biologics platforms currently in development," said Elliott Sigal, MD, PhD, Executive Vice President and Chief Scientific Officer, Bristol- Myers Squibb. "By uniting Adnexus' innovation and discovery expertise with our internal capabilities in oncology and other therapeutic areas, we intend to fuel the company's biologic growth strategy and importantly, deliver innovative new treatment options for patients."

"This is an exciting milestone for our scientists, investors, and company and is a unique opportunity to further accelerate advancement of Adnectin-based medicines and our lead product, Angiocept," said John Mendlein, PhD, JD, CEO of Adnexus. "We are proud to bring the strength of our science, team, and intellectual property to Bristol-Myers Squibb. We have enjoyed a highly productive and collaborative relationship to date, and look forward to helping Bristol-Myers Squibb advance its innovative pipeline."

Adnectins are an emerging, proprietary protein therapeutic class that can be designed to address a broad range of diseases. They are based on human fibronectin, an extracellular protein that is naturally abundant in human serum. The intrinsic properties of an Adnectin align with the properties needed to make a successful drug, including high potency, specificity, stability, favorable half-life, and high yield E. coli production. Adnectins are designed using PROfusion, Adnexus' patented protein design engine, to achieve high potency and specificity for a therapeutic target while simultaneously selecting for ideal pharmaceutical product characteristics. PROfusion enables Adnexus to screen trillions of unique Adnectins for each drug discovery program to "redirect" naturally occurring human fibronectin to act as a protein therapeutic. This greatly accelerates Adnectin drug discovery and development.

Adnexus is the exclusive developer of Adnectins. Adnexus solely owns an Adnectin patent estate containing issued and pending patent properties to fundamental Adnectin forms. Because Adnectins have a different origin than antibodies, they are not bound by traditional antibody patents. In addition, Adnexus exclusively controls its patented PROfusion protein design engine. Adnexus has more than 100 issued and pending patent properties relating to Adnectins and PROfusion.

Market News and Trends

Anesiva Grants Specific-Use License of Its Needle-Free Technology to Particle Therapeutics for Diabetes Drug

Anesiva, Inc. and Particle Therapeutics Limited recently announced they have entered into an agreement granting Particle Therapeutics a specific-use license to incorporate Anesiva's drug delivery technology into its needle-free, intradermal delivery system for glucagon, a hormone commonly used for the treatment of hypoglycemia associated with type 1 and type 2 diabetes.

"This agreement exemplifies the potential of our technology to transform the delivery of proteins, peptides, and small molecules in a clinically meaningful way that is also safer, more comfortable, and more convenient," said John P. McLaughlin, Chief Executive Officer of Anesiva. "We intend to seek other opportunities for licensing this important platform technology."

"Patients experiencing a hypoglycemic condition may lose consciousness, and if not treated quickly, can suffer short- and long-term cerebral damage," remarked Fred Cornhill, Director of Particle Therapeutics. "Current methods of treating diabetic hypoglycemia require the mixing of glucagon powder with a sterile saline solution, followed by needle injection. At present, an estimated 1 to 1.5 million kits with glucagon powder are sold annually in the US and Europe. Those with type 1 diabetes typically have at least one to eight such events per year, requiring intervention of another person or summoning of medical assistance. Type 2, insulin-dependent diabetes patients have fewer incidents, but with lower glycemic targets, the incidence of hypoglycemia (requiring third-party intervention) is increasing. Particle Therapeutics' needle-free device provides a system that can be used quickly by those without special training and without the problems associated with needles."

Under the terms of the license agreement, Anesiva will receive an undisclosed up-front payment, along with milestone payments for certain key clinical and regulatory achievements, royalties on future sales, as well as royalties on revenues from any future sub-licensing of the technology by Particle Therapeutics.

Anesiva owns intellectual property covering the delivery of solid particles of proteins, peptides, and small molecules (other than vaccines) into the skin at high velocity by pressurized gases. The technology aims to provide subcutaneous and systemic delivery of drugs without the pain and inconvenience associated with injections and needles. With Anesiva's drug delivery technology, patients may benefit from better control of their disease, reduced dosing schedules, and less pain compared to the administration of drugs with needles. Anesiva is utilizing this technology in its recently FDA-approved product Zingo (lidocaine hydrochloride monohydrate) powder intradermal injection system (0.5 mg) for the rapid needle-free local delivery of lidocaine to reduce pain associated with venous access procedures.

Anesiva, Inc., based in South San Francisco, CA, is a late-stage biopharmaceutical company that seeks to be the leader in the development and commercialization of novel therapeutic treatments for pain. The company has one approved product and one drug candidate in development for multiple pain-related indications. This past August, the FDA approved Anesiva's first product Zingo. The second product in the portfolio, Adlea (formerly 4975), has been shown to reduce pain after only a single administration for weeks to months in multiple settings in numerous mid-stage clinical trials for site-specific, moderate-to-severe pain.

BDSI Exercises Option to Acquire US BEMA™ Rights From QLT USA; Receives $30-Million Upfront Payment Under Commercialization Agreement With Meda AB

BioDelivery Sciences International, Inc. (BDSI) has exercised its option to acquire the US rights to the BEMA drug delivery technology that BDSI licensed from QLT USA, Inc. The acquisition gives BDSI full ownership of the BEMA technology and eliminates any payment of royalties to or the sharing of milestone payments with QLT USA going forward for any BEMA product. More specifically, now that the technology has been purchased, BDSI is not required to share the upfront payment, or any future financial benefit it expects to receive from the partnership agreement signed with Meda AB involving BEMA Fentanyl.

This acquisition was undertaken concurrently with BDSI's entry into a license and supply agreement with Meda AB for the commercialization rights to BDSI's BEMA Fentanyl product in the US, Canada, and Mexico. BDSI anticipates a $30-million non-refundable upfront milestone payment from Meda upon the approval of the required Hart Scott Rodino (HSR) antitrust review.

To acquire the U.S. rights to the BEMA technology, BDSI paid QLT $3 million at the closing of the acquisition and has issued a promissory note in the amount of $4 million. The note is payable to QLT in two future $2-million installments triggered by the occurrence of specific milestones, including the NDA approval of BDSI's first BEMA product. BDSI financed the initial $3-million payment with a short-term bank note and expects to repay the note with a portion of the $30-million milestone payment it expects to receive from Meda upon the conclusion of the HSR review period. This is anticipated to occur in October 2007.

"We are pleased to have been able to take full ownership of this technology, which plays such a significant strategic role to our company," said Mark Sirgo, BDSI President and CEO. "We are following through on our strategic plan, initiated last year, when we acquired the non-US BEMA assets. This acquisition was integral to consummating our licensing agreement with Meda. By doing so, QLT is eliminated from receiving any future milestone or royalty payments on BEMA Fentanyl or any BEMA product. This brings a tremendous benefit to our stockholders."

BEMA Fentanyl consists of a small, dissolvable, polymer delivery system, formulated with the opioid narcotic Fentanyl, for application to the buccal (inner lining of cheek) membranes. BEMA Fentanyl has shown in Phase III clinical studies important patient advantages compared to competing products, especially fewer side effects.

BioDelivery Sciences International, Inc. is a specialty pharmaceutical company focused on developing innovative products to treat acute conditions such as pain. The company utilizes its owned and licensed patented drug delivery technologies to develop, partner, and commercialize, clinically significant new products using proven therapeutics. BDSI's pain franchise currently consists of two products in development utilizing the company's patented BEMA oral adhesive disc technology: BEMA Fentanyl, a treatment for "breakthrough" cancer pain, and BEMA LA, a second analgesic with a target indication of the treatment of moderate-to-severe pain. The company is also working with both its BEMA technology and its patented Bioral nanocochleate technology on products targeted at other acute treatment opportunities, such as insomnia, nausea and vomiting, and infections.

Adams Respiratory Therapeutics & Lipocine Enter Into License & Collaboration Agreement

Adams Respiratory Therapeutics, Inc. and Lipocine Inc., a privately held, leading drug delivery company that uses clinically validated proprietary technologies to address key unmet drug delivery and therapeutics needs, recently announced they have entered into a license and collaboration agreement to develop new prescription adult cough products.

"This collaboration with Lipocine provides Adams with access to an additional proprietary platform technology and fits with our strategy of taking established compounds and adding increased functionality to create patent-protected, value-added products, said Adams' COO Robert D. Casale. "The products developed through this collaboration could offer doctors a non-narcotic prescribing option to treat cough with an enhanced dosing regimen. In addition, these products will help Adams compete in the $1.1-billion prescription cough and cold market in the United States."

"Given the large and growing size of the respiratory market, and how patients can benefit from enhanced dosage forms and regimens, we are very pleased to partner with Adams, a company highly respected for its commercialization accomplishments," added Dr. Mahesh Patel, President and CEO of Lipocine Inc.

Lip'ral™ and Lip'ral™-SSR are clinically proven oral delivery technologies for water-insoluble drugs that improve absorption and can be extended to enable controlled release of insoluble drugs and drugs with pH-sensitive solubility. Multiple patents have been issued and are pending on these proprietary technologies.

Under the terms of the agreement, Adams receives an exclusive, royalty-bearing license from Lipocine to develop and market multiple prescription adult cough products in North America. Lipocine is responsible for completing the product development work and will be eligible to receive reimbursements and payments in exchange for completing certain pre-defined development milestones. Adams will be responsible for performing all aspects of clinical development, regulatory submission, manufacture, and commercial operations. Financial terms of the deal are not being disclosed. Adams reconfirms that it expects diluted earnings per share in fiscal 2008 to be in the range of $1.55 to $1.75, as previously disclosed in an August 21, 2007, press release.

Adams is a specialty pharmaceutical company focused on the late-stage development, commercialization, and marketing of OTC and prescription pharmaceuticals for the treatment of respiratory disorders.

Lipocine Inc. is a pharmaceutical company leveraging its proprietary drug delivery technologies to commercialize innovative pharmaceutical products. Lipocine business objectives are to develop products with established drugs that have patient-friendly attributes, such as faster absorption, lower dose, fewer side effects, less frequent dosing, and no food effect.

Boost Your Options.

Lipocine delivers proprietary product opportunities for your portfolio, and realistic solutions for product development of your challenging drug. Lipocine can help you realize the full potential of your currently marketed drug with its pioneering technologies leading to better therapeutics, and retain or expand your market share with added exclusivity. Lipocine options offer lower development costs, increase success rate, and faster market entry.

Lipocine currently has a portfolio of superior differentiated products for branding opportunities available for partnering.

...Let's Talk

LIPOCINE™
INCORPORATED

The Innovative Therapeutics Company

675 Arapeen Drive, Suite 202, Salt Lake City, Utah 84108 • (801) 994-7383 • www.lipocine.com

Market News and Trends

Northern Lipids Builds Clinical Manufacturing Facility

Northern Lipids Inc. (NLI) recently announced it has completed the renovation and build-out of its new Burnaby facility. Located only minutes from Vancouver airport, just off Boundary Road in South Burnaby, the building is designed to support preclinical development of pharmaceutical products, and houses a facility that is suitable for the manufacture of sterile drug products for clinical trials.

Recognizing a need to expand its operations, NLI purchased the Burnaby facility in June 2006. The building had previously been occupied by two local biotechnology companies, Response Biomedical and ID Biomedical.

"Though we were able to keep much of the existing office and wet-laboratory space, the 15-year-old building needed a general face-lift and specific upgrade of selected utilities," said Dr. Clay Flowers, NLI Director of Operations. "Renovations also included the build-out of a dedicated QC laboratory, a room designed for scale-up of our proprietary manufacturing processes, and most importantly, the addition of a cleanroom designed for clinical product manufacture."

"We are very pleased to have successfully completed the renovation and expansion," added Dr. Tom Redelmeier, President and Chief Executive Officer of NLI. "It has taken a complete team effort that included not only Chernoff Thompson Architects and our General Contractor, but included important contributions from all members of the company. Since 1991, NLI has successfully grown its Contract Research Operations by listening to clients, remaining flexible, and expanding our range of services to meet their growing needs. We believe this investment in equipment and facilities will help our client's fast-track their programs."

Northern Lipids Inc (NLI) is a Contract Research Organization (CRO) that provides products and services to biotechnology companies engaged in the development of pharmaceutical products. It specializes in providing services to companies that are actively developing lipid-based (liposome, emulsion, micelle) drug delivery systems. NLI has experience working with virtually all classes of pharmaceuticals, ranging from small molecules to peptides, proteins, DNA, antisense, and siRNA. The company offers a range of CMC (Chemistry Manufacturing Controls) related services, including small- and large-scale LIPEX equipment for preparing liposomes, lead prototype identification, manufacturing process development & scale-up, analytical method development & validation, clinical trial manufacturing under cGMP, and stability programs.

Capsugel Announces License Agreement With Teijin Pharma to Offer Vcaps® HPMC Capsules for Dry Powder Inhalation

Capsugel, a leading global provider of dosage form solutions, recently announced it will offer its Vcaps HPMC (hypromellose) capsules for use in dry powder inhalation (DPI) products worldwide. The announcement follows the successful conclusion of a license agreement between Capsugel and Teijin Pharma Limited, part of the Teijin Group of Japan. The agreement grants Capsugel a license to Teijin's entire patent portfolio related to the use of HPMC capsules for inhalation products.

"We are extremely pleased with this agreement as it allows us to offer our innovative HPMC capsules in new therapeutic areas and new geographic markets," said Guido Driesen, President of Capsugel. "It supports our strategy to offer a wider range of drug delivery solutions to our customers around the world."

Inhalation drug delivery technology offers benefits to patients beyond the traditional treatments for asthma and chronic obstructive pulmonary disorder. The technology holds promise for systemic inhalation therapies that improve speed-of-onset of action and provide an alternative to needle injection. DPI devices are one of the preferred ways to administer these drugs. HPMC-based capsules have a number of advantages when used in DPI devices, such as low moisture content and easy piercing of capsules. These characteristics allow optimal release of the drug formulation from the capsule. Capsugel's Vcaps capsules will ensure minimum powder retention after use.

As the world's leading provider of HPMC capsules, Capsugel focuses on superior quality and process controls, assuring consistent batch-to-batch performance. A division of Pfizer Inc., the company offers a diverse array of products and services and is at the forefront of drug delivery innovation. Recent product launches include the CFS 1200 Liquid Filling and Sealing Machine and the Xcelodose Precision Powder Micro-filling System. Both utilize advanced technology that can better enable R&D scientists to accelerate the pace of drug development.

Akela Pharma Announces Positive Results for the Extension Part of its Phase IIb Fentanyl Taifun® Trial

Akela Pharma Inc., a drug development company focused on developing therapies for the inhalation, pain, and CNS markets, recently announced positive results from the double-blind extension part of its Fentanyl Taifun Phase IIb trial. The results demonstrated statistically significant differences compared to placebo in the measured primary and secondary efficacy variables resulting in faster and superior pain relief. Fentanyl Taifun is a fast-acting Fentanyl formulation delivered using the company's Taifun dry powder inhaler platform.

A total of 50 patients were randomized and started the extension part of the study. In the Intent-To-Treat (ITT) population, the median time to significant pain relief in the Fentanyl Taifun group as measured by a decrease of at least 2 points on the numerical pain scale (NPS) was 5.2 minutes, which was statistically significantly faster when compared to placebo ($P = 0.007$). The mean difference in sum of pain intensity difference (SPID) was also statistically significantly in favor of Fentanyl Taifun for the whole 60-min pain episode ($P = 0.050$). This was already seen in numerical pain scale scores up to 15 minutes ($P = 0.008$) when compared to placebo.

"We are extremely satisfied to have demonstrated beyond doubt the faster and superior pain relief provided by Fentanyl Taifun to patients. The additional knowledge and data accumulated during this clinical trial, as well as the positive feedback by the authorities during the recent End-of-Phase II meetings makes us confident when preparing our Phase III study protocols," said Dr. Halvor Jaeger, CEO of Akela.

Phase IIb for Fentanyl Taifun was a multi-center, multinational clinical trial in cancer patients with severe persistent pain on maintenance opioid therapy. The first part of the trial was a single-arm, open-label dose titration to evaluate the effective individual dose for significant pain relief with Fentanyl Taifun in the treatment of breakthrough cancer pain. The second part included responders from the open-label part randomized to receive the titrated doses or placebo.

Chronic pain associated with advanced cancer is commonly treated with strong opioid analgesics, such as Fentanyl. Breakthrough pain episodes are sudden and intense flares of pain that "break through" a long-acting continuous treatment, such as a transdermal patch or a slow-release tablet. Breakthrough pain episodes are common in cancer patients, often occurring several times a day.

Glatt Pharmaceutical Services Inaugurates New Solid Dosage Facility

On September 19, Glatt Pharmaceutical Services, a division of Glatt Air Techniques, Inc., hosted an Open House with over 350 pharmaceutical industry representatives and other guest at their facility in Ramsey, NJ, to celebrate the inauguration of its New Solid Dosage Facility. The event was part of a week-long set of activities that included a symposium on Industry Trends in Controlled Release Pharmaceutical Dosage Form Development. The symposium speaker roster was a collection of thought leaders who provided their insight on a wide variety of subjects related to controlled-release dosage forms. The Open House activities included a keynote address by Mark McClellan, MD, former Commissioner, US FDA. Dr. McClellan discussed how pharmaceutical manufacturing can impact the improvement of healthcare in the US.

As part of the inauguration event, the guests toured the new and enhance facility, which concentrates on complex controlled-release pharmaceutical product research & development and manufacturing. The investment in the new solid dosage facility focused on expanded capabilities in the area of Glatt's Wurster HS™ coating and drug layering systems, fluid bed and high shear granulation, fluid bed drying, blending, tablet compression, encapsulation, perforated pan coating, Glatt's proprietary CPS™ pellet system, organic solvent coating capability, and controlled substance handling at increasing capacities.

"We were both honored and privileged to host the over 350 pharmaceutical industry contemporaries who chose to join us during this exciting facility inauguration. With our new state-of-the-art solid dosage plant, coupled with our ever-expanding depth of knowledge and talent, Glatt Pharmaceutical Services is poised to assure our continued commitment to the unrivaled development and manufacturing of the most challenging modified and immediate-release products," said Mr. Oliver Mueller, Executive Vice President of Glatt Pharmaceutical Services.

During the Open House, guests had the opportunity to speak with Glatt management, scientists, and engineers about the variety of product development and manufacturing services offered, as well as details about Glatt equipment design and functionality and the turnkey engineering services provided by Glatt in the completion of the new facility.

Catalent Upgrades Clinical Supply Facility in the UK to Meet Increased Customer Demand

Catalent Pharma Solutions, a leading provider of outsourced clinical and commercial packaging services to the global pharmaceutical and biotechnology industry, recently announced it is expanding its temperature-controlled warehouse in Bolton, UK, to meet increased customer demand for clinical supply services, especially cold-chain storage and distribution. This expansion involves a purpose-built extension of the existing facility and is expected to be operational in June 2008. With a floor space of over 7,500 sq. ft. (700 sq. m.) and over 2,700 controlled ambient storage locations, the new temperature-controlled warehouse will also house a 320-pallet refrigerator. This development comes soon after two already completed expansions at Catalent's other clinical supply facilities in Europe (Schorndorf, Germany) and the US (Philadelphia). Through these expansions, Catalent has enhanced capability to support global projects requiring cold-chain storage and distribution of clinical materials.

"Customers are increasingly outsourcing clinical development, especially cold-chain distribution," explained Frank Lis, VP & General Manager of Global Clinical Supplies. "By continuing to expand our global clinical supply service facilities, we are able to better serve our expanding customer base throughout the world. Catalent is dedicated to providing its pharmaceutical and biotechnology customers access to a comprehensive world-class clinical supply network."

Flamel Technologies Announces Medusa® License Agreement With Wyeth Pharmaceuticals

Flamel Technologies recently announced it has entered into a development and license agreement with Wyeth Pharmaceuticals, a division of Wyeth. The agreement is for the development and licensing of a marketed protein to be delivered using Flamel's Medusa technology. Flamel will receive an up-front payment and potential development fees, milestones, and royalty payments, the terms of which are not disclosed.

"We are pleased to announce this license agreement with Wyeth Pharmaceuticals," said Stephen H. Willard, Flamel's CEO. "As with the four previous Medusa relationships that we have entered into this year, this agreement concerns our new uniform polymer, which is applicable to a wide variety of proteins and peptides. This new relationship contributes to our goal of building a diverse set of relationships for our Medusa platform, which we expect will continue to grow. We are pleased that Wyeth has chosen to license our Medusa technology and are looking forward to working in the development of this exciting opportunity."

Flamel Technologies, S.A. is a biopharmaceutical company principally engaged in the development of two unique polymer-based delivery technologies for medical applications. Flamel's Medusa technology is designed to deliver controlled-release formulations of therapeutic proteins and peptides and other molecules, without reduction in bioactivity. Micropump is a controlled-release and taste-masking technology for the oral administration of small molecule drugs; it is the intellectual platform licensed by GlaxoSmithKline for Coreg CR.

A Review of Development & Design Technology for Next-Generation Dry Powder Inhalers

By: James C. DiNunzio, MS; James W. McGinity, PhD; and Robert O. Williams III, PhD

Dry powder inhalers are different from other forms of pulmonary delivery systems in that the drug or drug:carrier formulation is delivered as a dry solid particle to the patient utilizing the individual's respiration. For many years, the dry powder inhaler (DPI) has been the second choice to the pressurized metered dose inhaler (pMDI); however, due to the changing technological and political climate, DPIs are experiencing a resurgence. In 1987, the US signed the *Montreal Protocol*, limiting the use of CFCs and helping increase the development of other pulmonary delivery methods, including the DPI and pMDI systems based on hydrofloroalkane (HFA).[1] Other initiatives, such as the *Kyoto Protocol*, not formally signed by the US, seek to further limit the use of ozone-depleting materials, placing the continued use of these propellants into question.[1] Further interest in the DPI platform systems has grown recently, spurred by these legal requirements as well as the benefits offered by this technology, including improved ease of use by not requiring precise timing of actuation and inhalation; the ability to provide a platform for combination products; the avoidance of first-pass metabolism by pulmonary administration; the potential for delivery of sensitive compounds, such as proteins; and the generally accepted benefits of pulmonary administration for delivery of localized therapy.[2]

Due to this increase in product and platform development, the Food and Drug Administration (FDA) issued the Draft Guidance for Industry – Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products: Chemistry, Manufacturing, Controls and Documentation in 1998, which identified DPIs as unique combinations of drug substance and delivery device.[3] The guidance also detailed guidelines for the development and testing of these devices.

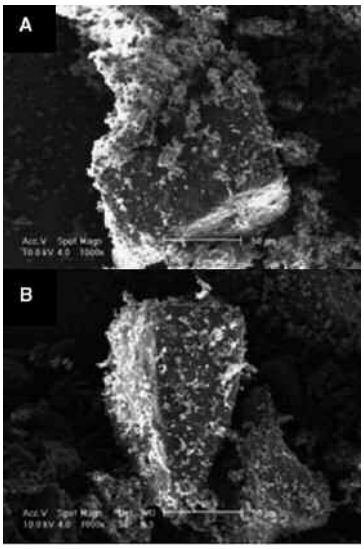
The ability of a delivery system to provide good deposition in the lungs is dependent on the formulation, the device, the user, and the corresponding interactions. In recent years, numerous studies have been conducted to address these issues by developing novel formulations and new delivery devices to allow for improved use, increased patient compliance, and enhanced therapy. This article provides a summary of current developments in the DPI field by describing current research in powder formulation and device design, while detailing examples of DPI systems currently under development utilizing these technologies.

POWDER FORMULATION DESIGN

When a DPI is used, the powder dose transfers through the device, where the drug or primary particles of drug and excipient are separated from the carrier, and the dose is delivered to the patient's lungs. In these systems, the physical properties of the drug, such as particle size, particle shape, particle morphology, surface charge, hygroscopicity, flow, dispersion, and dissolution can significantly influence the performance of the system.[4] Additionally, most dry powder systems have heterogeneous formulations composed of drug substance adhered to the surface of larger carrier particles due to electrostatic and/or van der Waals forces. Figure 1 shows an example of such a system, with the larger lactose carrier particles coated in a layer of smaller nedocromil sodium trihydrate particles. As a result of the complicated particle interactions involved, interfacial properties, such as adhesion and cohesion, significantly influence performance.[5] Addressing these issues is of paramount concern in the formulation development of new DPI systems.

FIGURE 1

Images of Lactose Carrier Systems (reprinted with permission from reference 6)



BD Hypak™
Glass Prefillable Syringes

BD

Helping all people live healthy lives

Customizable Solutions & Unparalleled Support

Strategic Marketing
- An understanding of market trends for parenteral delivery systems
- Recognized leader in safety solutions
- Capable of adapting your product to meet regional needs in a global world

Quality and Regulatory Specialists
- BD Hypak Syringe materials conform to US, European, and Japanese pharmacopoeias
- Drug Master File and a Technical Dossier for product registration worldwide
- Our regulatory experts are ready to assist you

Technical Expertise
- Partnering with machine manufacturers to meet all your processing requirements
- Our Technical Support Team is ready to assist you during any phase of processing
- Expert project teams are ready to propose innovative solutions to meet your specific drug-delivery needs

For more information, please call 800.225.3310 or visit www.bdpharma.com

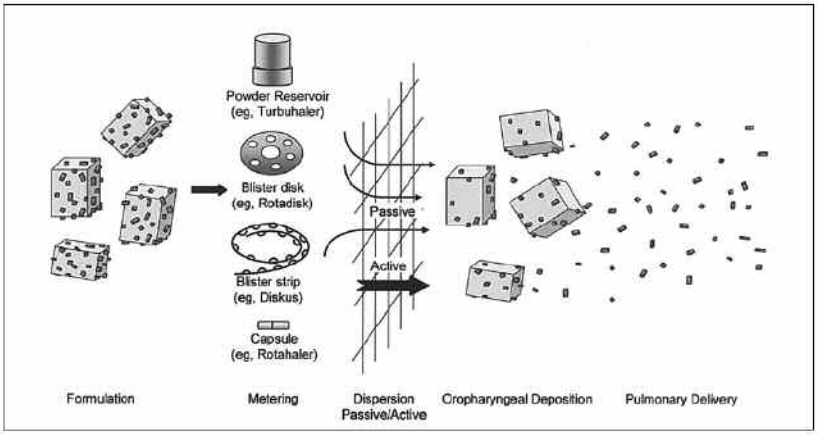
BD Medical
Pharmaceutical Systems
1 Becton Drive
Franklin Lakes, NJ 07417

BDPS_marketing@bd.com

Upon administration to the lung, particles deposit primarily due to impaction and sedimentation driven by the mass and geometric properties of the material. Primary particle size, or more specifically, the aerodynamic diameter, influences the extent of lung deposition. Generally, particles having aerodynamic diameters between 1 and 5 microns have been shown to deposit effectively in the lower airways and deep lung.[7] For production of primary particles within these size ranges, technologies, such as controlled crystallization, spray drying, supercritical fluid processing, spray-freeze drying, and milling, have been used successfully, each of which provide particles of varying densities and morphologies.[8-12] Following primary particle manufacturing, the material is typically processed for incorporation with a carrier using ordered mixing or triboelectrification. These techniques do have their limitations however, particularly when one or more of the components contains an amorphous fraction or when the drug:carrier ratio is low, generally less than 0.5% drug. Several suspension techniques have also been recently developed by companies including Astra and Leiras Oy to produce homogeneous drug:carrier mixtures at low concentrations without disturbing the crystallinity of the sample.[13,14] To produce ordered mixtures using these methods, the drug and carrier are dispersed into an aqueous or organic phase in which the materials have minimal solubility, the suspension is mixed for a predetermined amount of time to evenly distribute the components of the mixture, and the suspending phase is removed by drying. The drug:carrier systems are then incorporated into the DPI systems for administration to the patient.

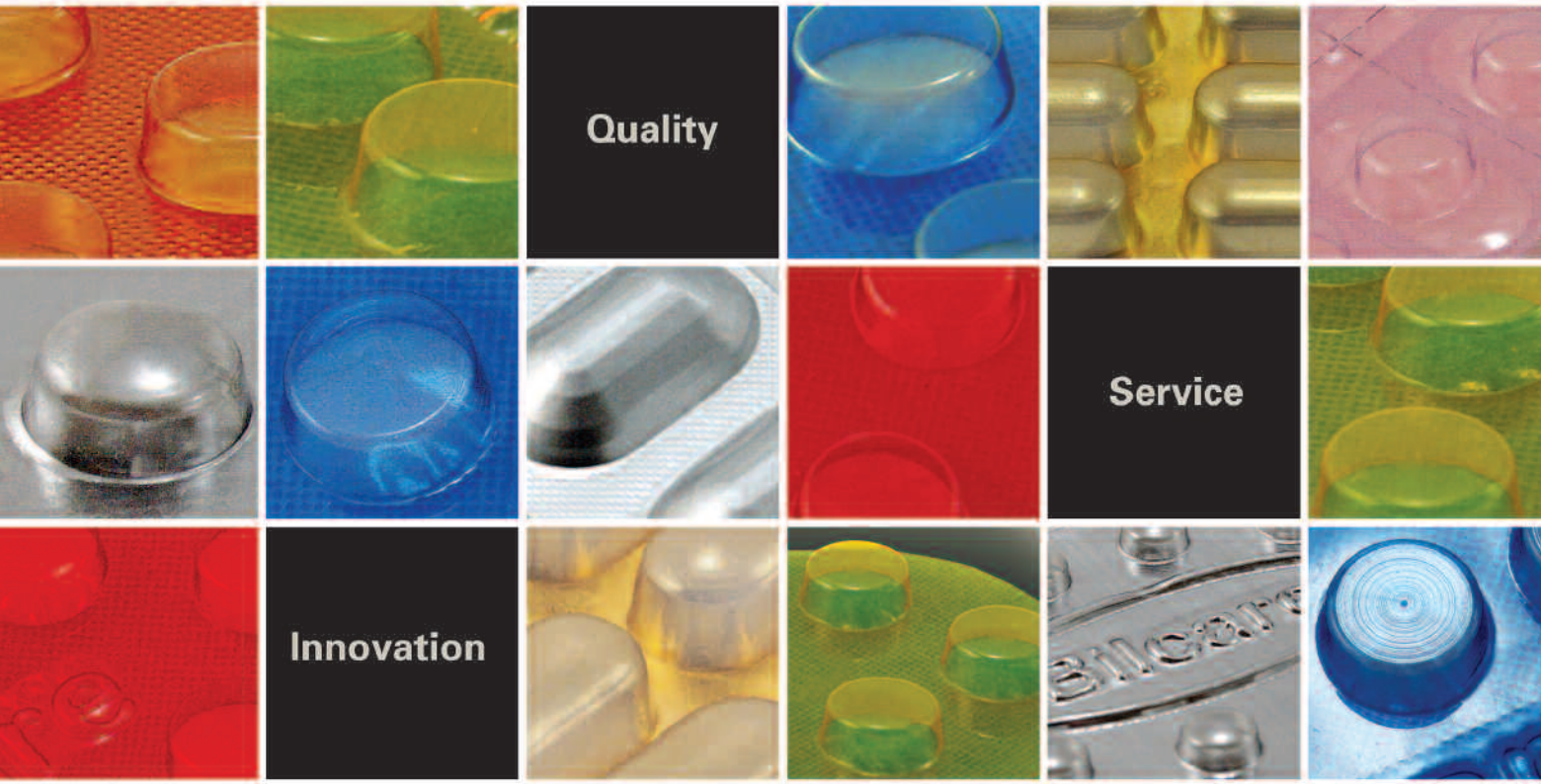
FIGURE 2

Schematic Diagram of Dry Powder Inhaler Operation (reprinted with permission from reference 24)



In most dry powder applications, a carrier is used to function as a bulking agent to improve dosing, support the micronized drug substance, and to allow for aerosolization of the powder before the drug is deagglomerated from the carrier due to the forces induced by respiration and device design. Not only is the aerosolization of the drug:carrier particle essential for effective drug delivery, but so is the ability of drug particle to deagglomerate from the carrier. Young and co-workers recently studied the effect of median carrier particle size, fine carrier particle content, and carrier amorphous content on the *in vitro* delivery of nedocromil sodium trihydrate.[6] Lactose monohydrate samples of various sizes were prepared by ball milling and stored as needed at elevated humidity to control crystallization. Blends of nedocromil sodium trihydrate (5% w/w) and lactose monohydrate with varying particle sizes, fine fractions, and amorphous contents were prepared by geometric dilution in a glass mortar and pestel, dosed into capsules, and tested using a Cyclohaler™. The study demonstrated that the presence of fine carrier particles up to 15% could improve the fine particle fraction of drug delivery *in vitro* and also suggested that increased amorphous content could reduce delivery due to increased drug:carrier interaction.[6] The type of carrier material selected for the formulation was also shown to significantly influence the performance. Lactose is the most commonly used DPI carrier material; however, it is also a reducing sugar that prevents its use with certain drugs, such as peptidic drugs.[15] A study conducted by Saint-Lorant and co-workers evaluated the *in vitro* performance of mannitol, maltitol, and lactose as DPI carriers for two model drugs (terbutaline sulphate and formoterol fumarate) by twin-stage impingement to measure aerodynamic behavior and air-jet sieving analysis to characterize adhesional forces.[15] These results also showed carrier in the amorphous form provided the greatest drug:particle adhesion; however, the magnitude was dependent on the

Break through the packaging barrier.



Bilcare has years of pharmaceutical experience developing innovative packaging solutions. Our proprietary, **quantitative methodology** examines product sensitivity to provide **optimum barrier design**. Maintain your brand while protecting your product with attractive and cost-effective blister packaging materials from Bilcare.

> Standard and Specialty Films & Foils
> cGMP, Class 100,000 Manufacturing Facilities
> ISO 9001 and ISO 14001 Accredited
> DMFs with USFDA

Bilcare™
pharma packaging research

Stay ahead of the pack with Bilcare.
Call 610.935.4300 or visit Bilcare.com today to find out more.

TABLE 1

Examples of Currently Marketed DPI Products

Product Name	Drug Substance	Dose Type	Dose Packaging	Indication	Company
Spinhaler™	Sodium Cromoglycate	Single Unit	Capsule	Asthma	Sanofi-Aventis
Rotahaler™	Salbutamol & Beclometasone Dipropionate	Single Unit	Capsule	Asthma	GlaxoSmithKline
Aerohaler™	Ipratropium Bromide	Multiple Unit Dose	Capsule	Asthma	Boehringer-Ingelheim
Turbuhaler™	Budesonide	Multi-Dose	Reservoir	Asthma	AstraZeneca
Clickhaler™	Albuterol	Multi-Dose	Reservoir	COPD	Innovata Biomed
Easyhaler™	Beclomet	Multi-Dose	Reservoir	Asthma	Orion Pharma
Diskhaler™	Zanamivir	Multiple Unit Dose	Blister	Influenza	GlaxoSmithKline
Diskus™	Fluticasone propionate / Salmeterol	Multiple Unit Dose	Blister	COPD	GlaxoSmithKline
Exubra®	Human Insulin	Single Unit	Blister	Diabetes	Pfizer
Handihaler™	Tiotropium	Single Unit	Capsule	COPD	Boehringer-Ingelheim
Twisthaler™	Mometasone Furoate	Multi-Dose	Reservoir	Asthma	Schering-Plough
Taifun™	Salbutamol	Multi-Dose	Reservoir	Asthma	LAB Pharma

drug substance used. The incorporation of additives, such as amino acids, has also been studied for their deagglomeration effect in DPI systems. Li and co-workers recently characterized the fine particle fraction deposition efficiency of several spray-dried formulations composed of lipid/polycation/DNA complexes, lactose, and varying types of amino acids by use of gene expression from multi-stage liquid impingement. Their work demonstrated the incorporation of arginine, threonine, phenylalanine, and aspartic acid improved *in vitro* deposition without a reduction in gene expression.[16]

Studies have also been conducted to evaluate the effect of other surface properties, such as roughness and geometry. In a recent study by El-Sawabi and co-workers, lactose monohydrate was partially dissolved by heating a saturated lactose solution to remove surface roughness. Modified carrier particles were blended with salbutamol sulphate and filled into hard gelatin capsules, with *in vitro* drug delivery from a Cyclohaler® characterized using a twin stage impinger. The results showed that when heated above 30°C, the saturated solution produced lactose monohydrate particles with decreased surface roughness and a corresponding increase in the fine particle fraction and dose emitted.[17]

These studies demonstrate the complex nature of the particle:particle interaction and highlight the importance of several factors, including material type, particle morphology, particle size, and crystal structure, all of which must be carefully evaluated to develop the optimum formulation.

In addition to the physico-chemical properties at the time of manufacturer release, the device is also required to maintain appropriate stability of both the formulation and device performance.[3] Zeng and co-workers recently studied the effects of time and relative humidity on the *in vitro* performance of salbutamol with carriers of lactose, dextrose, maltose, and sorbitol by laser diffraction and multistage liquid impingement.[18] Their work showed that storage under elevated humidity conditions significantly reduced the fine particle content for formulations with dextrose, maltose, and sorbitol due to surface and particle interface changes induced by moisture adsorption and adsorptive capability of the carrier material.[18] The lactose formulations did not show statistically significant changes over time; however, the data did exhibit a general downward trend, suggesting that although lactose has superior stability compared to other carriers, its performance can also be affected by moisture. The results also showed that samples stored for 2 years in dessicators did not exhibit changes in fine particle content, further demonstrating the importance of minimizing moisture exposure throughout the shelf-life.

Driven by the emerging possibilities for localized delivery, protein delivery, and systemic delivery of poorly water-soluble compounds, research in the field of DPI formulation design has rapidly accelerated throughout the past several years to include techniques for enhancing bioavailability using lipid carriers, delivery of nanoparticles, and delivery of proteins.[19-22] Lipid-based carrier formulations are typically produced using spray-drying techniques similar to those described by Sebti and Amighi, in which lipid carriers and the drug substances are dissolved, spray dried, and typically milled to control the

First in Iontophoresis . . .

The Leader in Active Drug Delivery Systems

IOMED, the first company to commercialize iontophoretic products, continues as a leader in developing new, non-invasive technologies and products that deliver drugs safely to site-specific areas of the body.

Expertise

- Electrical and mechanical engineering
- Analytical chemistry
- Biological sciences
- Material sciences

Research and Development

- Prototype design
- Radio-labeled material handling
- Clinical and regulatory
- In vitro and in vivo drug screening

Manufacturing

- Flexible and efficient processes
- State of the art automated equipment
- Compliant with FDA QSR and ISO 13485

Milestones

- First commercial iontophoretic product
- First NDA approved for an iontophoretic system
- Substantial U.S. and foreign patents and others pending

IOMED®
First in Iontophoresis

IOMED, Inc.
Phone: 801 975 1191
Fax: 801 972 9072
info@iomed.com
www.iomed.com
AMEX: IOX

TABLE 2

Lung Deposition Efficiency of Selected Second-Generation DPIs[35,38-40,43]

Product Name	Drug Substance	Inspiratory Flow Rate (L/min)	Deposition Efficiency Mean (S.D.)
Taifun®	Budesonide	15	29.6 (5.9%)
		30	34.3% (5.8%)
MAGhaler®	Salbutamol	30	21.1% (5.1%)
		60	26.4% (4.3%)
Novolizer®	Budesonide	54	19.9%
		65	25%
		99	32.1%
AIR®	Placebo (Gamma Scintigraphy)	38	51% (18%)

final particle size. It has been reported, however, that these post-processing treatments can result in damage to the lipid structures, reducing their effectiveness. Recently, Desai and co-workers developed a novel self-forming lipid-based system that demonstrated high dispersibility with fine particle fractions greater than 50%.[20] They also demonstrated that the technique could be successfully applied to a variety of compounds, including proteins. Nanoparticles, inherently smaller than 1 micron, are inefficiently delivered to the lung using traditional ordered mixing techniques due to the small size. Delivery of nanoparticles, as well as proteins, can be achieved using similar spray-drying or spray freeze-drying techniques by incorporation into a soluble non-interacting carrier and then spray-dry processing to create particles of 1 to 5 microns.[21,22] These particles may be optionally treated thereafter with a carrier for use in DPI applications.

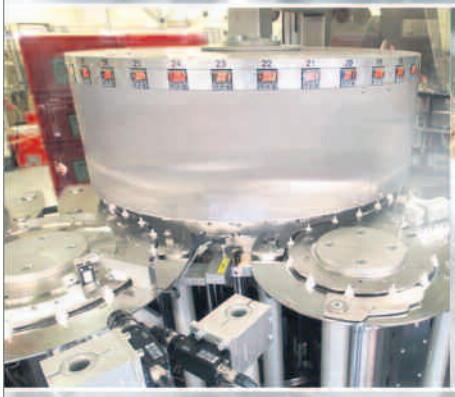
Although several techniques have been described in detail, the past 5 to 10 years have seen a rapid development of formulation technology for dry powder inhalers. For additional information, the reader is referred to reviews by Chow, Telko, and Newman.[23-25] Ultimately, as formulation technology continues to develop and the applications for DPI technology continue to expand, the pharmaceutical scientist will still be required to develop systems capable of achieving the desired therapeutic effect, while maintaining product stability and dose reproducibility. By developing an understanding of drug:carrier interactions, drug substance properties, carrier properties, and how these properties affect drug delivery, more efficient DPI systems can be designed.

DEVICE DESIGN

The first DPI, the Spinhaler™, was introduced in 1967 due to the large dose of sodium cromoglycate required for treatment, which could not be accommodated by pMDIs.[26] Since then, device technology has continued to grow and develop, with a variety of therapeutic agents currently delivered with this platform. An abbreviated list of currently available devices is provided in Table 1. The basic design of DPIs provide for simpler use than pMDIs by eliminating coordination of inspiration and activation; however, the performance of the device can still be dependent on the patient's ability to generate the required inspiration. The design and development of DPI devices is governed by a number of factors that can impact the effectiveness and perception of the device, including the number of doses contained in the device, difficulty in refilling the device, the resistance of the device during inhalation, the device material, product packaging, and mouthpiece geometry. By carefully controlling these design factors, systems can be developed to minimize formulation-device interaction, maximize lung deposition, and improve patient perception and compliance.

The majority of DPIs operate by maintaining the dose, either as a drug or a drug:carrier system in an individual unit or bulk reservoir. Prior to inspiration, the device is primed by pressing (Rotahaler™), sliding (Spinhaler™), or rotating (Twisthaler™) the dose preparation mechanism to prepare the dose for fluidization. Upon inhalation, the powder is fluidized, typically passed through a screen within the device to prevent large particles from entering the oropharangeal cavity, thereafter drug enters the deep lung. A schematic diagram of this process is provided in Figure 2. DPIs are currently classified into two major design types based on the delivery mechanism: pre-metered and device-metered.[3] Pre-metered devices supply the drug product in individually packaged single doses and are available in single-use and multi-use designs; while device-metered units, also referred to as reservoir units, are generally available in multi-use designs only. Single-unit devices, including the Spinhaler™, Rotahaler™, and Handihaler™, consist of individually measured doses typically filled into gelatin capsules or blisters; whereas multi-unit devices, including

THREE GOOD REASONS TO PUT YOUR TRUST IN PFEIFFER



Our engineering systems are utilized in a manufacturing environment dedicated to the production of precision products resulting in superior quality.

Five decades of detail design and manufacturing experience are translated into operational excellence.

Superior service and customer satisfaction are achieved by tailoring the benefits of our systems to meet and exceed all of your requirements effectively and efficiently.

| Pfeiffer |

Pfeiffer of America 742 Alexander Road | Suite 201 | Princeton, NJ 08540 | United States | Phone +1 609 987 0223 | Fax +1 609 987 1511| www.pfeiffer-group.com

FIGURE 3

Taifun® Inhaler Image

the Turbuhaler™, Clickhaler™, Twisthaler™, Easyhaler™, Cyclohaler™, and Taifun™ consist of a reservoir of drug/drug:carrier powder or a series of individual packaged units, which are accurately dispensed by the device prior to use and capable of delivering multiple doses without the requirement for refilling. When developing a device, it is essential to provide the patients with a system that allows for simple preparation and use. Many patients, particularly the young and the elderly, can find inserting single-unit capsules or blisters and actuation of the dose-priming mechanism difficult, which can reduce patient compliance and result in suboptimal therapy.

In addition to designing the device for optimum patient comfort, devices are also designed to ensure maximum lung deposition. All DPI devices have four major components: the drug storage system, the air inlet, the deagglomeration chamber, and the mouthpiece. The storage system, whether for a single-dose or multi-dose system, provides formulation protection against moisture, light, and oxygen, which can significantly reduce product performance. The air inlet and source of the air are also important considerations in the design of DPIs. The air flow can be generated by the user's respiration (passive) or by a secondary source (active), such as that used in the Dura Dryhaler® or the Aspirair™ system. The Aspirair™ system, recently described by Tobyn and co-workers, utilizes a novel vortex separation chamber and secondary compressed air source triggered by an airflow sensor to enhance the deagglomeration of drug particles and improve deep lung deposition.[27] Additionally, the size of the inlet air flow section determines the development of the air stream, which in turn can affect the deagglomeration of particles. In general, longer air inlets will produce more developed flow that will improve deagglomeration.[28] Separation of drug particles from the carrier particles is essential for good lung deposition, and the design of the device plays a critical role in achieving this. DPIs are designed to induce significant turbulence and particle-particle collisions to separate drug particles from the carrier. The cyclone separation system of the Airmax™, described by Zeng and co-workers, utilized two tangential inlets to induce cyclonic flow within the system, which in combination with the unique geometry resulted in a high degree of turbulence and particle collisions to produce highly efficient and reproducible delivery.[29] The design of the mouthpiece and screen are another critical device property. In work by Coates and co-workers using both *in vitro* testing and computational fluid dynamics, the importance of mouthpiece geometry, length, and screen size was demonstrated. Their results showed that use of cylindrical mouthpiece openings, reduction of mouthpiece length, and minimization of the grid voidage all improved the ability of the modified inhalers to deliver drug.[30,31] Using the principles of device design, Wang and co-workers recently developed a single-dose DPI utilizing a using rapid-prototyping stereolithography technique to produce a plastic base, which was coated to improve the interior finish and included a 38-micron screen. The novel device was shown to be capable of delivering much higher doses of budesonide *in vitro* when compared to Pulmicort/Turbuhaler®.[32]

In addition to the general device concerns, there is also the potential for formulation device interaction, primarily triboelectrification of powder that can occur with DPI systems due to the high particle surface area and organic nature of the pharmaceutical powders, which can be particularly high for systems using individual capsule shells.[33] Telko and co-workers studied the effect of lactose type, drug load, capsule fill, capsule material, and inhaler on the charge magnitude and polarity of DPI aerosols. Their work demonstrated that the magnitude and sign of the charge acquired by the particles was highly dependent on the type of inhaler, carrier particle size, and type of capsule shell used, highlighting the complicated nature of interactions between the device and the formulation.

Although the design requirements for DPI devices have not been studied to the same degree as DPI formulations, there is a clear need to understand how fundamental design changes affect the device performance and formulation: device interactions. Continued academic studies with new analysis techniques, such as computational fluid dynamics, will help elucidate a more detailed first principle understanding of the behavior of aerosols in these systems. By combining this fundamental knowledge with the use of

KISS YOUR GLASS GOODBYE...

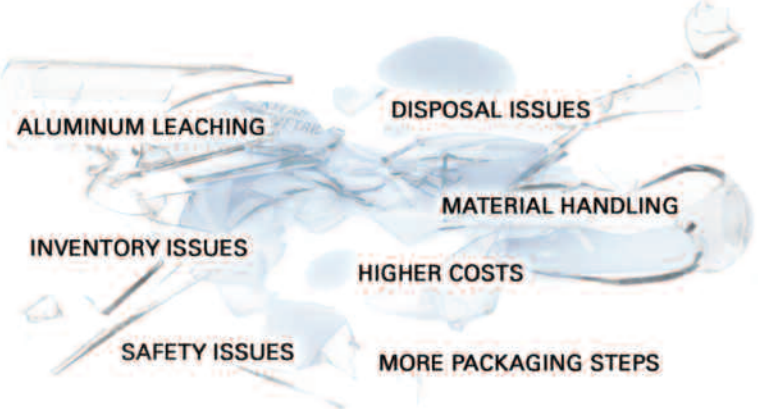
WITH THE ADVANTAGES OF PLASTIC USING ASEP-TECH® BLOW/FILL/SEAL TECHNOLOGY

ASEP-TECH® Blow/Fill/Seal packaging machines from Weiler Engineering are simply the better alternative to conventional filling of glass vials for parenteral (injectable) products. This advanced aseptic technology is also widely used to package ophthalmic and respiratory therapy products.

Check the ASEP-TECH® Blow/Fill/Seal Advantage:

- ✓ Increased safety for both the patient and healthcare provider
- ✓ Lower product to market cost
- ✓ "Green" container manufacturing – recyclable container materials
- ✓ Improved product quality – no aluminum leaching issues
- ✓ Less material handling reduces probability of product contamination
- ✓ Fewer packaging steps
- ✓ Reduced raw material inventory

Now is the time to kiss your glass goodbye and switch to ASEP-TECH® Blow/Fill/Seal packaging machines from Weiler Engineering. To learn more, visit our website at www.weilerengineering.com or call 847-697-4900.



WEILER®

Driven by Science and Technology

1395 Gateway Drive • Elgin, Illinois 60123 • Phone: 847-697-4900 • Fax: 847-697-4915
E-mail: solutions@weilerengineering.com • Website: www.weilerengineering.com

new technologies for fabrication and design, the applications for DPI device manufacturing will continue to expand.

NEXT-GENERATION DPI SYSTEMS

Since the launch of the Spinhaler™, numerous DPI systems have been approved by the FDA for use. These systems have been studied both in academic and industrial settings prior to and after launch. The proper design of clinical trials to study the effectiveness of delivery devices is complicated and can be confounded by a number of different issues, including differences in drugs used, inappropriate dose administered, formulation variations between test groups, number of test subjects, and the duration of the study.[34] In addition to functionality, patient compliance and proper usage are critical for effective therapy. Furthermore, numerous research papers and review articles have been written discussing the efficiencies of these systems, and the reader is referred to a recent article by Newman for a general overview of the available DPI platforms and their performance.[25] Given the vast number of approved devices, with an abbreviated list presented in Table 1, this section will focus on four new second-generation DPI systems: the Taifun®, the MAGhaler®, the Novolizer®, and the AIR® Pulmonary Delivery System, highlighting their use of the formulation and device technologies described previously.

Taifun®

The Taifun® inhaler is a dry powder inhaler that has been approved in Europe for the delivery of salbutamol and is currently being developed as a platform for the delivery of fentanyl citrate. The device utilizes a vortex desegregation chamber, desiccant capsule based humidity-controlled reservoir system, and novel wet suspension surface treated carrier formulation; combining aspects of both formulation and device design to provide optimum delivery. The device can carry up to 200 doses of medication, reducing the burden for cumbersome refilling by the patient. The device is operated by activating the loading mechanism to fill the dosing reservoir, inhaling to draw the dose through the vortex chamber where drug is separated from the carrier for delivery to the lungs. Several recent studies have shown the device to function independently of patient inhalation and provide more efficient lung deposition than other currently marketed devices.[35-37] The respiration-independent delivery and efficient lung deposition make the Taifun® an excellent delivery system for pulmonary applications with strict dosing requirements, such as pulmonary delivery of opiods and proteins. Currently, LAB International is testing the Taifun® in clinical trials for use in delivering fentanyl with results of the Phase II clinical trials showing that the system can be successfully used to achieve significant pain relief with rapid onset of action.

MAGhaler®

The MAGhaler®, also known as the Jethaler®, was developed by Mundipharma GmbH and utilizes a novel isostatically compressed powder ring to ensure accuracy of the dosing. The novel isostatic compression technique used for production prevents the development of a compression gradient and produces tablets with density variations of less than 0.01%.[38] This ring, composed of drug and lactose, is scraped by a grinding wheel upon actuation of the primer mechanism to separate a predetermined aliquot of powder. After actuation, the dose is administered to the patient by inhalation. The dosing dynamics of this system were recently evaluated in a 10-patient two-way cross-over study using radiolabeled powder to assess the lung deposition.[38] The results showed that the device was capable of delivering drug effectively at both low and high inhalation rates with slight increases in efficiency based on increasing inhalation flow rate. Currently, a budesonide product using the Jethaler® delivery system is marketed in Germany by Ratiopharm.

FIGURE 4

MAGhaler® Image

FIGURE 5

Novolizer® Image

Novolizer®

The Novolizer® is another second-generation DPI system that is currently marketed in Europe for the delivery of budesonide by Viatris. The device utilizes a large powder reservoir to store approximately 200 doses and is prepared by depressing the priming actuator to meter the individual dose into the loading channel. The patient then inhales under moderate device resistance to generate a flow of 35 to 50 L/min, and the dose is separated by the cyclonic motion of the powder to provide efficient delivery to the lungs.[39] The efficiency of this delivery system was demonstrated in an *in vivo* study conducted using γ-scintigraphy to assess the lung deposition. This study showed that the Novolizer® provided superior lung deposition compared to the Turbuhaler® at optimally maximal flows; although the lung deposition efficiency of the Novolizer® was affected by the flow rate.[40] The Novolizer® was also shown to significantly reduce the dose variability of delivered drug and lung deposited drug compared to the Turbuhaler®. The superiority of the Novolizer® over the Jethaler® was also demonstrated in a recent study by De Boer and co-workers, where it was shown the Novolizer® generated superior fine particle fractions compared to the Jethaler®.[41] Additionally, several large population clinical trials have also demonstrated the safety and effectiveness of this system, indicating the viability of this delivery platform for future products.[42]

AIR® Pulmonary Delivery System

The AIR® Pulmonary Delivery System is a combination of formulation technology and device design technology, intended to provide optimum delivery characteristics. This system, developed by Alkermes, Inc., utilizes low density (< 0.4 g/cc) and large geometric diameter (> 5 microns) particles composed of drug contained in a solid lung surfactant matrix produced by spray drying to achieve effective aerodynamic diameters.[43,44] The spray-dried powders are then dosed into capsules for use in the DPI. The design of the DPI is ingenious in its size and simplicity, providing the patient with a portable, easy-to-use system of about 5 inches in length. The device is operated by placing the capsule into the chamber, compressing the inhaler to puncture the capsule and breathing through the mouthpiece to inhale the dose. Lung deposition studies conducted with γ-scintigraphy by radiolabeling particles with rhodamine B during spray drying have demonstrated mean efficiencies of 51% over a range of inhalation flow rates, and the system demonstrated the highest lung deposition efficiency of any of the second-generation systems summarized in this review (Table 2).[43] Additionally, Phase II clinical trial results of the AIR® system for insulin delivery in diabetic patients (types I and II) were recently reported by Alkermes and co-developer Eli Lilly. The results demonstrated good product safety, reductions in hemoglobin A1c, and postprandial blood glucoses similar to subcutaneous insulin injections.[45] Based on these results, continued development of the AIR® Pulmonary Delivery System is planned for use in a variety of treatments.

FIGURE 6

AIR® Image

SUMMARY

Since the inception of the DPI, the development of the platform has been driven by both technological and legislative requirements. In addition to these requirements, treatment applications for pulmonary administration are also rapidly expanding to include areas such as protein delivery, opiod delivery, systemic delivery of poorly water-soluble compounds, and targeted antibiotic delivery. The requirements for these new applications, in combination with the increasing knowledge of DPI formulation and DPI device design, have allowed for new systems to be developed that more effectively deliver drug, provide enhanced patient compliance, and are capable of supporting a variety product classifications. As shown in this article, several second-generation DPI systems are currently in development, and their use of formulation and device design principles have allowed them to surpass previous systems in terms of efficiency, simplicity, and applicability. Given the current

status of pulmonary delivery and the potential benefits provided by the DPI delivery platform, development of next-generation systems will continue for the foreseeable future with continued interest in providing enhanced lung deposition, improved ease of use, and increased scope of application. ◆

REFERENCES

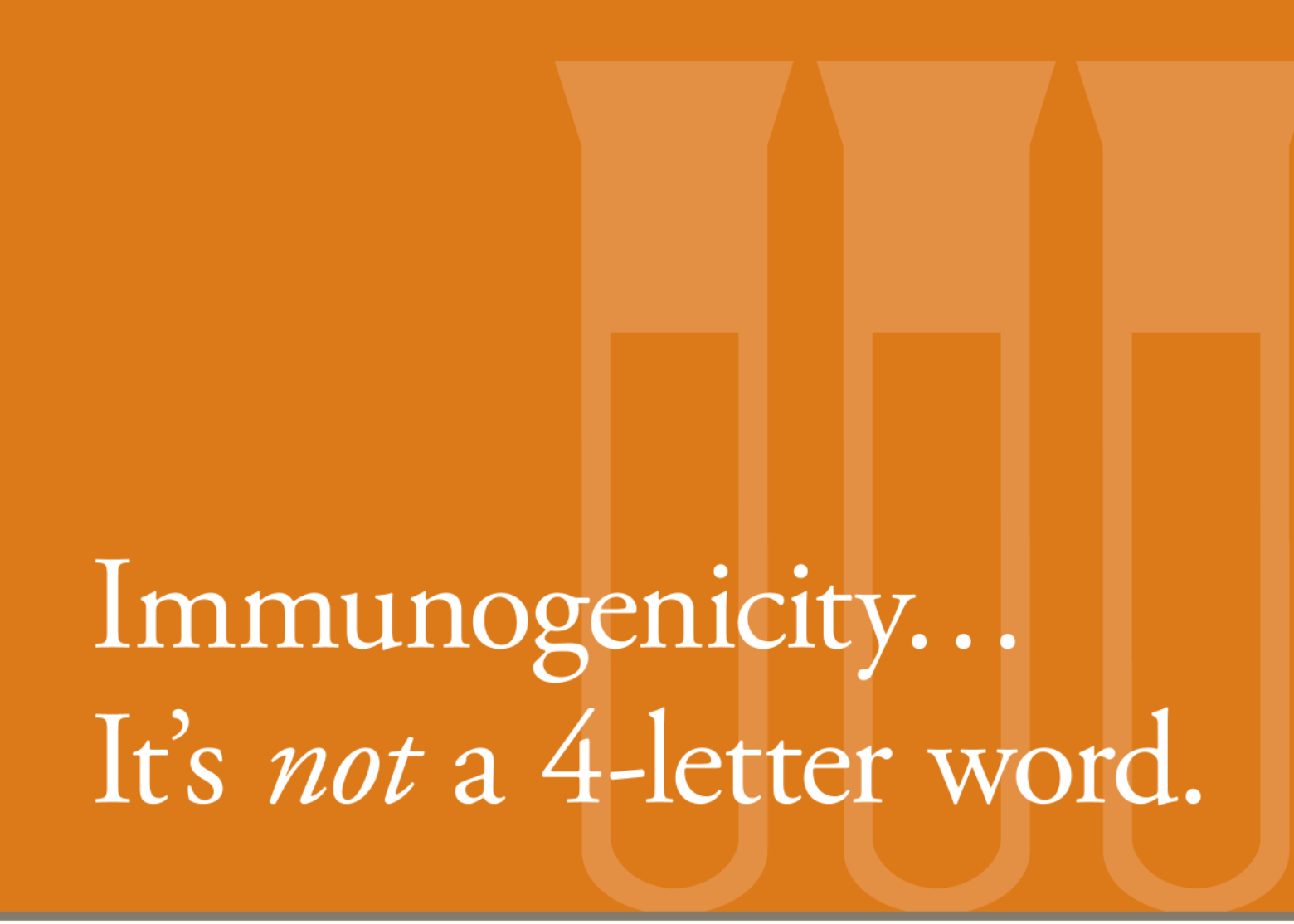
1. Forte R, Dibble C. The role of international environmental agreements in metered dose inhaler technology changes. J Allergy Clin Immunol. 1999;104(6):s217-s220.
2. Dalby R, Suman J. Inhalation therapy: technological milestones in asthma treatment. Adv Drug Del Rev. 2003;55(7):779-791.
3. Draft Guidance for Industry – Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products: Chemistry, Manufacturing, Controls and Documentation, F.D.A. U.S. Department of Health and Human Services, Center for Drug Evaluation and Research (CDER), Editor. 1998:65.
4. Hickey AJ, Concessio NM. Descriptors of irregular particle morphology and powder properties. Adv Drug Del Rev. 1997;26(1):29-40.
5. Buckton G. Characterisation of small changes in the physical properties of powders of significance for dry powder inhaler formulations. Adv Drug Del Rev. 1997;26(1):17-27.
6. Young PM, Chan H-K, Chiou H, Edge S, Tee THS, Traini D. The influence of mechanical processing of dry powder inhaler carriers on drug aerosolization performance. J Pharmaceut Sci. 2007;96(5):1331-1341.
7. Finlay WH. The Mechanics of Inhaled Pharmaceutical Aerosols: An Introduction.San Diego, CA: Academic Press; 2001.
8. Ikegami K, Kawashima Y, Takeuchi H, Yamamoto H, Isshiki N, Momose D-I, Ouchi K. Primary crystal growth during spherical agglomeration in liquid: designing an ideal dry powder inhalation system. Powder Technol,. 2002;126(3):266-274.
9. You Y, Zhao M, Liu G, Tang X. Physical characteristics and aerosolization performance of insulin dry powders for inhalation prepared by a spray drying method. J Pharmacy Pharmacol. 2007;59(7):927-934.
10. Lobo JM, Schiavone H, Palakodaty S, York P, Clark A, Tzannis ST. SCF-engineered powders for delivery of budesonide from passive DPI devices. J Pharmaceut Sci. 2005;94(10):2276-2288.
11. Shekunov BY, Chattopadhyay B, Gibson A, Lehmkuhl C. Influence of spray-freezing parameters on particle size and morphology of insulin. Presented at Proceedings of the Conference on Respiratory Drug Delivery. Boca Raton, Florida;2006.
12. Irngartinger MV, Camuglia M, Damm J, Goede, Frijlink HW. Pulmonary delivery of therapeutic peptides via dry powder inhalation: effects of micronisation and manufacturing. Eur J Pharmaceutics Biopharmaceutics. 2004;58(1):7-14.
13. Trofast E, Briggner L-E. Process for Conditioning Substances. W.I.P. Organization, Editor. Astra Aktiebolag;1995
14. Lankinen T. Method for making a pharmaceutical formulation. U.S.P.a.T. Office, Editor. Leiras Oy;2000.
15. Saint-Lorant G, Leterme P, Gayot A, Flament MP. Influence of carrier on the performance of dry powder inhalers. Int J Pharmaceutics. 2007;334(1-2):85-91.
16. Li H-Y, Seville PC, Williamson IJ, Birchall JC. The use of amino acids to enhance the aerosolisation of spray-dried powders for pulmonary gene therapy. J Gene Med. 2005;7(3):343-353.
17. El-Sabawi D, Price R, Edge S, Young PM. Novel temperature controlled surface dissolution of excipient particles for carrier based dry powder inhaler formulations. Drug Devel Indust Pharm. 2006;32(2):243-251.
18. Zeng X-M, MacRitchie HB, Marriott C, Martin GP. Humidity-induced changes of the aerodynamic properties of dry powder aerosol formulations containing different carriers. Int J Pharmaceutics. 2007;333(1-2):45-55.
19. Sebti T, Amighi K. Preparation and in vitro evaluation of lipidic carriers and fillers for inhalation. Eur J Pharmaceutics Biopharmaceutics. 2006;63(1):51-58.
20. Desai TR, Hancock REW, Finlay WH. Delivery of liposomes in dry powder form: aerodynamic dispersion properties. Eur J Pharmaceut Sci. 2003;20(4-5): 459-467.
21. Sham JO-H, Zhang Y, Finlay WH, Roa WH, Löbenberg R. Formulation and characterization of spray-dried powders containing nanoparticles for aerosol delivery to the lung. Int J Pharmaceutics. 2004;269(2):457-469.
22. Shoyele SA, Slowey A. Prospects of formulating proteins/peptides as aerosols for pulmonary drug delivery. Int J Pharmaceutics. 2006;314(1):1-8.
23. Chow AHL, Tong HHY, Chattopadhyay P, Shekunov BY. Particle engineering for pulmonary drug delivery. Pharmaceut Res. 2007;24(3):411-437.
24. Telko MJ, Hickey AJ. Dry powder inhaler formulation. Respiratory Care. 2005;50(9):1209-1227.
25. Newman SP, Busse WW. Evolution of dry powder inhaler design, formulation, and performance. Respiratory Medicine, 2002. 96(5): p. 293 - 304.
26. Chrystyn H, The Diskus™: a review of its position among dry powder inhaler devices. Int J Clin Pract. 2007;61(6):1022-1036.
27. Tobyn M, Staniforth JN, Morton D, Harmer Q, Newton ME. Active and intelligent inhaler device development. Int J Pharmaceutics. 2004;277(1-2):31-37.
28. Chan H-K, Young PM, Traini D, Coates M. Dry powder inhalers: challenges and goals for next-generation therapy. Pharmaceut Technol Eur. 2007;19(4):19-24.
29. Zeng X-M, Jones S, O 'leary D, Phelan M, Colledge J. Delivery of formoterol from a novel multi-dose inhaler AirmaxTM. Respiratory Med. 2002;96(6):397-403.
30. Coates MS, Chan H-K, Fletcher DF, Chiou H. Influence of mouthpiece geometry on the aerosol delivery performance of a dry powder inhaler. Pharmaceut Res. 2007;24(8):1450-1456.
31. Coates MS, Fletcher DF, Chan H-K, Raper JA. Effect of design on the performance of a dry powder inhaler using computational fluid dynamics: part 1: grid structure and mouthpiece length. J Pharmaceut Sci. 2004;93(11):2863-2876.
32. Wang ZL, Grgic B, Finlay WH. A dry powder inhaler with reduced mouth-throat deposition. J Aerosol Med. 2006;19(2):168-174.
33. Telko MJ, Kujanpää J, Hickey AJ. Investigation of triboelectric charging in dry powder inhalers using electrical low pressure impactor (ELPI™). Int J Pharmaceutics. 2007;336(2):352-360.
34. Barry PW, O'Callaghan C. The influence of inhaler selection on efficacy of asthma therapies. Adv Drug Del Rev. 2003;55(7):879-923.
35. Pitcairn GR, Lankinen T, Seppälä O-P, Newman SP. Pulmonary drug delivery from the taifun dry powder inhaler is relatively independent of the patient's inspiratory effort. J Aerosol Med. 2000;13(2):97-104.
36. Newman SP. Optimizing delivery of drugs to the lungs. Clin Asthma Rev. 1998; 2:123-128.
37. Newman SP. Drug delivery to the lungs from dry powder inhalers. Curr Op Pulmonary Med. 2003;9(Supplement 1):S17-S20.
38. Newman S, Malik S, Hirst P, Pitcairn G, Heide A, Pabst J, Dinkelaker A, Fleischer W. Lung deposition of salbutamol in healthy human subjects from the MAGhaler dry powder inhaler. Respiratory Med. 2002;96(12):1026-1032.
39. von Berg A, Kremer H-J, Ellers-Lenz B, Conrad F, Erb K, Maus J, Hermann R. Peak inspiratory flow rates generated through the Novolizer® and the Turbuhaler® dry powder inhaler devices by children with stable Aasthma. J Aerosol Med. 2007;20(1):50-58.
40. Newman SP, Pitcairn GR, Hirst PH, Bacon RE, O'Keefe E, Reiners M, Hermann R. Scintigraphic comparison of budesonide deposition from two dry powder inhalers. Eur Respiratory J. 2000;16(1):178-183.
41. De Boer AH, Gjaltema D, Hagedoorn P, Frijlink HW. Comparative in vitro performance evaluation of the Novopulmon® 200 Novolizer® and Budesonid-ratiopharm® Jethaler: two novel budesonide dry powder inhalers. Pharmazie. 2004;59(9):692-699.
42. Fenton C, Keating GM, Plosker GL. Novolizer: a multidose dry powder inhaler. Drugs. 2003;63(22):2437-2445.
43. De Long MJ, Wright M, Dawson T, Meyer KS, Dunbar C. Dose delivery characteristics of the AIR® pulmonary delivery system over a range of inspiratory flow rates. J Aerosol Med. 2005;18(4):452-459.
44. Muchmore DB, Silverman B, Pena ADL, Tobain J. The AIR® inhaled insulin system: system components and pharmacokinetic/glucodynamic data. Diabetes Technol Therapeut. 2007;9(Supplement 1):S41-S47.
45. Ellis SL, Gemperline KA, Garg SK. Review of phase 2 studies utilizing the AIR® particle technology in the delivery of human insulin inhalation powder versus subcutaneous regular or lispro insulin in subjects with type 1 or type 2 diabetes. Diabetes Technol Therapeut. 2007;9(Supplement 1):S48-S56.

BIOGRAPHIES

Mr. James C. DiNunzio is currently a graduate student in the Division of Pharmaceutics at The University of Texas at Austin. Prior to entering the PhD program, he spent 3 years working as a Scientist in the Pharmaceutical Technology & Development Group at Forest Laboratories, where his responsibilities included supervising scale-up, process optimization, and clinical trial manufacturing activities for developmental products. He earned his MS in Chemical Engineering from Columbia University and his BS (cum laude with distinction) in Chemical Engineering from the State University of New York at Buffalo.

Dr. James W. McGinity is Professor and Division Head of Pharmaceutics in the College of Pharmacy, The University of Texas at Austin. He earned his BS in Pharmacy in 1967 at the University of Queensland, Australia, and his PhD in Pharmaceutics in 1972 from the University of Iowa. Dr. McGinity's research interests and publications are focused on solid dosage forms, aqueous film coating of pellets and tablets, powder technology, materials science, transdermal systems, hot-melt extrusion, and controlled and targeted drug delivery systems. Hot-melt extrusion technology has been investigated as a pharmaceutical process to prepare transmucosal films, transdermal patches, tablets, granules, pellets, and fast-dissolving oral dosage forms. Dr. McGinity is an author or co-author on over 150 scientific publications, and he has been issued 23 US patents. He is an AAPS Fellow, the US Editor for *The European Journal of Pharmaceutics and Biopharmaceutics*, and a charter member of *Drug Delivery Technology's* Editorial Advisory Board.

Dr. Robert O. (Bill) Williams III is the Johnson & Johnson Centennial Professor of Pharmaceutics at the College of Pharmacy, University of Texas at Austin. He earned a BS in Biology, a BS in Pharmacy, and Doctor of Philosophy in Pharmaceutics, all from the University of Texas at Austin. Dr. Williams worked 9 years in the pharmaceutical industry in the US and France before returning to the University of Texas at Austin. Dr. Williams was elected a Fellow of the AAPS in 2006 and is a member of the AACP, ACS, Association de Pharmacie Galenique Industrielle, CRS, and European Federation of Biotechnology. He was the Co-founder and President of PharmaForm LLC from 1996 to 2007, and is a Director of Akela Pharma, Inc. Dr. Williams' research interests include development of novel drug delivery systems for oral, pulmonary, nasal, injectable, buccal, and topical applications; development of novel particle engineering technologies for low molecular weight drugs, peptides, and proteins; and analytical technologies to characterize actives, excipients, and polymers. He has published over 225 articles, abstracts, and book chapters in the fields of pharmaceutical technology and drug delivery, is an inventor on numerous patents and patent applications, is the Editor-in-Chief of the research journal *Drug Development and Industrial Pharmacy,* and serves as a reviewer for many national and international journals.



Immunogenicity... It's *not* a 4-letter word.

We know that Immunogenicity testing is no simple matter.

With our technical expertise and experienced scientists, you can rest assured your assays will be conducted in full regulatory compliance at PBI.

P·B·I

Who is PBI?
Pacific Biometrics, Inc. is a Specialty Central Laboratory providing comprehensive clinical trial support in full regulatory compliance; now also including multiplexing and immunogenicity testing.

Why choose PBI?
We have an established reputation as the premier lab with scientific expertise, protocol consultation, reliable results and outstanding client service.

We also know that service is not a 4-letter word. Give us a call.

SPECIALTY CENTRAL LAB SERVICES Pacific Biometrics, Inc. • 800 767 9151 • www.pacbio.com

TRANSDERMAL DELIVERY

Exploring the Properties of Gel-Matrix Technology

By: Christopher Adams

INTRODUCTION

Throughout the years, transdermal systems have provided an alternative to conventional dosage forms, and have proven to be highly advantageous in a variety of ways. For patients, perhaps the most significant is an improvement of the "therapeutic index" of a compound while also providing a more convenient dosing regime. For many actives, the transdermal route can provide clear advantages in efficacy, tolerability, and compliance when compared to other routes of administration.

However, not all transdermal technologies are equal in their ability to satisfy patient needs, and the tolerability of transdermal products ranges widely. This is becoming increasingly apparent as more transdermal products become available, and patients, doctors, and regulatory agencies are becoming more educated about the differences in performance characteristics of transdermal systems.

With this in mind, the development of transdermal technology with a primary goal of providing optimal tolerability and wear properties has become a unique and yet valuable focus. The challenge in recent years has been to develop polymer systems that not only provide superior wear properties, but to achieve this in a manner that can be broadly applied to multiple compounds.

FIGURE 1

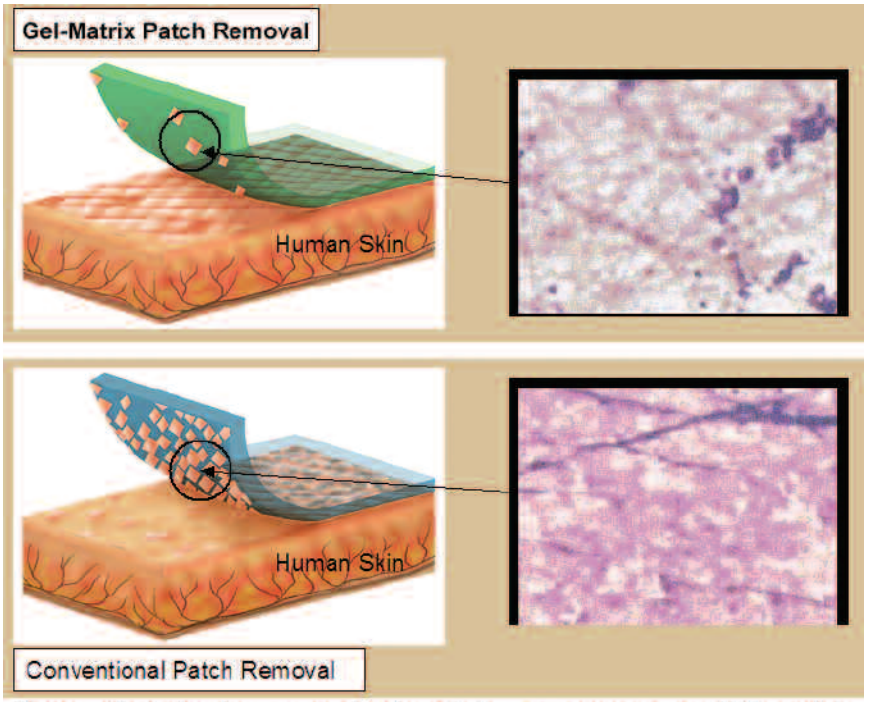


Diagram & photomicroscopy showing stratum corneum removal. The patch surface is shown following patch removal, with minimum stratum corneum removal for the gel-Matrix System (top), compared with greater corneum cell removal for a conventional system (bottom).

CONVENTIONAL MATRIX TECHNOLOGY

Typically, transdermal companies utilize pressure sensitive adhesives obtained from well-known polymer adhesive manufacturers, and incorporate these polymers into transdermal formulations. The most widely used adhesives include those composed of acrylic, silicone, and polyisobutylene polymers. While the physical properties of these types of adhesives can be modified to some extent by the addition of various excipients or other polymers, most patch makers find themselves limited by the inherent characteristics of the polymers.


Hospira
Newly Expanded!
The McPherson, Kansas facility increases aseptic fill and lyophilization capacity.
Your vision, in perfect reflection.
You have a pure vision for your parenteral product, but to make it a reality, every aspect of the development and commercialization process must be handled flawlessly. Recognizing the industry need for biologic fill/finish, Hospira has responded with an expansion of our lyophilization capabilities at both the McPherson, Kansas and Liscate, Italy plants. So when selecting a manufacturer, take a close look at One2One® bio/pharmaceutical services – our facilities offer you unsurpassed capability and a continual focus on quality. To schedule a visit, contact us by phone at 224-212-2267 or via the Custom Manufacturing link at www.Hospira.com.
ONE2ONE®
Producing confidence at every stage
©2006 Hospira, Inc.
9-252/R2-Jan., 06

In particular, formulators have identified a need for an adhesive matrix to provide a more "gentle" experience to the user, especially upon patch removal. The challenge for transdermal formulators has been to develop such a matrix that is also widely applicable to a number of compounds, while still retaining characteristics such as high delivery rate, high solubility, and low cold-flow.

GEL-MATRIX PATCH TECHNOLOGY

Substantial development work by transdermal and polymer scientists led to the development of the Gel-Matrix adhesive. This adhesive system was found to have remarkable physical properties, particularly when applied to skin, while also having broad applicability, high-drug loading, and reduced cold-flow properties. This adhesive system is composed of an acrylic-based polymer that is cross-linked in such a way as to create a net-like structure that retains its cohesive strength while maintaining a low polymer density. The lower polymer density is achieved by incorporating into the polymer matrix a liquid component that can be as high as 60% of the total matrix weight. The liquid component of the system is typically a lipophilic substance that can also function as a drug solubilizer or permeation enhancer. By carefully modulating the polymer structure, liquid component, and the degree of cross-linking, an adhesive that is much "softer" than conventional adhesives is achieved.

The high percentage of liquid component allows the incorporation of active substances at relatively high concentrations. The liquid component may also be modified to accommodate compounds having different solubility properties. Interestingly, although the percentage of liquid in the matrix is high, the cohesive strength of the matrix is also high, preventing the phenomenon of cold-flow, which plagues most conventional adhesives.

ADHESIVE PROPERTIES

There are several beneficial characteristics that were discovered when Gel-Matrix technology was employed in transdermal formulations. First, it was noted that these formulations provide for a much more

FIGURE 2

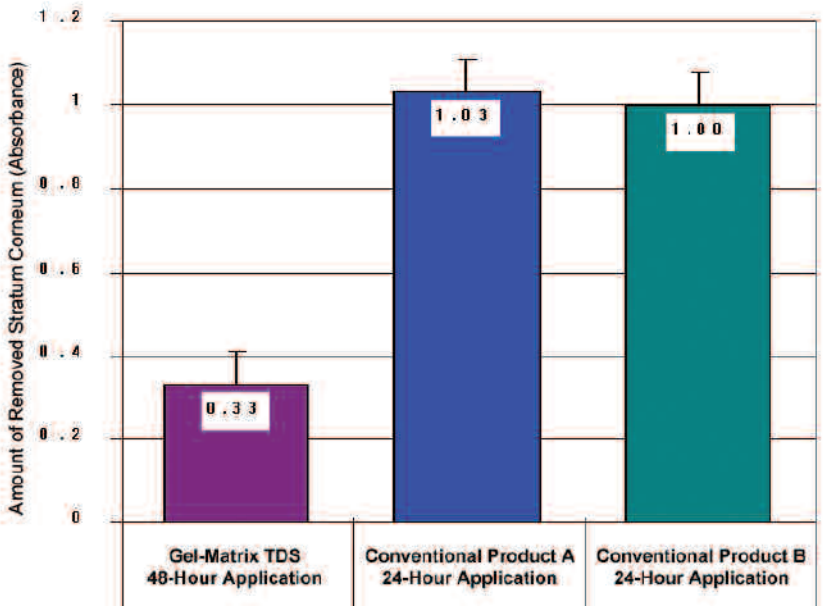
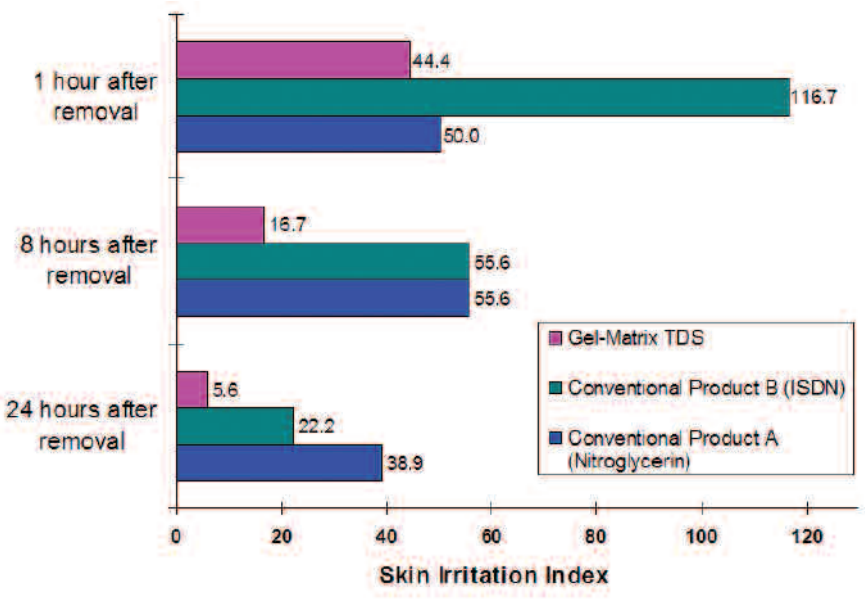


FIGURE 3



Penwest Oral Drug Delivery Technologies Available at Pii

TIMERx®
Controlled Release Delivery Systems

- Commercialized Technology
  - *Recently approved in a BID pain product in the U.S.*
  - *Previous approvals in cardiovascular and incontinence products in Europe and U.S.*
- Easy to scale-up and manufacture
- Precisely controls drug release
- Cost effective

Geminex®
Dual Drugs, Dual Releases

Dual-delivery system which can release drugs or isomers at two different rates.

SyncroDose™

Releases drug at the desired time and site in body.

For more information on the Timerx Technologies, please contact Penwest at:

Phone: 203-796-3700
Fax: 203-794-1393
Email:bizdev@penwest.com

www.penwest.com

Penwest

Pii

FIGURE 4

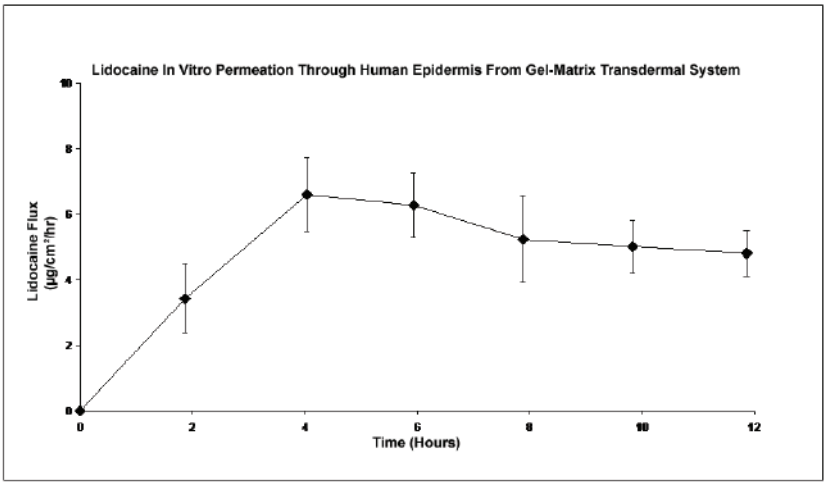


FIGURE 5

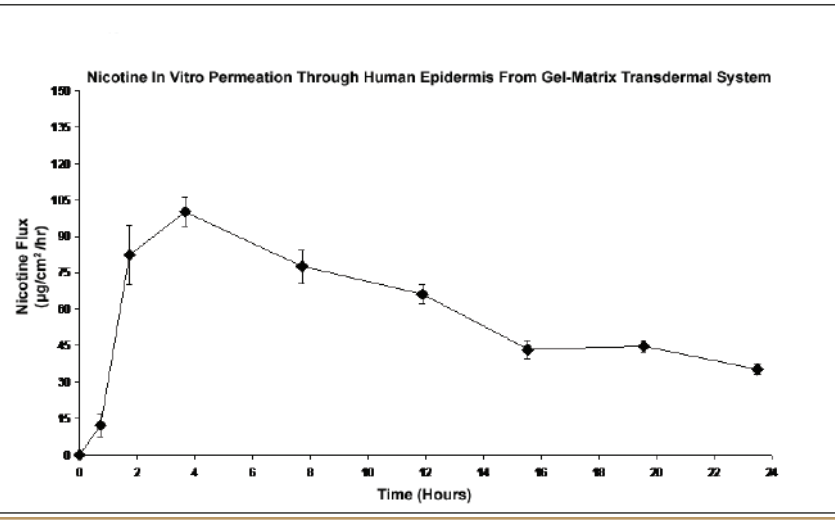
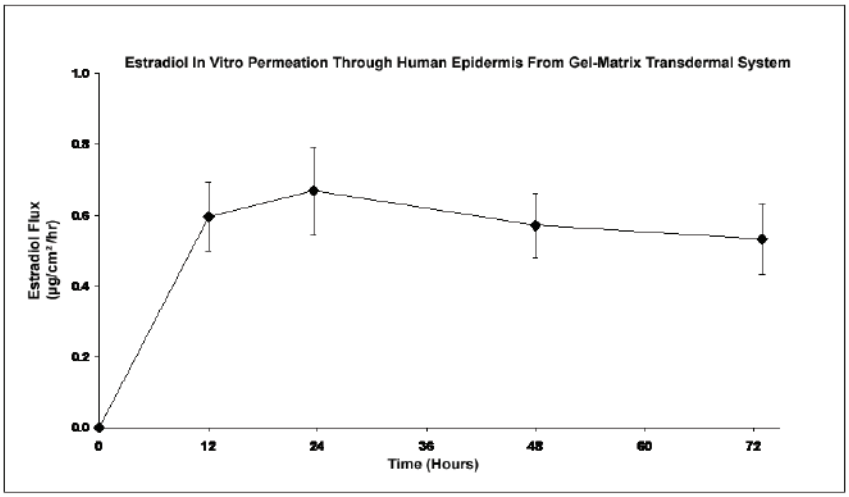


FIGURE 6



gentle wear experience when placed on human skin when compared to traditional silicone, acrylic, or polyisobutylene formulations.[1-5] Physical testing indicates that the adhesive reaches its maximum adhesive force almost immediately after application, and remains largely unchanged over time. This results from the ability of the adhesive to rapidly conform to the irregular surfaces of the skin. Because the matrix conforms very rapidly to the microscopic topography of the skin, the contact surface area is maximized, and a high skin adhesive bond is not required to maintain optimal wear properties.

In comparison, traditional adhesives do not conform as rapidly to the skin surface, and must compensate for the lack of surface area contact by adhering strongly to the surface cells to which they contact. Generally, these adhesives have a lower initial adhesive force, and then adhesion increases significantly as the polymer conforms itself to the surface over time or as pressure is applied.

These effects can be seen in Figures 1 and 2. Figure 1 shows a graphical representation of stratum corneum cell removal that occurs during patch removal of traditional and Gel-Matrix patches. A quantitative comparison of surface cell removal is shown in Figure 2.

IMPROVED TOLERABILITY

In addition to dermal skin stripping measurements, a measure of tolerability can be obtained by conducting a comparative dermal irritancy study. In one study, patches utilizing Gel-Matrix adhesive (Frandol® Isosorbide Dinitrate Transdermal System) were compared to conventional adhesive patch products (acrylic-based Isosorbide Dinitrate Transdermal "product A" and

commercial Nitroglycerin Transdermal System "product B"). In this study, the patches were worn for 24 hours, and skin irritancy was measured at 1 hour, 8 hours, and 24 hours post application (Figure 3). The results of this study demonstrate a significant reduction in skin irritancy levels for the Gel-Matrix adhesive.

APPLICATION TO VARIOUS COMPOUNDS: *IN VITRO* TESTING

In the following examples, Gel-Matrix technology is employed in conjunction with a range of compounds that represent very different compound classes. Lidocaine is selected as an example of formulations requiring a high dose and high loading of drug. Nicotine is selected as an example of a liquid drug, and Estradiol as a low dose, poorly soluble drug.

Formulations

The formulations were developed employing the Gel-Matrix adhesive with the three drugs. The liquid component of the adhesive matrix was optimized based on the solubility requirements of the drugs. The adhesive matrix was produced by conventional liquid mixing process followed by coating, drying, and laminating the solvent-based adhesive in a drying chamber. Patches of the appropriate sizes were then punched from the laminate sheets.

In Vitro Permeation Testing Using Human Epidermis: Methodology

Permeation tests were conducted using modified Franz-type diffusion cells for measurement of diffusion rates through human epidermis. The donor compartment volume is 7.5 ml, sample volume is 0.9 ml, and flux surface area is 0.712 cm^2. A solution of saline and azide is used as the receiving media. The epidermis is obtained from cryopreserved dermis, screened for integrity, and punched to the appropriate sizes for mounting on the cells. Sampling times are selected based on the duration of the study; for Lidocaine, a 12-hour duration is used, for Nicotine, 24 hours, and for Estradiol, 72 hours is used. The samples are taken and analyzed by HPLC, with drug concentrations plotted against time per unit area.

Results

Figures 4, 5, and 6 represent the permeation rates achieved from patch formulations of Lidocaine, Nicotine, and Estradiol, all utilizing the Gel-Matrix adhesive. The permeation rates and profiles achieved resemble those achieved by commercial products that employ conventional adhesives, such as silicone, acrylic, and polyisobutylene.

The permeation test results indicate the matrix provides acceptable delivery rates for a range of different compounds. Solubility within the matrix was high, as all formulations were below their saturation levels. Cold-flow was not observed, and the physical properties were characteristic of the Gel-Matrix adhesive.

CONCLUSION

When compared to conventional transdermal products, the Gel-Matrix technology improves patient comfort by minimizing the disruption of the stratum corneum during removal. This enhanced patient experience may be especially important in managing chronic conditions in which the patch needs to be applied to the same area or when noncompliance with other types of delivery systems is a significant issue. Furthermore, the technology has been applied to a range of different drug compounds with good results, indicating broad utility for development of future transdermal products.

ACKNOWLEDGEMENTS

The authors would like to thank Mr. Hidetoshi Kuroda, Mr. Hitoshi Akemi, Dr. Mitsuhiko Hori, and Mr. Takashi Kinoshita for their support with this paper.

REFERENCES

1. Kinoshita T, Akemi H, Higashio K, Otsuka S. Newly developed medical adhesive. Nitto Giho. 1993;31(2):62.
2. Akemi H, Kinoshita T, Otsuka S. Newly developed medical adhesive. Nitto Giho. 1995;33(2):54.
3. Shirai F, Ban Yu-Ki. Surgical tape developed to reduce skin irritation. Nitto Technical Report. 2001;39(1):32.
4. Tomita Y et al. Skin irritation study of an improved version (TY-0161) of Frandol® Tape-S: comparison with other nitrate preparations. The Clinical Report. 1993;27(5):1536.
5. Hori M. Transdermal drug delivery systems: contributing to an improved quality of life. Nitto Technical Report. 2004;42:53.

BIOGRAPHY

Mr. Christopher Adams is Associate Director of the Transdermal Development group at Aveva Drug Delivery Systems, a US subsidiary of Nitto Denko Corporation. He joined the company (formerly Sano Corporation) in 1994 and has developed several transdermal products that are either FDA approved or pending approval. He oversees the formulation, development, and scale-up of a substantial pipeline of transdermal products. Prior to joining Aveva, Mr. Adams specialized in organic chemistry, earning a BS from Florida International University, and worked on special projects at Oak Ridge National Laboratory in collaboration with Drs. M. Quirke and G. Van Berkel.

NANOSUSPENSIONS

Nanosuspensions as a Drug Delivery System: A Comprehensive Review

By: Tejal Shah, MPharm, Dharmesh Patel, MPharm, Jayshukh Hirani, MPharm, and Avani F. Amin, MPharm, PhD

ABSTRACT

One of the most challenging tasks for formulators in the pharmaceutical industry is the formulation of poorly soluble drugs. Conventional techniques employed for improving solubility of these drugs have gained limited success. This holds true more often when dealing with drugs having poor aqueous as well as organic solubility. Nanosuspension facilitates formulation of hydrophobic drugs to improve solubility and efficacy. Nanosuspensions are submicron colloidal dispersions of pure drug particles, stabilized by surfactants. This drug delivery system is simple and advantageous compared to other strategies. Techniques, such as media milling, high-pressure homogenization, and use of microemulsion as a template have been used for production of nanosuspensions. Nanosuspensions can be delivered by various routes, such as oral, parenteral, pulmonary, and ocular systems. It is also possible to convert nanosuspensions to patient-acceptable dosage forms like tablets, capsules, and lyophilized powder products. Nanosuspension technology has also been studied for active and passive targeted drug delivery systems. The present review focuses on various manufacturing and formulation perspectives and applications of nanosuspensions as a drug delivery system.

INTRODUCTION

The applications of nanotechnology for drug delivery systems have been introduced in recent times, and some of them include use of nanoparticles, solid lipid nanoparticles, and nanosuspensions.[1-3] Nanosuspensions of drugs are colloidal dispersions of nano-size drug particles stabilized by surfactants.

Nanosuspensions can be used to enhance solubility of drugs that are poorly water soluble and poorly lipid soluble. This particular advantage makes it a unique dosage form. It is also a simple strategy that has various advantages over other techniques. It provides benefits to BCS Class II, III, and IV candidates, which exhibit poor aqueous or lipid solubility and also for drugs having a log P value greater than 2.[4]

Strategies to overcome the solubilization problems include solubilization using micelles, complexation using cyclodextrins, micronization, use of penetration enhancers, solid and surfactant dispersions, and other common strategies like liposomes and microemulsions, which have also been attempted by researchers.[5-9] The present review mainly focuses on the various manufacturing and formulation aspects of nanosuspensions and its applications as a drug delivery system.

NEED FOR FORMULATING NANOSUSPENSIONS

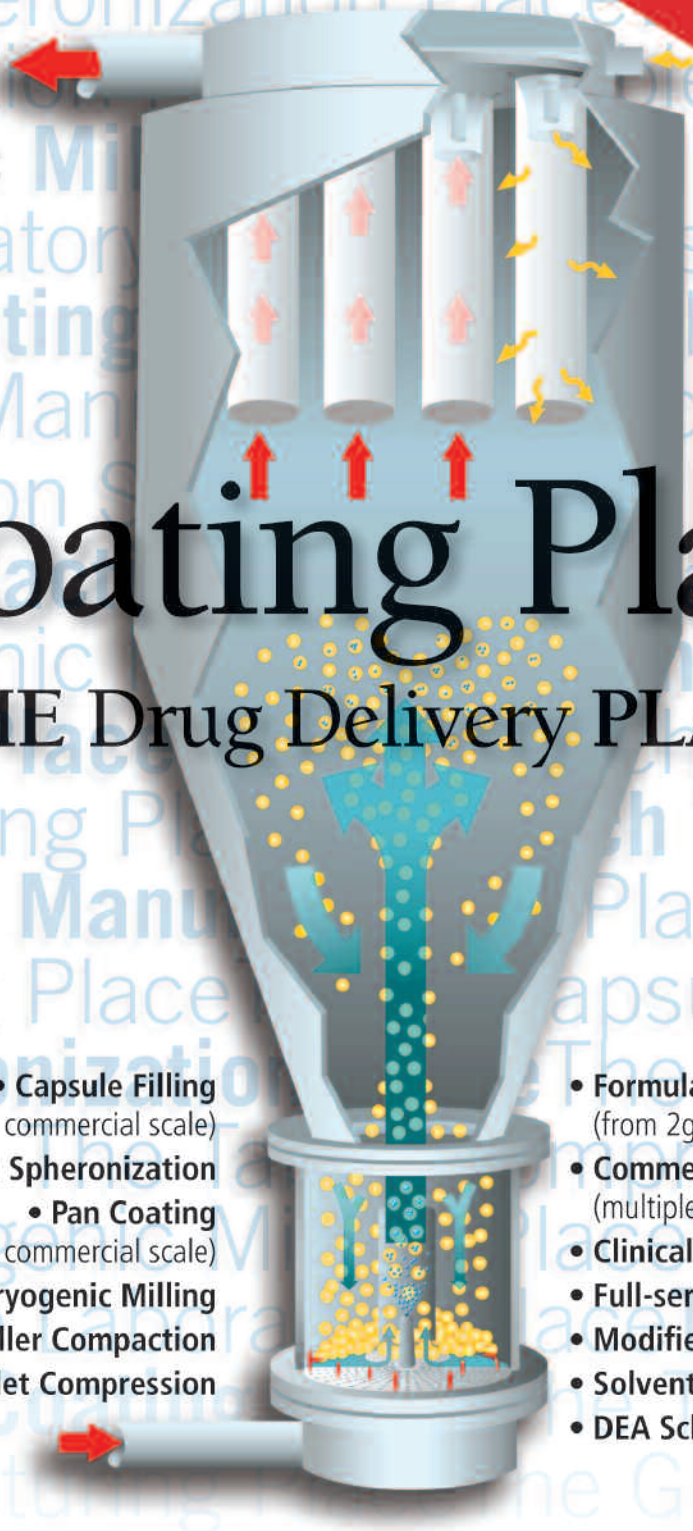
Lipidic systems, such as liposomes and emulsions, can be used for compounds that are water insoluble and soluble in oil (with high log P). In contrast, with the lipidic systems, nanosuspensions can also be used to formulate compounds that are insoluble in both water and oil. This is used when the crystal energy of the compound is high, which reduces the tendency of the crystal to dissolve, regardless of the solvent.[10] Nanosuspensions overcome this problem by obviating the need to dissolve them and by maintaining the drug in a preferred crystalline state of size sufficiently small enough for pharmaceutical acceptability. In addition, utilization of the dense, solid state confers an additional advantage of higher mass-per-volume loading. This is crucial when high dosing is required. A related benefit of the high loading is reduced administration volume, which is critical for low-volume intramuscular and ophthalmic applications.[11,12]

Conventional approaches often attempt to solubilize insoluble drugs using an excessive amount of co-solvents, but this poses toxicity problems. The need to administer very large doses of drugs must then be accomplished without the interference of toxic side effects caused by co-solvents.[13-14] The aforementioned drawbacks have driven the development of nanosuspension technology. The small size of nanosuspensions helps with injecting them parenterally, and thus, provides 100% bioavailability. Nanosuspensions have revealed their potential to tackle the problems associated with the delivery of poorly water-soluble and poorly lipid-soluble drugs and are unique because of their simplicity and the advantages they confer over other strategies. Anti-cancer, anti-infective, immunosuppressant, anti-emetic, lipid-lowering agents, anti-asthmatic drugs, as well as vaccine adjuvants may be formulated as nanosuspensions. The following are major advantages of nanosuspensions:

Visit us at AAPS booth #422

Coating Place

THE Drug Delivery PLACE.



- **Capsule Filling** (clinical to commercial scale)
- **Extrusion Spheronization**
- **Pan Coating** (development to commercial scale)
- **Cryogenic Milling**
- **Roller Compaction**
- **Tablet Compression**

- **Formulation Development** (from 2g to 35kg batch sizes)
- **Commercial batch sizes up to 600kg** (multiple units available)
- **Clinical Manufacturing**
- **Full-service Analytical Support**
- **Modified Release Coating Systems**
- **Solvent or Aqueous Coating Systems**
- **DEA Schedule II-V**

Coating Place Incorporated will reach a new milestone this year. With the addition of new research and commercial scale Wurster equipment, CPI will exceed 3 million kilograms of coating capacity. Our 85,000 sq. ft. expansion, to be completed in 2008, demonstrates our commitment to providing the resources necessary to meet your future needs. Call us to discuss your project (817) 477-2766 or email us at info@encap.com.

COATINGS™

Coating Place Inc.

THE ORIGINAL WURSTER TECHNOLOGY SOURCE

Coating Place, Inc., Box 930310 • Verona, Wisconsin 53593 U.S.A. • 1-608-845-9521 • www.encap.com

- Increase of drug loading in the dosage form without extreme pH conditions or use of toxic co-solvents. They reduce toxicity and offer increased efficacy.
- Increase in dissolution velocity and saturation solubility of the drug leading to an improvement in the in vivo performance of the drug, irrespective of the route used.
- Increase in drug loading with reduced administration volumes for parenteral and ophthalmic administration.
- Increases resistance to hydrolysis and oxidation and thereby improves physical stability.
- Potential for intravenous sustained release via monocyte phagocytic system targeting and potential for reduced first-pass hepatic metabolism for oral administration.
- Unlike nanoparticle carriers, such as polymeric nanoparticles, nanosuspensions are easy to manufacture and scale-up.

PRODUCTION TECHNOLOGIES

The general approach used for many years for nanosuspension preparation has been micronization by colloidal or jet mills for enhancing solubilization of poorly water-soluble drugs. This method increases the dissolution velocity of the drug due to the increase in surface area, but does not change the saturation solubility, and thus, does not help with increasing bioavailability of drugs.

In the 80s, drug nanoparticles were produced by Sucker and co-workers using a precipitation technique.[15] Precipitation was performed by dissolving the drug in a solvent and adding this solvent to a non-solvent (so-called via humida paratum). Addition of solvent to the non-solvent is necessary to yield a very fine product by passing the Ostwald Mier area fast.[16] Using NanoMorph technology is another precipitation technique developed by the SOLIQS/Abbott company.[17-18] The major advantages of this technique includes the use of relatively simple and low-cost equipment and easy scale-up by use of static blenders or micromixers. However, static blenders maintain precipitation conditions only in lab-scale production. It creates problems in stirring and mixing when taken up for large-scale production. The basic challenge of this technique is the need to retain particle size after precipitation, as crystal growth of drug occurs upon storage, which may form microcrystals. In addition, it is also necessary to maintain the crystalline state during shelf-life of the product to avoid a decrease in oral bioavailability. This problem may be overcome by the addition of a surfactant. The requirements limiting the applicability of the precipitation technique are the need of the drug to be soluble at least in one solvent and that this solvent needs to be miscible with a non-solvent. These prerequisites exclude the processing of drugs that are simultaneously poorly soluble in aqueous and non-aqueous media.

Nowadays, two principle technologies that are used for the production of nanosuspensions, are discussed in detail further.

Media Milling

Liversidge and coworkers prepared the product NanoCrystals® by applying disintegration techniques using the pearl milling approach. This patent-protected technology was developed in 1990 and formerly owned by the company NanoSystems, which was acquired by Elan.[19] NanoCrystals are produced by dispersing the drug powder in a surfactant solution and then pearl milling the suspension as required from either hours or up to several days.

Nanosuspensions are produced by using high-shear media mills or pearl mills. The media mill consists of a milling chamber, a milling shaft, and a recirculation chamber. The milling chamber is charged with the milling media, water, and stabilizer, and the milling media or pearls are then rotated at a very high shear rate under controlled temperature.[20]

The milling medium is composed of glass, zircon oxide, or highly cross-linked polystyrene resin. Very little batch-to-batch variation is observed in the quality of the dispersion. The high energy and shear forces generated as a result of the impaction of the milling media with drug particles provides energy for size reduction of microparticulate drug molecules into nanoparticles. The major advantages of this technique are useful for very poorly soluble drugs, ease of scale-up, little batch-to-batch variation, and high flexibility in handling large quantities of drugs.

The major drawback of this technology is the generation of residues of milling media, which may be introduced in the final product as a result of erosion.[21] The erosion depends upon the hardness of the drug and milling materials as well as the milling time required. This could pose a problem when nanosuspensions are intended to be administered for chronic therapy. Scaling up with this milling is possible, but pearls contain two-thirds the volume of the mill, leading to heavy weight of the machinery thus, limiting the maximum batch size. The batch size can be increased by using a mill with suspension circulation. The suspension is continuously pumped through the mill in circles. This improves the batch size, but also increases the milling time because the required total exposure time of the drug particles per mass unit to the milling material remains unchanged.

Homogenization Techniques

The two types of homogenization techniques (Microfluidization Microfluidics, Inc.) and Piston-gap homogenizers (eg, APV Gaulin, Avestin, etc.) are discussed further.

MICROFLUIDIZATION: Microfluidizers are based on the principle of the jet stream in which the suspension passes with a high velocity in the specially designed homogenization chamber. In the Z-type chamber, the suspension changes the direction according to the letter Z, leading to particle collision and shear forces. In the Y-type chamber, the suspension stream is divided into two streams, which then collide frontally. The microfluidization technique has been owned by the Canadian company Research Triangle Pharmaceuticals (acquired by SkyePharma PLC).[22] A major drawback of this technology is the high number of passes through the microfluidizer, which is not very production friendly. In addition, the product obtained by microfluidization can contain a relatively large fraction of microparticles (especially in the case of hard drugs) thus, losing the special benefits of a real homogeneous drug nanosuspension.

PISTON-GAP HOMOGENIZERS:

A) *High-pressure homogenization in water*- Homogenization involves the forcing of suspension under pressure through a valve that has a narrow aperture. This technology, known as DissoCubes, was developed by R. H. Muller et al in 1998. The patent rights were owned by Drug Delivery Services GmbH in Germany (now owned by SkyePharma PLC).[23]

A high-pressure homogenizer consists of a high-pressure plunger pump with a subsequent relief valve (homogenizing valve). The task of the plunger pump is to provide the energy level required for the relief. The relief valve consists of a fixed valve seat and an adjustable valve. These parts form an adjustable radial precision gap. The gap conditions, the resistance and thus the homogenizing pressure, vary as a function of the force acting on the valve. An external impact ring forms a defined outlet cross-section and prevents the valve casing from being damaged due to flow.[24] The instrument is available in continuous and discontinuous versions. The continuous version is suitable for optimizing the various parameters of the homogenization process. The discontinuous

DISCOVER. DESIGN. DELIVER.

LIPOBRIDGE®

LIPOMASK™

DESIGN FOR
PEPTIDE DELIVERY℠

CERENSE℠

genzyme
Pharmaceuticals

Genzyme Pharmaceuticals
[illegible] West Kendall Street
[illegible]mbridge, MA 02142, USA
Tel 800 868 8208; 617 374 7248
Fax 617 [illegible] 9765
[illegible]cals@genzyme.com

Genzyme Pharmaceuticals
Eichenweg 1
CH-4410 Liestal, Switzerland
Tel +41 61 906 5959
Fax +41 61 906 5958
pharmaceuticals.swiss@genzyme.com

www.genzymepharmaceuticals.com

version is used if the drug is very costly or has limited availability. The instrument can be operated at pressures varying from 100 to 1500 bars. In some instruments, a maximum pressure of 2000 bars can also be reached. High-pressure homogenizers are available with different capacities ranging from 40 ml (for laboratory purpose) to a few thousand liters (for large-scale production). It is advisable to start with the micronized drug for production of nanosuspensions in order to prevent blocking of the homogenization gap. The fracture of drug particles is brought about by cavitations, high-shear forces, and the collision of the particles against each other during homogenization. The drug suspension, contained in a cylinder of diameter about 3 mm, passes suddenly through a very narrow homogenization gap of 25 micrometers, which leads to a high streaming velocity. In the homogenization gap, according to the law by Bernoulli, the dynamic pressure of the fluid increases with the simultaneous decrease in static pressure below the boiling point of water at room temperature. In consequence, water starts boiling at room temperature, leading to the formation of gas bubbles, which implode when the suspension leaves the gap (called cavitations) and normal air pressure is reached again. The implosion forces are sufficiently high enough to break down the drug microparticles into nanoparticles. Additionally, the collision of the particles at high speed helps to achieve the nano-sizing of the drug. The addition of viscosity enhancers are advantageous in certain cases as increasing the viscosity improves the powder density within the dispersion zone (homogenization gap).

The mean particle size in the nanometer range depends on the pressure and number of cycles applied; in addition it is affected by the hardness of the drug. For example, for budesonide a pressure of 1500 bar and 10 cycles lead to a mean particle diameter of 511 nm, increasing the cycle numbers to 15 reduces the size to 462 nm, and increasing the pressure to 2500 bar and 10 cycles leads to particles with a diameter of 363 nm.[25] A mean diameter of 660 nm, 330 nm, and 600 nm could be achieved for ketoconazole, paclitaxel, and clofazimine nanosuspension, respectively.[26-27] For each drug, a minimum size exists that can be achieved by applying a certain pressure; this minimum size depends on the powder density in the homogenizer and the hardness of the drug itself.

Homogenizers to be used on a laboratory scale are available from the APV Micron LAB 40 (APV Deutschland GmbH, Lubeck, Germany).[28] Other piston-gap homogenizers are available from Avestin (Avestin Inc., Ottawa, Canada) and Stansted (Stansted Fluid Power Ltd., Stansted, UK). The LAB 40 has a minimum batch volume of 20 ml and a maximum of 40 ml, thus allowing the cost-effective processing of even expensive drug materials. Smaller volumes can also be prepared by using the Avestin EmulsiFlex-B3 (volume 3.5 ml). The optimum particle size of nanosuspension depends on the nature of the drug (therapeutic field) and the desired biopharmaceutical properties. A size of approximately 100 to 200 nm is preferred when fast dissolution is required. In cases where prolonged dissolution is desired (eg, mucoadhesive nanosuspensions for treatment of *Cryptosporidium* infections), the mean particle diameter might be achieved in the upper nanometer range, ie, 800 to 1000 nm.[29]

To produce nanosuspensions with a higher concentration of solids, it is preferential to start with a very fine drug powder. To avoid blocking of the homogenization gap, it is recommended to perform so-called premilling. A few cycles are run at lower pressures, increasing the pressure from one cycle to the next until the final production pressure is reached. Typical sequence for premilling is two cycles at 100 bar, two cycles at 200 bar, two cycles at 500 bar, and two cycles at 1000 bar.[30]

The major advantages of high-pressure homogenization over media milling are that it can be additionally useful for formulations of very dilute as well as highly concentrated nanosuspensions and allow aseptic production of nanosuspensions. The major drawbacks of this technology are prerequisite for drug to be in a micronized state and suspension formation using high-speed mixers before subjecting it to homogenization.

B) Homogenization in water-free media & water mixtures (Nanopure)- In the Dissocubes technology, the cavitation was considered as the determining factor in the homogenization process. In contrast to water, oils and oily fatty acids have a very low vapor pressure at room temperature and a higher boiling point. The boiling points of olive oil and oleic acid are 210°C and 350°C, respectively. In the homogenization gap, the static pressure falls below the vapor pressure of water at room temperature, and cavitation can develop. In the case of oils and oily fatty acids, the drop in the static pressure is not sufficient enough to initiate cavitation, or at least there will be very limited cavitation compared to water.

It is mentioned in some patents covering the disintegration of polymeric material by high-pressure homogenization that higher temperatures in the range of about 80°C promote particle disintegration; however, for chemically labile pharmaceutical compounds, homogenization at around 80°C does not seem to be sensible.[31] In Nanopure, the drug suspensions in non-aqueous media, such as propylene glycol, were homogenized. In addition to homogenization at room temperature, the process was performed at 0°C and well below the freezing point (eg, -20°C), the so called "deep-freeze" homogenization. Based on this theory, this should be even less effective because the vapor pressure of liquids decreases with decreasing temperature, thus leading to even less or no cavitation. Again, homogenization results were comparable to Dissocubes. This opens the perspective to process chemically labile substances at very mild conditions. For example, in azodicarbonamide, decomposition occurred during homogenization at room temperature, observed by the formation of a foamy nanosuspension (formation of carbon dioxide due to decomposition of azodicarbonamide).[32]

However, when using the second generation of the technology and homogenizing azodicarbonamide at 0°C, no foamy nanosuspension was formed. This indicated that the compound was more chemically stable.

C) *Combination technology: precipitation & homogenization (Nanoedge™)*- The disadvantages of the precipitation technique discussed earlier include crystal growth and problems of long-term stability during shelf-life, which can be solved by combining the precipitation technique with the homogenization.[33] In general, precipitated particles in suspension are subsequently homogenized, which reduces the particle size and basically preserves the size range after precipitation. In addition, the "annealing" process converts all precipitated particles to crystalline material, which would remove problems of physical stability. The basic principles for Nanoedge are the same as the precipitation and high-pressure homogenization. Combination of these techniques results in smaller particle size (140 to 300 nm), sterile filtration, and better suspension stability in a shorter time. Normally, the precipitation is performed in water using water-miscible solvents, such as methanol, ethanol, and isopropanol. Despite the fact that solvents, such as ethanol, can be tolerated to a certain extent in liquid, oral, or parenteral formulations, it is desirable to remove it. The basic tendency is the need for ethanol-free formulations (eg, ethanolic plant extracts are being continuously replaced by water-based extracts). Removal of solvent is relatively easy on a lab scale (eg, by counter current flow) but is more problematic when producing larger batches. Moschwitzer and Muller developed a new method for the effective production of ultra-fine submicron nanosuspensions using Nanoedge technology. The method involved an evaporation step to

Would you like to convert your drugs from IV to subcutaneous (SC) delivery or enhance the dispersion of your existing SC compounds? With Enhanze™ Technology, microgram quantities of a fully human recombinant enzyme act as a "molecular machete" to clear the subcutaneous "jungle." Based upon this mechanism of action, co-delivery with Enhanze is anticipated to permit the SC administration of large volumes of antibody drugs, speed onset of action relative to SC delivery without Enhanze, and improve patient comfort. Backed by a robust IP portfolio, Enhanze may extend a compound's patent life and potentially reduce COGS for products that are expensive to manufacture.

Enhanze Technology employs the first and only human recombinant enzyme for injectable drug dispersion. The enzyme in Enhanze has been used in two FDA-approved formulations. Enhanze is being developed to deliver an optimized pharmacokinetic profile and thus offers a potential competitive advantage for partners' products. Potential benefits of this technology include:

- Enhancing the dispersion and absorption of other injected drugs
- Allowing SC injection of up to 10 mL in a single push or a mean infusion rate of ~500 mL/hour
- Dispersing drugs away from injection site, potentially reducing concentration-dependent injection site reactions
- Compared to SC administration without Enhanze, reducing Tmax and increasing bioavailability for large molecule compounds
- Enabling conversion of certain IV drugs to SC self-delivery

Learn how Enhanze Technology might revolutionize your drug delivery by contacting Mark Wilson, Vice President of Business Development at mwilson@halozyme.com or (858) 794-8881 x3006.

Halozyme
THERAPEUTICS

provide a solvent-free modified starting material (hydrocortisone acetate) followed by high-pressure homogenization. It was also observed that use of coprocessed spray dried material (9:1 drug/poloxamer 188) distinctly reduced the number of homogenization cycles compared to jet-milled drug powder.[34]

Other Techniques

Supercritical fluid technology can be used as an excellent alternative to both milling and constructive nanoparticle formation processes. It produces particles from drug solutions. Thus, it shortens the processing time and also overcomes the current limitations of the conventional precipitation techniques in terms of process scale-up, product purity, and wastage incurred.[35] The processes used for preparation include precipitation with a compressed anti-solvent (PCA) and rapid expansion of supercritical solutions (RESS). In the PCA method, drug and/or polymer solutions are atomized into a chamber containing compressed CO_2. This causes intense atomization of two liquids into micronized droplets that are dried and finally precipitated as fine crystals. The rapid expansion from the supercritical to aqueous solution (RESAS) method induces rapid nucleation of the supercritical fluid-dissolved gases in the presence of surface-modifying agents, which results in particle formation with a desirable size distribution in a shorter span of time. This process incorporates aqueous stabilizing solutions into the RESAS process to trap smaller particles (500 nm) of insoluble drugs.[36] Surface modifiers inhibit the crystal growth of newly formed particles. Pace et al used RESAS with high-pressure homogenization to obtain a stable and high-payload drug delivery system. This technique was patented by RTP Pharmaceuticals, Inc. and was later out-licensed to Baxter Healthcare Corporation and incorporated as a part of Nanoedge technology. The process produces surface-modified particles having a size range of 5 to 100 nm.[37]

Emulsions and microemulsions can also be used as templates to produce nanosuspensions. The use of emulsions as templates is applicable for those drugs that are soluble in either volatile organic solvent or partially water-miscible solvent. Such solvents can be used as a dispersed phase for emulsion.

In the first method, an organic solvent or mixture of solvent loaded with drug is dispersed in the aqueous phase containing suitable surfactant to form the emulsion. This organic phase is then evaporated under reduced pressure so that the drug particles precipitate instantly to form a nanosuspension stabilized by surfactant. Because one particle is formed in each emulsion droplet, it is possible to control the particle size of nanosuspensions. Another method makes use of partially water-miscible solvents, such as butyl lactate, benzyl alcohol, and triacetin, as the dispersed phase instead of hazardous solvents. The emulsion is formed by conventional methods, and the nanosuspension is obtained by simply diluting the emulsion. Dilution of the emulsion with water causes complete diffusion of the internal phase into the external phase, leading to instantaneous formation of a nanosuspension.[38] The nanosuspension thus formed has to be made free of the internal phase and surfactants by means of diultrafiltration in order to make it suitable for administration. The major drawbacks are use of hazardous solvents and use of a high amount of surfactants and stabilizers as compared to other production techniques.[39]

The advantages, such as high-drug solubilization, long shelf-life, and ease of manufacture, make microemulsion an ideal vehicle.[40] Oil-in-water microemulsions are preferred for this purpose. The internal phase of these microemulsions could be either a partially miscible liquid or a suitable organic solvent.[41] The drug can be either loaded in the internal phase, or preformed microemulsion can be saturated with the drug by intimate mixing. The suitable dilution of the microemulsion yields the drug nanosuspension by using the mechanism described earlier. The influence of the amount and ratio of surfactant to co-surfactants on the uptake of the internal phase and globule size of the microemulsions should be investigated and optimized to achieve the desired drug loading.

FORMULATION ADJUVANTS

Stabilizer

It is the most important adjuvant in the formulation of nanosuspensions. The high-surface energy of nano-size particles induce agglomeration of the dry crystals. The main function of the stabilizer is to wet the dry particles thoroughly to prevent the Oswald's ripening and agglomeration of the nanosuspension and form a physically stable formulation by providing steric or ionic barriers.[42] In some cases, a mixture of stabilizers is required to obtain a stable nanosuspension. The type and amount of stabilizer has a significant effect on the physical stability and in vivo behavior of nanosuspensions.

The drug-to-stabilizer ratio is critical for a stable formulation. Typical examples of stabilizers in nanosuspensions are cellulosics, poloxamers, polysorbates, lecithin, potassium oleate, and povidones. Lecithin may be preferred in the development of parenteral nanosuspensions.

Solvents (Water-Miscible & Organic)

Organic solvents should be selected after considering parameters like toxicity, pharmaceutically acceptability, and ease of removal. Less hazardous water-miscible solvents like ethyl acetate, ethyl formate, butyl lactate, triacetin, and propylene carbonate and benzyl alcohol are commonly employed in the formulation of nanosuspensions. Dichloromethane being hazardous is not much preferred. When nanosuspensions are formulated from microemulsion, partially water-miscible solvents may also be used.[43]

Co-Surfactants

Co-surfactants are an important component of nanosuspension formulation. Co-surfactants have an influence on the uptake of the internal phase and drug loading. The choice of co-surfactant is critical when using microemulsions to formulate nanosuspensions. Because co-surfactants can greatly influence phase behaviors, the effect of co-surfactant on the uptake of the internal phase for selected microemulsion composition and on drug loading should be investigated. Bile salts and dipotassium glycerrhizinate are commonly used co-surfactants by many researchers. Solubilizers, such as glycerol, ethanol, and isopropanol, are also safely used as co-surfactants in the formulation of nanosuspensions when prepared using microemulsions as a template.[3]

Others

Nanosuspensions may contain other additives, such as buffers, salts, polyols, osmogent, and cryoprotectant, depending on the route of administration or the properties of the drug.

CHARACTERIZATION OF NANOSUSPENSIONS

Particle Size & Size Distribution

The particle size and size distribution of nanosuspensions significantly affect the saturation solubility, dissolution velocity, physical stability, and in vivo performance. The mean particle diameter, width, and particle size distribution can be determined by photon correlation spectroscopy.[44] The measuring range of photon correlation spectroscopy is approximately 3 nm to 3 micrometers. Additionally, laser diffraction techniques may also be used to detect and quantify particles in the micrometer range or aggregates of drug nanoparticles. This technique is fast and suitable for screening large numbers of samples. The measuring range is 0.05 to 80 micrometers and up to

World-wide leader in DDS

NOF CORPORATION provides outstanding quality, innovative drug modifiers, carriers and emulsifiers. NOF has an exellent reputation producing these products in their cGMP facilities.

Activated PEGs

- Outstanding Quality PEGs and Activated PEGs
- Narrow Polydispersity & Low Diol content
- cGMP production
- New Branched PEGs and Multi-arm PEGs

NOF Activated PEG

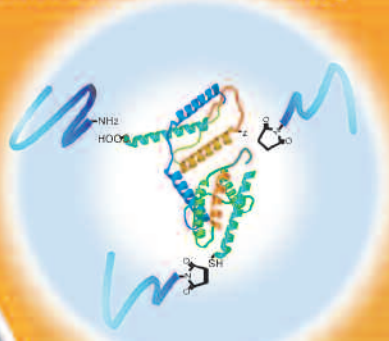
GPC Chart

Low Polydispersity: Mw/ Mn=1.03
Low diol content

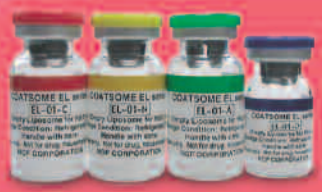
New GMP Plant
&
DDS R&D

PEGylation

- Wide Range Selection of Activated PEGs
- Advanced PEGylation Technology
- PEGylation of protein, peptide, nucleic acid, etc.
- Prolonged blood circulation of the Drug



PEG-DRUG

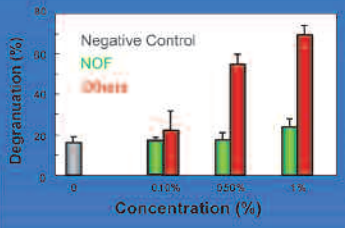


Empty-Liposome Kit

- Outstanding Quality & GMP production
- Numerous Drug Master Files
- Ready-to-use freeze-dried liposome kit
- PEGylated & Targeting Liposome Technology

Phospholipids and Liposome

NOF Others



- Outstanding Quality
- Multi-Compendial NF, EP, and JP
- Low Impurities and Peroxide
- Low Toxicity & Hemolysis
- Low Degranulation (Low Allergic Reaction)

Ultra-pure Polysorbate 80

NOF CORPORATION

DDS Development Department
Yebisu Garden Place Tower
20-3,Ebisu 4-Chome
Shibuya-ku, Tokyo 150-6019 JAPAN

http://www.nof.co.jp/dds/ E-mail: ddsinfo@nof.co.jp
Tel:+81-3-5424-6741 Fax:+81-3-5424-6769

NOF America Corporation
11 Martine Avenue, Suite 1170, White Plains, NY 10606, USA
TEL: +1-914-681-9790 FAX: +1-914-681-9791
E-mail: info@nofamerica.com

NOF Europe (Belgium) NV
Bouwelven 1, Industriezone Klein-Gent, B-2280 Grobbendonk, Belgium
TEL: +32-14-230001 FAX: +32-14-224563
E-mail: takuya.saigo@nofeurope.com

2000 micrometers. Measurement of the polydispersity index is also an important tool in determining the stability of the suspensions. A nanosuspension with a polydispersity index of 0.1 to 0.25 indicates a narrow particle size distribution. This reduces Oswald ripening, thereby helping in long-term stability of the suspension.

For nanosuspensions to be administered intravenously, additional analysis using techniques like a coulter counter may also be used. In contrast to the laser diffraction techniques providing only a relative size distribution, the coulter counter gives absolute data (ie, absolute number of particles per volume unit for the different size classes). For intravenous injection, particles larger than 5 micrometers are critical, considering that the smallest size of blood capillaries is 5 to 6 micrometers, a higher particle size would lead to capillary blockade and embolism. Thus, this factor needs to be assessed by coulter counter analysis. Visualization of particle shape by atomic force microscopy has also been reported for evaluation of nanosuspensions.

Particle Charge (Zeta Potential)

Determination of particle charge (zeta potential) of nanosuspensions is important as it is an indication about the stability of the dosage form. The zeta potential depends on the type of stabilizer and property of drug. For a physically stable nanosuspension solely stabilized by electrostatic repulsion, a zeta potential of ± 30 mV is required as a minimum value.[45] In the case of a combined electrostatic and steric stabilization, a zeta potential ± 20 mV would be sufficient.

Crystalline Status

The crystalline structure of the nanosuspensions can be assessed by X-ray diffraction analysis and differential scanning calorimetry. This is of importance when a drug exists in different polymorphic forms. Nanosuspensions prepared by high-pressured homogenization might undergo a change in their crystalline structure. Thus, it is likely that drug particles are generated in an amorphous state, which may lead to enhanced saturation solubility for poorly soluble drugs. The extent of such a transformation can be quantified and used for assessing stability during storage. The wide angle X-ray diffraction analysis is preferred because it is easily accessible as compared to small angle X-ray diffraction analysis. Scanning electron microscopy may also be used to study the particle morphology.

Dissolution Velocity & Saturation Solubility

The assessment of saturation solubility and dissolution velocity of nanosuspensions helps to determine their behavior in vivo, including peak plasma concentration and bioavailability. Nanosuspensions are formulated to improve the saturation solubility, thus, this parameter is of great importance. The dissolution velocity and saturation solubility of drug nanosuspensions should be determined in various physiological buffers as per the method mentioned in the pharmacopoeia. These evaluation parameters help the formulator to highlight the benefits of the nanosuspensions over conventional dosage forms.

In Vivo Studies

Determination of the behavior of nanosuspensions in vivo and set-up of an in vitro/in vivo correlation are important parameters of the formulation. Surface hydrophilicity/hydrophobicity are considered important parameters affecting the in vivo organ distribution after intravenous injection. The surface hydrophobicity determines the interaction with cells prior to phagocytosis.[46-47] In addition, it is a relevant parameter for the adsorption of plasma proteins, the key factor for organ distribution. The surface hydrophobicity needs to be determined in the original environment of the drug nanoparticles, which is in aqueous dispersion medium to prevent misinterpretation. A suitable technique is hydrophobic interaction chromatography, previously employed to determine the surface hydrophobicity of bacteria and now used for characterization of nanoparticles.[48-50]

Protein Adsorption Pattern

The qualitative and quantitative composition of the protein adsorption pattern observed after intravenous injection of the particles is currently recognized as the essential key factor for organ distribution.[51-52] Protein analysis by 2-D Poly-acrylate gel electrophoresis was modified and especially adapted to the analysis of protein adsorption patterns of nanoparticles. Time-dependent adsorption patterns of proteins on nanoparticles were determined after incubation of polymeric particles with plasma or serum and after collection of intravenous injected particles in animals.[53-54]

APPLICATIONS

Nanosuspensions have proven to be effective via many routes and for a variety of drugs in various indications. Most of the nanosuspension formulations for drugs like paclitaxel, busulfan, insulin, and fenofibrate administered via intravenous and/or other routes are under clinical trials. Oral nanosupensions, ie, Rapamune (immunosuppressant) and Emend (anti-emetic), are already available on the market.[10] Indibulin, a novel anti-cancer agent (ZIO-301, Ziopharm Oncology, Inc.) is available as a nanosuspension for both oral and intravenous routes. The oral form is currently in a Phase I trial, and the intravenous form is currently in the late preclinical development stage.[55]

Oral

The oral route for drug delivery is the most preferred route. Nanosuspensions find important application in the formulation of poorly water-soluble drugs. Dissolution is the rate-limiting step for such drugs having poor aqueous solubility and hence may lead to problems in low and varied bioavailability. Nanosuspension formulation of these drugs leads to an increase in oral absorption and improved bioavailability.[56-57] Nanosuspensions also provide an increase in surface area, saturation solubility, and dissolution velocity. An increase in bioavailability leads to more cost-effective drug therapy with reduction in drug dose and obviates drug dumping.

Liversidge and coworkers suggested significant improvement in bioavailability when danazol (a poorly bioavailable gonadotropin inhibitor) was administered as a nanosuspension in comparison with a conventional 10-micrometer danazol macrosuspension, Danocrine. Danazol nanosuspensions lead to an absolute bioavailability of 82.3%, whereas the marketed danazol suspension Danocrine was only 5.2 % bioavailable. In addition, danazol nanosuspensions resulted in a reduction in inter-subject variability and fed/fasted ratio of danazol.[58]

Kayser et al developed a nanosuspension of amphotericin-B, which produced a substantial improvement in its oral absorption in comparison to orally administrated conventional commercial formulations, such as Fungizone or micronized amphotericin-B. Orally administered nanosuspension brought about a high uptake of nanoparticulate drug through the gastrointestinal tract. This is reflected by the considerable reduction brought about in the number of L. donovani parasites in the liver of infected female albino mice as compared to other commercial formulations.[59]

Scholer and researchers stated that atovaquone showed poor bioavaibility (10% to 15%) because of its dissolution rate limited absorption and had to be administered in high doses (750 mg twice a day). Oral administration of nanosuspensions overcame this problem because of the high adhesiveness of drug particles sticking on biological surfaces and prolonging the absorption time. Atovaquone was formulated as nanosuspensions and given orally to Leishmania infected mice. The parameter for increased absorption was related to the infectivity score of each animal and to the reduction of the parasite load in the liver. In

Introducing...

New Commercial cGMP Contract **Manufacturing Capacity**

- Glatt Wurster HS™ Pelletizing & Coating
- Glatt CPS™ Pelletizing
- Glatt Fluid Bed Granulation & Drying
- Glatt High Shear Granulation
- Organic Solvent Processing
- DEA Controlled Substance Capability

Glatt Pharmaceutical Services specializes in the development and cGMP manufacture of difficult-to-craft modified and immediate release solid dosage products and is the global leader in fluid bed related product formulation, processing technology and full scale commercial manufacturing.

To learn more, contact us to schedule a visit with our accomplished staff at our newly expanded facility.

Glatt®
Pharmaceutical Services
A Division of Glatt Air Techniques, Inc.

Ramsey, New Jersey
www.glattpharmaceuticals.com
201.825.8700

Experience the Glatt Expansion!

comparison to Wellvone®-treated mice, containing a micronized atovaquone, nanosuspensions at equivalent doses and reduced infectivity from 40% to 50 % at a reduced concentration of only 7.5 mg/kg. These results reflect the potency of this technique. A reduction in the drug loading from 22.5 mg/kg (Wellvone) to 7.5 mg/kg with increased activity (2.5-fold) could be achieved.[60]

Naproxen, an NSAID, produced severe gastric irritation. Liversidge and Conzentino proved that gastric irritancy could be reduced by nano-sizing. In this case, reduction in the particle size from 20 to 30 micrometers to 270 nm lead to faster absorption (t_{max}= 23.7 versus 33.5 mins). The decrease in gastric residence time, associated with local high and prolonged concentration of naproxen, was presumed to be responsible for the reduced gastric irritancy scores. These effects may be due to an increase in dissolution rate and increased surface area of the drug.[61]

Nanosuspensions, on the other hand, enable incorporation of all hydrophobic drugs in well-established sustained-release technologies. However, while doing so, the effect and the interaction of dosage form excipients with the nanocrystalline drug must be critically investigated. Drug nanosuspensions can be incorporated into dosage forms, such as tablets, capsules, and fast melts by means of standard manufacturing techniques. A ketoprofen nanosuspension has been successfully incorporated into pellets to release the drug over a period of 24 hrs.[62] This approach would facilitate delivery of the compounds belonging to BCS class IV that exhibit poor water solubility and poor membrane permeability.

Langguth et al developed a nanosuspensions containing spironolactone as a model low-solubility drug. Seven oral and one intravenous formulations were tested in an in vivo pharmacokinetic study in rats. The DissoCubes nanosuspension of spironolactone yielded a highly significant increase in bioavailability averaging 3.3-fold in AUC and 3-fold for C_{max}.[63]

The adhesiveness of the nanosuspensions not only helps to improve bioavailability but also improves targeting of parasites persisting in gastrointestinal tract. Cryptosporidium parvum, identified as the main pathogen causing severe diarrhea in immunosuppressant HIV patients, has attracted much interest. There is still no effective therapy or availability of clinically useful drugs for AIDS patients. Formulating drugs to combat Cryptosporidium parvum depends on targeting the drug to the pathogen, which is located in the epithelial membrane gut wall, and secondly, increasing the time for the drug in the gastrointestinal tract to prolong the pharmacological window with regard to the fast washing out during diarrhea. Bupravaquone nanosuspensions have been reported to demonstrate advantages, in TRC-alpha-deficient mice infected with Cryptosporidium parvum oocysts.[64] Formulating poorly soluble drugs for the treatment of Cryptosporidium infections or other gastrointestinal tract infections, like helminthes, will be important strategies in future. In addition, nanosuspension technology is considered as suitable new colon delivery systems for the treatment of colon cancer, helminth infections, gastrointestinal inflammation, and associated diseases like sprue.

Parenteral

The parenteral administration of drugs is an important route because it provides quick onset of action, rapid targeting to the site of action, and reduced dosage of drug. It is also the preferred route for drugs not absorbed through the gastrointestinal tract or which undergo extensive first-pass metabolism. Although the formulation is associated with problems like proper selection of choice and quantities of additives, stringent aseptic procedures and critical safety issues need to be addressed. Numerous approaches in the formulation of drugs via the parenteral route include solubility enhancement by salt formation, use of co-solvency, complexation, and preparation of liposomes. These are, however, associated with drawbacks like limited solubilization (which may provoke anaphylactic reaction and pain), issues with acceptance and stability (especially for liposomes), as well as cost and scale-up concerns.[65-68]

To establish a more comprehensive approach, the formation of injectable drugs as nanosuspensions has emerged. Nanosuspensions meet almost all requirements of an ideal drug delivery system for the parenteral route. However, they are applicable for poorly soluble drugs having solubility less than several hundred ppm.[69] Moreover, the absences of any harsh solvents/co-solvents and/or any potential toxic ingredients in nanosuspension enables them to bypass the limitation of the parenteral administration attributed to conventional formulation strategies.

Donnelly and coworkers formulated itraconazole (an anti-fungal agent) as a nanosuspension that exhibited less toxicity after intravenous injection than the commercially available cyclodextrin-solubilized drug itraconazole (Sporanox, Janseen Pharma). Comparison of pharmacokinetic parameters of a nanocrystal suspension of itraconazole, as determined in a clinical trial, with those of the commercial Sporanox solution was found to be better.[70-72]

A nanosuspension enables significant improvement in the parenterally tolerable dose of a drug, leading to a reduction in the cost of therapy and also improved therapeutic performance. Merisko et al stated that the maximum tolerable dose of paclitaxel nanosuspension was found to be three times higher than currently marketed Taxol. Similarly, the nanosuspension of other anti-cancer agents, such as Etoposide and Camptothecin, revealed an improvement in the tolerance level of the drugs compared to marketed preparations.

Moschwitzer and coworkers developed intravenously injectable and chemically stable aqueous omeprazole formulations using nanosuspension technology. Omeprazole is a poorly soluble, chemically liable drug with a high degradation rate in aqueous media. The researchers have stated that even after 1 month of production, no discoloration or recognizable drug loss was observed when nanosuspensions were formulated at 0°C. As a result, it can be proven that the production of nanosuspensions by high-pressure homogenization is suitable for preventing degradation of labile drugs.[73]

Pulmonary

Drugs that exhibit poor solubility in pulmonary secretions need to be formulated as suspension aerosols or inhalable dry powders. These dosage forms have a particle size distribution in microns and thus, the drugs have limited diffusion and dissolution, rapid clearance, and low residence time. An alternative approach for the pulmonary delivery of poorly soluble drugs is the formulation of nanosuspensions. The nanoparticles improve the diffusion and dissolution of drugs. They also increase adhesiveness and thus cause the prolonged residence time. Nanosuspension formulations also provide a very narrow and uniform particle size distribution of the drugs into the lung. They are easily formulated in aerosols and nebulizers. For conventional solid-in-liquid dispersions to be formulated as aerosols, the solid drug should have an aerodynamic diameter of 1 to 5 micrometers.[74] This leads to a statistical inhomogenity partitioning of drug particles. Nanosuspensions minimize this by increasing the number of particles per droplets. Kraft reported the pharmacokinetics of nebulized nanocrystal budesonide suspension in healthy volunteers. The comparable AUC, higher C_{max} and lower t_{max} were observed with 0.5 nanobudenoside compared to Pulmicort Respules. Suspended drug particles were in the range of 75 to 300 nm in nanobudenoside compared to 4400 nm-size Pulmicort Respules.[75] Nanosuspension targeting to

alveolar macrophages in diseases like tuberculosis in which the mycobacteria are in macrophages have also proved successful.[10]

Hernandez-Trejo and coworkers stated that the poorly soluble drug bupravaquone is proposed for an alternative treatment of lung infection (pneumonia), which is caused by Pneumocystis Carinii. Physically stable nanosuspensions were formulated to deliver bupravaquone at the site of lung infection using nebulization.[76]

Ocular

Drugs that exhibit poor solubility in lachrymal fluid could be successfully formulated as nanosuspensions. Nanosuspensions, by their ability to improve the saturation solubility of drugs, represent an ideal approach for ocular drug delivery of hydrophobic drugs. To achieve sustained release of the drug for the longer time period, nanosuspensions can be incorporated in a suitable hydrogel base or mucoadhesive base or even in ocular inserts, an approach that has recently been investigated to achieve desired duration of action.

Bucolo and researchers prepared nanosuspensions of ibuprofen and flubiprofen using acrylic polymers, such as Eudragit RS 100 and Eudragit RL 100 for ocular anti-inflammatory activity. The pharmacological profile of topical ibuprofen- Eudragit RS nanosuspension formulations indicate that the dispersion of the drug within Eudragit RS polymer nanoparticles increases ocular bioavailability and ultimately pharmacological activity.[77-79] Nanosuspension showed superior performance in vivo as compared to the commercially available formulations.

Pignatello and coworkers prepared polymeric nanosuspensions of Eudragit RS100, RS and RL100, RL for various drugs. To verify the absence of toxicity toward ocular structure, blank RS and RL nanosuspensions were applied to rabbit eyes, and a modified Draize test was performed. Polymeric nanoparticles appeared to show absence of any irritant effect on cornea, iris, and conjunctiva up to 24 hrs after its application.[80]

Targeted Drug Delivery

Nanosuspensions can be used for targeted delivery as their surface properties and changing of the stabilizer can easily alter in vivo behavior. Their versatility and ease of scale-up and commercial production enables the development of commercially viable nanosuspensions for targeted drug delivery. The natural targeting process could pose obstacles when macrophages are not the desired targets. Hence, in order to bypass the phagocytic uptake of drugs, its surface potential needs to be altered.[81] Kayser developed the formulation of aphidicolin as a nanosuspension to improve the drug targeting effect against Leishmania-infected macrophages. He stated that aphidicolin was highly active at a concentration in the microgram range.[82]

Nanosuspensions afford a means of administrating poorly water-soluble drugs to the brain with decreased systemic effects. Significant efficiency has been associated with microparticulate busulfan in mice administered intrathecally.[69] Another example is successful targeting of the peptide Dalargin to the brain by employing surface-modified polyisobutyl cyanoacrylate nanoparticles.[83]

CONCLUSION

For pharmaceutical scientists, the formulation of nanosuspensions provides a unique process suitable for formulation development and commercialization of various types of drugs. Nanosuspensions are an attractive drug delivery method for enhancing solubility and bioavailability of drugs that are poorly soluble in water and simultaneously in organic solvents. Large-scale production is possible by employing media milling and high-pressure homogenization techniques. Improved characteristics of nanosuspensions, such as an increase in dissolution velocity and saturation solubility, improved bioadhesion, and ease of large-scale manufacturing, have improved the applications of nanosuspensions as a drug delivery system. Nanosuspensions can be administered using various delivery routes like oral, parenteral, ocular, and pulmonary. Oral nanosuspensions can be converted to more patient-convenient dosage forms like tablets and capsules. Site-specific delivery of nanosuspensions needs more investigation. The success of nanosuspensions will be evident by the increase in the commercially available products of this drug delivery system in the near future.

REFERENCES

References available upon request; please contact Dan Marino at dmarino@drugdeliverytech.com.

BIOGRAPHIES

Ms. Tejal Shah is currently working as an Assistant Professor in Pharmaceutics, Nirma University of Science & Technology. Ms. Shah has 8 years of teaching experience. She has 5 publications and a chapter written by her in a multi-authored book on Novel Drug Delivery Systems. She earned her MPharm in Pharmaceutics and is actively working toward her PhD at Sardar Patel University.

Dr. Avani F. Amin is currently working as an Assistant Professor in Pharmaceutics, Nirma University of Science & Technology. Dr. Amin has 5 years of regular teaching, 6 years as a visiting faculty and research scientist, and 2 years of industrial experience. She has more than 25 research publications in international and national pharmaceutical journals. She has also presented papers at various conferences. Dr. Amin is the recipient of the Motan Devi Dandiya Prize in Pharmacy, the Prof. M. L. Khurana Memorial Prize in Pharmaceutics, the G. P. Nair IDMA award, and other state level prizes. She earned her MPharm and PhD in Pharmaceutics.

BUCCAL DELIVERY

Mucoadhesive Buccal Drug Delivery: A Review

By: Vishnu M. Patel, PhD; Bhupendra G. Prajapati (PhD student); and Karshanbhai M. Patel, MPharm

ABSTRACT

The buccal mucosa offers excellent opportunities for the delivery of both locally and systemically active drugs. The mucosa is relatively permeable and robust, shows short recovery times after stress or damage, is tolerant to potential allergens, and has a rich blood supply. Administering drugs via this route is advantageous due to the rich vasculature of the oral mucosa and the absence of gastrointestinal and first-pass hepatic degradation. Today, research is more focused on the development of suitable delivery devices, permeation enhancement, and buccal delivery of drugs that undergo a first-pass effect, such as cardiovascular drugs, analgesics, and proteins and peptides. In this review, the overview of the oral mucosa, followed by discussion of recent literature on novel mucoadhesive polymers, buccal permeation enhancement, and protein and peptide delivery are detailed. The various dosage forms in different stages of development are also reviewed.

INTRODUCTION

Absorption of therapeutic agents from the oral cavity provides direct entry into the systemic circulation, thus avoiding the hepatic first-pass effect and degradation in the gastrointestinal tract, ease of administration, and the ability to terminate delivery when required.[1-3] However, the buccal route of drug delivery has received much more attention because of its unique advantages over other oral transmucosal routes.[2,4] The oral mucosa can be categorized into sublingual, gingival, and buccal mucosa through which oral transmucosal delivery can be achieved. Buccal formulations have been developed to allow prolonged localized therapy and enhanced systemic delivery. The advances in bioadhesive and controlled-release technology have stimulated a renewal of interest in the delivery of drugs to or via the buccal route.[5]

OVERVIEW OF THE ORAL MUCOSA

Structure

The oral mucosa is roughly classified into three types: masticatory, lining, and specialized mucosa. The major difference among the types is the presence or absence of a keratinized outermost layer as part of the epithelium. The oral mucosal thickness varies depending on the site. The buccal mucosa measures at 500 to 800 microns, while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue, and the gingival measure at about 100 to 200 microns.

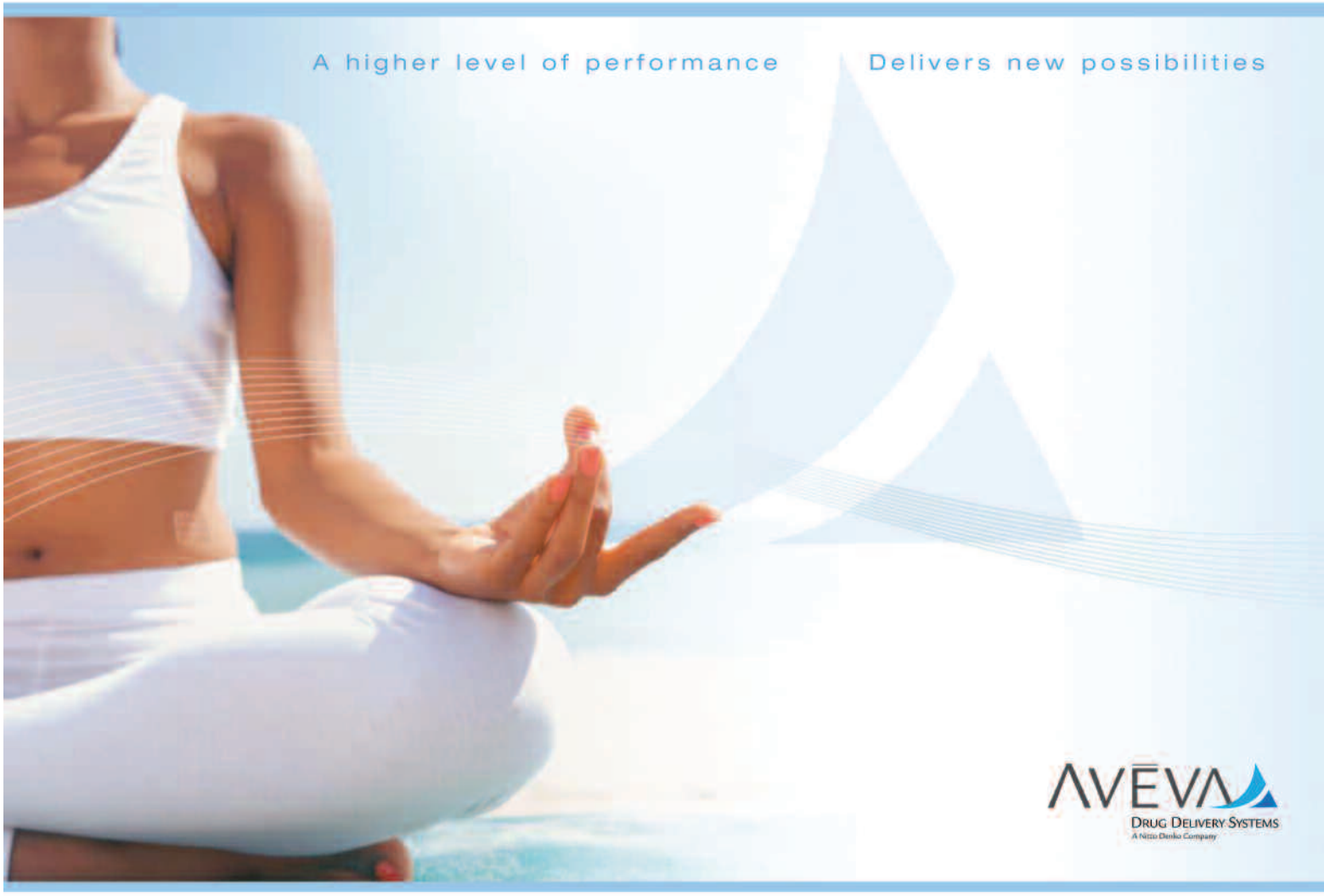
The buccal mucosa has a surface lining consisting of a non-keratinized, squamous epithelium supported by a connective tissue lamina propria. The non-keratinized epithelium of the buccal mucosa is more permeable than the keratinized one. The superficial layers (approximately the outermost quarter) of the buccal epithelium represent the primary barrier to the entry of substances from the exterior. The principle barrier to the movement of compounds across the buccal epithelium is provided by an accumulation of neutral lipids and glycolipids in the intercellular spaces of these superficial cell layers. This material originates from the extrusion of the contents of the membrane-coating granules (MCG) as the epithelial cells move superficially.[6]

Environment

The cells of the oral epithelia are surrounded by an intercellular ground substance, mucus, which is secreted by the major and minor salivary glands as part of saliva.[7,8] This mucus may actually play a role in cell-cell adhesion, as well as acting as a lubricant, allowing cells to move relative to one another.[7] Along the same lines, the mucus is also believed to play a role in bioadhesion of mucoadhesive drug delivery systems.[9] At physiological pH, the mucus network carries a negative charge (due to the sialic acid and sulfate residues), which may play a role in mucoadhesion.

Another feature of the environment of the oral cavity is the presence of saliva produced by the salivary glands. It protects the soft tissues from abrasion by rough materials and from chemicals. Saliva is an aqueous fluid with 1% organic and inorganic materials. The major determinant of the salivary composition is the flow rate, which in turn depends upon three factors: the time of day, the type of stimulus, and the degree of stimulation.[7,8] The salivary pH ranges from 5.5 to 7, depending on the flow rate. The daily salivary volume is between 0.5 to 2 L, and it is this amount

TRANSDERMAL TRANSCENDENCE



That's the promise of Aveva Drug Delivery Systems, combining innovation and unparalleled industry experience to advance drug delivery and pioneer new frontiers in transdermal drug delivery for new chemical entities and life cycle management opportunities to enhance existing products.

As one of the world's largest manufacturers of transdermal patches offering a full range of research, development and manufacturing capabilities, Aveva transcends traditional limitations of patch technology and business partnerships to achieve new levels of product and corporate performance.

- Customizing solutions to the unique characteristics of each drug
- Masterfully balancing the patch properties of adhesion reliability and gentleness that lead to an enhanced patient experience.
- Managing a higher drug concentration in a smaller patch

A flexible, customer-oriented business philosophy that adds value to projects and exceeds customer expectations.

To license a product or to see how we can add value to your project, call Robert J. Bloder, Vice President Business Development, at **954.624.1374** or visit **www.AvevaDDS.com**

NITTO DENKO GROUP

of fluid that is available to hydrate oral mucosal dosage forms.

Permeability of Buccal Mucosa & Drug Permeation

It is estimated that the permeability of the buccal mucosa is 4 to 4000 times greater than that of the skin.[10] As indicative by the wide range in this reported value, there are considerable differences in permeability between different regions of the oral cavity because of the diverse structures and functions of the different oral mucosae. In general, the permeabilities of the oral mucosae decrease in the order of sublingual greater than buccal, and buccal greater than palatal.[11] This rank order is based on the relative thickness and degree of keratinization of these tissues, with the sublingual mucosa being relatively thin and non-keratinized, the buccal thicker and non-keratinized, and the palatal intermediate in thickness but keratinized.

The epithelial barrier must be crossed by the drug molecules in order to reach their intended sites of action. The basic drug transport mechanism for buccal epithelium is the same as for other epithelia in the body. There are two major routes involved: transcellular (intracellular) route and paracellular (intercellular).[12] In general, for many drugs, permeation across the buccal epithelium is thought to be via the paracellular route by passive diffusion. Nevertheless, Kurosaki et al suggested the presence of a specialized transport system for cephadroxyl in the human buccal membrane.[13]

TABLE 1

Mucosal Permeation Enhancers With Their Mechanism of Action

Classification	Mechanism	Examples
Surfactants	Perturbation of intercellular lipids, protein domain integrity	**Anionic**: sodium lauryl sulfate[42], sodium laurate lipids, 23-lauryl ether[42] **Cationic**: cetylpyridinium chloride[43] **Non-ionic**: poloxamer, brij, span, myrj, tween **Bile salts**: sodium glycodeoxycholate[44], sodium glycocholate[45], sodium taurodeoxycholate[1], sodium taurocholate[46], Azone[45]
Fatty acids	Increase fluidity of phospholipids domains	Oleic acid [47], caprylic acid, methyloleate[47]
Chelators	Interfere with Ca^{+2}	Sodium EDTA[42], sodium citrate, polyacrylates
Cyclodextrins	Inclusion of membrane compounds	α-, β-, γ-cyclodextrin[46], methylated β-cyclodextrins
Positively charged polymers	Ionic interaction with negative charge on the mucosal surface	Chitosan[48,49], trimethyl chitosan
Cationic compounds		Poly-L-arginine, L-lysine

MUCOADHESION

The term *mucoadhesive* is commonly used for materials that bind to the mucin layer of a biological membrane. In the development of these drug delivery systems, mucoadhesion of the device is a key element. Many theories have been proposed to describe mucoadhesion, namely the electronic theory, adsorption theory, wetting theory, diffusion theory, and fracture theory.[14-16] Mucoadhesion is believed to occur in three stages: wetting, interpenetration, and mechanical interlocking between mucin and polymer.

Mucoadhesive Polymers

To serve as mucoadhesive polymers, the polymers should possess some general physiochemical features, such as predominantly anionic hydrophilicity with numerous hydrogen bond-forming groups, suitable surface property for wetting mucus/mucosal tissue surfaces, and sufficient flexibility to penetrate the mucus network or tissue crevices.[17] The efficacy of oral bioadhesive drug delivery systems is affected by the biological environment and the properties of the polymer and the drug.

The various polymers considered suitable for the development of bioadhesive devices are cellulosic derivatives (methyl cellulose, sodium carboxymethylcellulose, hydroxy ethyl cellulose, hydroxy propyl cellulose, and hydroxy propyl methyl cellulose), natural gums (guar gum, karaya gum, xanthan gum, locust bean gum, veegum), sodium alginate, polyoxyethylenes, polyacrylates (carbopol and polycarbophil), and chitosan.[3,18-28] [26,27,32,33]

Novel Mucoadhesive Polymers Under Development

An AB block copolymer of oligo (methyl methacrylate) and PAA has been synthesized for prolonged mucosal drug delivery of hydrophobic drugs. These block copolymers form micelles in an aqueous medium, which was confirmed by a fluorescence probe technique using pyrene. A model drug, doxorubicin hydrochloride, when incorporated into these micelles, results in its release being prolonged at a slower rate. Polymers with thiol groups were also investigated as a new generation of mucoadhesive polymers.[34]

Shojaei and Li designed and

TABLE 2

Related Research on Buccoadhesive Polymers & Bioadhesive Tablets

Drug	Bioadhesive Polymers	Dosage Form	References
Ketoprofen	Chitosan & sodium alginate	Table	26
Nifedipine, propranolol	Chitosan, polycarbophil, sodium alginate, gellan gum	Bilaminated films, bilayered tablets	27
Diltiazem, metclopramide	CP, HPMC, PC, SCMC, PAA	Tablets, bilayer tablets	18
Propranolol	HPMC, PC	Tablets	23
Propranolol	SCMC, CP- 934	Bilayered tablets & multilayer tablets	22
Nystatin	Carbomer, HPMC	Double-layered tablet	24
Verapamil HCl	HPC-M, CP-934	Tablet	60
Triamcinolone acetonide	HPC, CP-934	Table	3
Lidocaine	CP-934, HPC-H	Multilayered tablet	20
Metronidazole	CP-934, HPMC	Tablet	25
Sodium fluoride	Modified starch, CP-934	Slow release tablet	61
Miconazole	Modified starch, CP-934	Tablet	58
Metoclopramide	CP-907, CP-941	Disc	62
Triamcinolone acetonide	HPMC, PADH	Tablet	63
Pentazocine	CP-934P, HPMC	Tablet	64
Chlorpheniramine/ Calcitonine	Hakea gum	Tablet	65
Omeprazole	Sodium alginate, HPMC, CP-934P, PC	Tablet	28
Nicotine	HPC, CP-934, PVP	Biphasic tablet	21
Propranolol	CP- 934, SCMC	NBAS	22
Clotrimazole	CP-974 P, HPMC-K4M, PEG-6000	Bioerodible tables	4

Abbreviations: CP=carbopol, **HPMC**=hydroxy propyl methyl cellulose, **PC**=polycarbophil, **SCMC**=sodium carboxymethyl cellulose, **PAA**=polyacrylic acid, **HPC**=hydroxy propyl cellulose, **PVP**=poly(vinyl pyrrolidone), **PADH**=poly (acrylic acid-2,5-dimethyl –1,5 – hexadience, **NBAS**=novel buccal adhesive system

formulated a series of novel copolymers of acrylic acid and poly ethylene glycol monomethylether monomethacrylate [P(AA-co-PEG)]. The addition of PEG into the polymer increased the potential for hydrogen bond formation because the lone pair electrons of oxygen in the repeat unit (CH_2CH_2O) of PEG served as hydrogen bond acceptors. The surface properties of PAA for mucoadhesion were also improved by the PEG incorporation.[35]

Using copolymeric hydrogel discs of HEMA (monomer) and Polymeg (macromer), a buccal mucoadhesive device for controlled release of buprenorphine was developed. The hydrogel containing a monomer:macromer ratio of 80:20 (w/w) yielded the best result both in terms of adhesion and drug release. The device was applied for a 3-hour application time, and steady state levels were maintained for the time of application.[36]

Novel polymers of PAA complexed with PEGylated drug conjugate were investigated by Lele et al.[37] Only a carboxyl group containing drugs, such as indomethacin, could be loaded into the devices made from these polymers. An increase in the molecular weight of PEG in these copolymers resulted in a decrease in the release of free indomethacin, indicating that drug release can be manipulated by choosing different molecular weights of PEG.

A new class of hydrophilic pressure-sensitive adhesives (PSAs) that share the properties of both hydrophobic PSAs and bioadhesives has been developed by Corium Technologies.[38] These Corplex adhesive hydrogels have been prepared by non-covalent (hydrogen bond) cross-linking of a film-forming hydrophilic polymer (for example PVP) with a short-chain plasticizer (typically PEG) bearing complementary reactive hydroxyl groups at its chain ends. The specific balance between enhanced cohesive strength and large free volume in PVP-PEG miscible blends influences their PSA behavior.

Bernkop-Schnurch et al demonstrated that introduction of a sulphahydryl group increased the adhesive properties of mucoadhesive polymers.[39] In this study, cysteine was attached covalently to polycarbophil by using carbodiimide as a mediator, forming amide bonds between the primary amino group of the amino acid and the carboxylic acid moieties of the polymer. The results showed that there was considerable improvement in the overall behavior of

adhesion and adhesive properties when tested on porcine intestinal mucosa at a pH level above 5.

BUCCAL PERMEATION ENHANCERS

Membrane permeation can be a limiting factor for many drugs administered via the buccal route, and the epithelium that lines the oral mucosa is a very effective barrier to the absorption of drugs. In order to deliver broader classes of drugs across the buccal mucosa, reversible methods of reducing the barrier potential of this tissue must be employed. This requisite has fostered the study of penetration enhancers that will safely alter the permeability restrictions of the buccal mucosa. Substances that help to promote drug permeation through the buccal epithelium are referred to as penetration enhancers.[40] They should be safe and non-toxic, pharmacologically and chemically inert, non-irritant, and non-allergenic.[41] Penetration enhancers can be divided into many categories (Table 1) according to their structure, mechanism of action, and the type of drugs whose permeation they enhance.

PROTEIN & PEPTIDE DELIVERY

The buccal mucosa represents a potentially important site for controlled delivery of macromolecular therapeutic agents, such as peptide and protein drugs with some unique advantages, such as the avoidance of hepatic first-pass metabolism, acidity, and protease activity encountered in the gastrointestinal tract.[50,51] Another interesting advantage is its tolerance (in comparison with the nasal mucosa and skin) to potential sensitizers. A variety of proteins/peptides, including insulin, octreotide acetate, recombinant human interferon-alpha, gonadotropin-releasing hormone, buserelin, leutinizing hormone-releasing hormone (LHRH), and glucagon-like peptide-I, have all been studied.[29,42,44,52-57] The studied were performed on different animal models (dog, rabbit, rat, pig, and human) with or without a penetration enhancer.[33,42,44,52-57]

TABLE 3

Some Reported Mucoadhesive Buccal Patches

Drug	Bioadhesive Polymers	Dosage Form	References
Plasmid DNA, beta-galactosidase	Noveon & Eudragit S-100	Bilayer films	**70**
Ipriflavone	PLGA, chitosan	Multilayer films	**32**
Chlorhexidine gluconate	Chitosan	Film	**33**
Propranolol hydrochloride	Chitosan	Buccal patch	**71**
Protirelin	HEC, HPC, PVP, PVA	Laminated patches	**19**
Propranolol hydrochloride	Eudragit, CP-934	Buccal patch	**72**

Abbreviations: PLGA=poly(D,L-lactide-co-glycolide), **CP**=carbopol, **HPMC**=hydroxy propyl methyl cellulose, **PAA**=polyacrylic acid, **HPC**=hydroxy propyl cellulose, **HEC**=hydroxy ethylcellulose, **HPC**=hydroxy propyl cellulose, **PVP**=poly(vinyl pyrrolidone), **PVA**=poly(vinyl alcohol), **PEG**=poly ethylene glycol

BUCCOADHESIVE FORMULATIONS

Buccal drug delivery formulations include buccal tablets, buccal patches, and buccal gels. The clinical success of buccal drug delivery depends on the ability to achieve and maintain the therapeutic levels for a defined period of time. The availability of this amount of drug depends mainly on the formulation factors of the delivery system. Therefore, the drug delivery pattern from the delivery system is crucial and must be carefully considered.

Buccal Tablets

In order to improve the bioavailability of administered drug in the oral cavity, several bioadhesive tablet systems (Table 2) have been developed in recent years.[58] Adhesive buccal tablets can be applied to different sites in the oral cavity, ie, the palate, mucosa of the cheek, and between the upper lip and gum. The tablet softens and adheres to the substrate and is retained in position until release is complete. After a short time, the presence of the tablet is reported to be no longer noticeable to the patient. The tablet should not be moved about the mouth once in position because this causes more rapid drug release. The position of successive tablets can be alternated on either side of the mouth. The location of the tablet in the mouth appears to have a great impact on the tolerance and the retention time. Depending on the location, either palatal or gingival, retention times varied from 4 to 6 hrs to 7 to 12 hrs, respectively.[59] Factors such as nature of the polymer, the drug/polymer ratio, and swelling kinetics influence the drug release from bioadhesive tablets. The limitations of buccal tablets are their lack of physical flexibility, the small surface area for drug release with mucosa, and irritation following chronic application on the buccal and sublingual mucosa.

Buccal Patches

Bioadhesive patches (Table 3) are systems that may range from simple erodible and nonerodible adhesive films to more sophisticated systems, which can be designed to provide either unidirectional or multidirectional release of drug.[66-68] The ideal characteristics of a buccal drug delivery system should include flexibility, elasticity, softness, adequate strength to withstand breakage due to stress from the mouth activities, and good bioadhesive

properties so that it can be retained in the oral cavity for the desired duration. Patches should be able to meet these requirements and swell to a certain extent when placed in aqueous medium. Thus, the mechanical, bioadhesive, and swelling properties of film are critical, and their evaluation is essential.[68] They also ensure more accurate dosing of the drug compared to gels and ointments.[69]

Buccal Gels

A major difficulty for the successful eradication of fungal infections of the oral cavity and periodontal diseases is the dilution and rapid elimination of topically applied drugs due to the flushing action of saliva. The delivery system in which the drug is incorporated is therefore an important consideration and should be formulated to prolong retention of the drug in the oral cavity. The application of bioadhesive gels cover a wider area of mucosa and provide a long stay in the oral cavity, adequate drug penetration, high efficacy, patient acceptability, and physical protection.[73] Different polymers were used for the development of hydrogel systems, including cellulose derivatives (methylcellulose, carboxymethylcellulose, and hydroxy propyl cellulose), natural gums (xanthan gum, guar gum, karaya gum, and agarose), poly acrylates (poly(acrylic acid), poly(vinyl pyrrolidone) and poly(ethylene glycol), and chitosan.[20,74-76]

SUMMARY

The buccal mucosa offers several advantages for systemic and local delivery of drugs. The mucosa is well supplied with both vascular and lymphatic drainage and the absence of gastrointestinal and first-pass hepatic degradation. The area is well suited for a retentive device and appears to be acceptable to the patient. The efficacy of buccal drug delivery systems is affected by the biological environment and the properties of the polymer. With the right dosage form design and formulation, the permeability and the local environment of the mucosa can be controlled and manipulated in order to accommodate drug permeation. Buccal delivery is a promising area for continued research with the aim of systemic and local delivery of orally inefficient drugs. It is a feasible and attractive alternative for non-invasive delivery of potent peptide and protein drug molecules.

REFERENCES

1. Junginger HE, Hoogstraate JA, Verhoef JC. Recent advances in buccal drug delivery and absorption: in vitro and in vivo studies. J Control Release. 1999;62:149-159.
2. Pramodkumar TM, Desai KGH, Shivakumar HG. Buccal permeation enhancers. Ind J Pharm Edu. 2002;36:147-151.
3. Nagai T, Konishi R. Buccal/gingival drug delivery systems. J Control Release. 1987;6:353-360.
4. Khanna R, Agarwal SP, Ahuja A. Preparation and evaluation of bioerodible buccal tablets containing clotrimazole. Int J Pharm. 1996;138:67-73.
5. Ponchel G. Formulation of oral mucosal drug delivery systems for the systemic delivery of bioactive materials. Adv Drug Delivery Rev. 1994;13:75-87.
6. Wertz PW, Squier CA. Cellular and molecular basis of barrier function in oral epithelium. Crit Rev Ther Drug Carrier Syst. 1991;8:237-269.
7. Tabak LA, Levine MJ, Mandel ID, Ellison SA. Role of salivary mucins in the protection of the oral cavity. J Oral Pathol. 1982;11:1-17.
8. Rathbone M, Drummond B, Tucker I. Oral cavity as a site for systemic drug delivery. Adv Drug Del Rev. 1994;13:1-22.
9. Peppas NA, Buri PA. Surface, interfacial and molecular aspects of polymer bioadhesion on soft tissues. J Control Release. 1985;2:257-275.
10. Galey WR, Lonsdale HK, Nacht S. The in vitro permeability of skin and buccal mucosa to selected drugs and tritiated water. J Invest Dermat. 1976;67:713-717.
11. Harris D, Robinson JR. Drug delivery via the mucous membranes of the oral cavity. J Pharm Sci. 1992;81:1-10.
12. Narawane L, Lee VHL. Absorption barriers. In: de Boer AG, ed. Drug Absorption Enhancement. Concepts, Possibilities, Limitations and Trends. Harwood Academic: Switzerland. 1994:1-66.
13. Kurosaki Y, Nishimura H, Terao K, Nakayama T, Kimura T. Existence of specialized absorption mechanism for cephadroxyl, an aminocephalosporin antibiotic, in the human oral cavity. Int J Pharm. 1992;82:165-169.
14. Huntsberger JR. Treatise on adhesion and adhesives. Patrick R, ed. Marcel Dekker, Inc: New York, NY. 1967;1:221-239.
15. Mikos AG, Peppas NA. Measurement of the surface tension of mucin solutions. Int J Pharm. 1989;53:1-5.
16. Voyutskii SS. Autohesion and Adhesion of High Polymers. Wiley Press: New York, NY. 1963;1:102-124.
17. Lenaerts V, Gurny R. Bioadhesive Drug Delivery Systems. CRC Press: Boca Raton, FL. 1990:25-42.
18. Nafee NA, Ismail FA, Boraie NA, Mortada LM. Mucoadhesive delivery systems. II. formulation and in vitro/in vivo evaluation of buccal mucoadhesive tablets containing water-soluble drugs. Drug Dev Ind Pharm. 2004;30:995-1004.
19. Anders R, Merkle H. Evaluation of laminated muco-adhesive patches for buccal drug delivery. Int J Pharm. 1989;49:231-240.
20. Ishida M, Nambu N, Nagai T. Mucosal dosage form of lidocaine for toothache using hydroxypropyl cellulose and carbopol. Chem Pharm Bull. 1982;30:980-984.
21. Park CR, Munday DL. Development and evaluation of a biphasic buccal adhesive tablet for nicotine replacement therapy. Int J Pharm. 2002;237:215-226.
22. Patel VM, Prajapati BG, Patel JK, Patel MM. Formulation, evaluation, and comparison of bilayered and multilayered mucoadhesive buccal devices of propranolol hydrochloride. AAPS PharmSciTech. 2007;8(1):Article 22.
23. Taylan B, Capan Y, Güven O, Kes S, Hincal AA. Design and evaluation of sustained-release and buccal adhesive propranolol hydrochloride tablets. J Control Release. 1996;38:11-20.
24. Llabot JM, Manzo RH, Allemandi DA. Double-layered mucoadhesive tablets containing nystatin. AAPS Pharm Sci Tech. 2002;3:1-6.
25. Ponchel G, Touchard F, Wouessidjewe D, Duchêne D, Peppas NA. Bioadhesive analysis of controlled release systems. III. bioadhesive and release behaviour of metronidazole containing poly (acrylic acid)-hydoxypropyl methylcellulose systems. Int J Pharm. 1987;38:65-70.
26. Miyazaki S, Nakayama A, Oda M, Takada M, Attwood D. Chitosan and sodium alginate based bioadhesive tablets for intraoral drug delivery. Biol Pharm Bull. 1994;17:745-747.
27. Remunan-Lopez C, Portero A, Vila-Jato JL, Alonso MJ. Design and evaluation of chitosan/ethylcellulose mucoadhesive bilayered devices for buccal drug delivery. J Control Release. 1998;55:143-152.
28. Choi HG, Kim CK. Development of omeprazole buccal adhesive tablets with stability enhancement in human saliva. J Control Release. 2000;68:397-404.
29. Merkle HP, Wolany G. Buccal delivery of peptide drugs. J Control Release. 1992;21:155-164.
30. Mortazavi SA, Smart JD. An in vitro method for assessing the duration of mucoadhesion. J Control Release. 1994;31:201-212.
31. Smart JD. An in vitro assessment of some mucosa-adhesive dosage forms. Int J Pharmacol. 1991;73:69-74.
32. Perugini P, Genta I, Conti B, Modena T, Pavanetto F. Periodontal delivery of ipriflavone: new chitosan/PLGA film delivery system for a lipophilic drug. Int J Pharm. 2003;18:1-9.
33. Senel S, Ikinci G, Kas S, Yousefi-Rad A, Sargon MF, H›ncal AA. Chitosan films and hydrogels of chlorhexidine gluconate for oral mucosal delivery. Int J Pharm. 2000;193:197-203.
34. Inoue T, Chen G, Nakamae K, Hoffman AS. An AB copolymer of oligo (methyl methacrylate) and poly (acrylic acid) for micellar delivery of hydrophobic drugs. J Control Rel. 1998;51:221-229.
35. Shojaei AH, Li X. Mechanisms of buccal mucoadhesion of novel copolymers of acrylic acid and polyethylene glycol monomethylether monomethacrylate. J Control Rel. 1997;47:151-161.
36. Cassidy JP, Landzert NM, Quadros E. Controlled buccal delivery of buprenorphine. J Control Rel. 1993;25:21-29.
37. Lele BS, Hoffman AS. Mucoadhesive drug carriers based on complexes of poly (acrylic acid) and PEGylated drugs having hydrolysable PEG-anhydride-drug linkages. J Control Rel. 2000;69:237-248.
38. Cleary GW, Feldstein MM, Singh P, Plate NA. A New Polymer Blend Adhesive With Combined Properties to Adhere to Either Skin or Mucosa for Drug Delivery. Podium abstract presented at the 30th Annual Meeting and Exposition of the Controlled Release Society, Glagsow, Scotland. July 2003.
39. Bernkop-Schnurch A, Schwarch V, Steininger S. Polymers with thiol groups: a new generation of mucoadhesive polymers? Pharm Research. 1999;16:876-881.
40. Chattaraj SC, Walker RB. Penetration enhancer classification. In: Smith EW, Maibach HI, eds. Percutaneous Penetration Enhancement. CRC Press: Boca Raton, FL. 1995:1-4.
41. Aungst A. Permeability and metabolism as barriers to transmucosal delivery of peptides and proteins. In: Hsieh DS, ed. Drug Permeation Enhancement. Theory and Applications. Marcel Dekker: New York, NY. 1994:323-343.
42. Oh CK, Ritschel WA. Biopharmaceutic aspects of buccal absorption of insulin. Methods Find Exp Clin Pharmacol. 1990;12:205-212.
43. Siegel IA, Gordon HP. Effects of surfactants on the permeability of canine oral mucosa in vitro. Tox Lett. 1985;26:153-157.
44. Hoogstraate AJ, Coos Verhoef J, Pijpers A, van Leengoed LA, Verheijden JH, Junginger HE, Bodde HE. In vivo buccal delivery of the peptide drug buserelin with glycodeoxycholate as an absorption enhancer in pigs. Pharm Res. 1996;13:1233-1237.
45. Wolany GJM, Munzer J, Rummelt A, Merkle HP. Buccal absorption of sandostatin (octreotide) in conscious beagle dogs. Proceed Intern Symp Control Rel Bioact Mater. 1990;17:224-225.
46. Steward A, Bayley DL, Howes C. The effect of enhancers on the buccal absorption of hybrid (BDBB) alpha interferon. Int J Pharm. 1994;104:145-149.
47. Manganaro AM, Wertz PW. The effects of permeabilizers on the in vitro penetration of propranolol through porcine buccal epithelium. Mil Med. 1996; 161:669-672.
48. Senel S, Kremer MJ, Ka SH, Wertz PW, H›ncal AA, Squier CA. Effect of chitosan in enhancing drug delivery across buccal mucosa. In: Peter MG, Muzzarelli RAA, Domard A, eds. Advances in Chitin Science. University of Potsdam. 2000;4:254-258.
49. Senel S, Kremer MJ, Ka SH, Wertz PW, H›ncal AA, Squier CA. Enhancing effect of chitosan on peptide drug delivery across buccal mucosa. Biomaterials. 2000;21:2067-2071.
50. De Vries ME, Boddé HE, Verhoef JC, Junginger HE. Developments in buccal drug delivery. Crit Rev Ther Drug Carrier Syst. 1991;8:271-303.
51. Ho NFH, Barsuhn CL, Burton PS, Merkle HP. Routes of delivery: case studies, mechanistic insights to buccal delivery of proteinaceous substances. Adv Drug Deliv Rev. 1992;8:197-235.
52. Ishida M, Machida Y, Nambu N, Nagai T. New mucosal dosage form of insulin. Chem Pharm Bull. 1981;29:810-816.

53. Al-Achi A, Greenwood RR. Buccal administration of human insulin in streptozocin-diabetic rats. Res Commun Chem Pathol Pharmacol. 1993;82:297-306.
54. Bayley D, Temple C, Clay V, Steward A, Lowther N. The transmucosal absorption of recombinant human interferon-alpha B/D hybrid in the rat and rabbit. J Pharm Pharmacol. 1995;47:721-724.
55. Chien Y, Nakane S, Lee Y, Kakumoto M, Yukimatsu K. Oral mucosa enhanced delivery of gonadotropin-releasing hormone: (II) in vivo evaluations of GnRH-mucoadhesive devices. In: Proceedings 1st World Meeting APGI/APV, Budapest.1995;813-814.
56. Nakane S, Kakumoto M, Yukimatsu K, Chien YW. Oramucosal delivery of LHRH: pharmacokinetic studies of controlled and enhanced transmucosal permeation. Pharm Dev Technol. 1996;1:251-259.
57. Gutniak MK, Larsson H, Sanders SW, Juneskans OT, Holst JJ, Ahren B. GLP-I tablet in type 2 diabetes in fasting and postprandial conditions. Diabetes Care 1997;20:1874-1879.
58. Bouckaert S, Schautteet H, Lefebvre RA, Remon JP, van Clooster R. Comparison of salivary miconazole concentrations after administration of a bioadhesive slow-release buccal tablet and an oral gel. Eur J Clin Pharmacol. 1992;43:137-140.
59. Vivien-Castioni N, Gurny R, Baehni P, Kaltsatos V. Salivary fluoride concentrations following applications of bioadhesive tablets and mouth rinses. Eur J Pharm Biopharm. 2000;49:27-33.
60. Gupta A, Garg S, Khar RK. Interpolymer complexation and its effect on bioadhesive strength and dissolution characteristics of buccal delivery systems. Drug Dev Ind Pharm. 1994;20:315-325.
61. Bottenberg P, Cleymaet R, De Muyncha C, Remon JP, Coomans D, Slop D. Development and testing of bioadhesive fluoride-containing slow-release tablets for oral use. J Pharm Pharmacol. 1991;43:457-464.
62. Carcia-Gonzalez N, Kellaway IW, Blanco-Fuente H. Design and evaluation of buccoadhesive metoclopramide hydrogels composed of poly (-acrylic acid) cross-linked with sucrose. Int J Pharm. 1993;100:65-70.
63. Mumtaz AM, Ch'ng HS. Design of a dissolution apparatus suitable for in situ release study of triamcinolone acetonide from bioadhesive buccal tablets. Int J Pharm. 1995;121:129-139.
64. Agarwal V, Mishra B. Design, development, and biopharmaceutical properties of buccoadhesive compacts of pentazocine. Drug Dev Ind Pharm. 1999;25:701-709.
65. Alur HH, Pather SI, Mitra AK, Johnston TP. Transmucosal sustained delivery of chlorpheniramine maleate in rabbits using a novel natural mucoadhesive gum as an excipient in buccal tablets. Int J Pharm. 1999;188:1-10.
66. DeGrande G, Benes L, Horriere F, Karsenty F, LaCoste C, McQuinn R, Guo J, Scherrer R. Specialized oral mucosal drug delivery systems: patches. In: Rathbone MJ, ed. Oral Mucosal Drug Delivery. Marcel Dekker: New York. 1996:285-318.
67. Guo JH, Cremer K. Development of bioadhesive buccal patches. In: Mathiowitz E, Chickering DE, Lehr M, eds. Bioadhesive Drug Delivery Systems. Marcel Dekker: New York, NY. 1999:541-562.
68. Peh KK, Wong CF. Polymeric films as vehicle for buccal delivey: swelling, mechanical, and bioadhesive properties. J Pharm Pharm Sci. 1999;2:53-61.
69. Nafee NA, Ismail FA, Boraie NA, Mortada LM. Mucoadhesive buccal patches of miconazole nitrate: in vitro/in vivo performance and effect of ageing. Int J Pharma. 2003;264:1-14.
70. Cui Z, Mumper RJ. Bilayer films for mucosal (genetic) immunization via the buccal route in rabbits. Pharm Res. 2002;19:947-953.
71. Patel VM, Prajapati BG, Patel JK, Patel MM. Physicochemical characterization and evaluation of buccal adhesive patches containing propranolol hydrochloride. Current Drug Delivery. 2006;3:325-331.
72. Patel VM, Prajapati BG, Patel JK, Patel MM. Effect of hydrophilic polymers on buccoadhesive eudragit patches of propranolol hydrochloride using factorial design. AAPS PharmSciTech. 2007;8(5):Article 145.
73. Needleman IG, Martin GP, Smales FC. Characterisation of bioadhesive for periodontal and oral mucosal drug delivery. J Clin Periodontol. 1998;25:74-82.
74. Nguyen-Xuan T, Towart R, Terras A, Jacques Y, Buri P, Gurny R. Mucoadhesive semi-solid formulations for intraoral use containing sucralfate. Eur J Pharm Biopharm. 1996;43:133-137.
75. Watanabe K, Yakou S, Takayama K, Machida Y, Nagai T. Drug release behaviors from hydrogel prepared with water-soluble dietary fibers. J Pharm Sci Techn Jpn. 1991;51:29-35.
76. Ikinci G, Senel S, Akincibay H, Kas S, Ercis S, Wilson CG, Hincal AA. Effect of chitosan on a periodontal pathogen Porphyromonas gingivalis. Int J Pharm. 2002; 20:121-127.

BIOGRAPHIES

Dr. Vishnu M. Patel is working as an Assistant Professor in Pharmaceutical Technology at Shree A.P.M.C. College of Pharmaceutical Education and Research, Himatnagar, Gujarat, India. He earned his MPharm in Pharmaceutics from Rajiv Gandhi University of Health Sciences, Bangalore, India, and his PhD in Pharmaceutical Sciences from Hemchandracharya North Gujarat University, Patan, India. He has presented various research at international and national conferences and has published various research papers in national and international journals. He is a referee of various reputed journals in the field of pharmaceutics. His is interested in the core research area of novel bioadhesive buccal drug delivery systems.

Mr. Bhupendra G. Prajapati is working as a lecturer and assistant professor at the S.K. Patel College of Pharmaceutical Education and Research, Ganpat University, Kherva, North Gujarat, India. He has joined the PhD program in the subject of Pharmaceutics. His area of interest focuses on transmucosal drug delivery systems. He has presented and published more than 20 national and international presentations.

Mr. Karshanbhai M. Patel is the Principal of the Shree S.K. Patel College of Pharmacy, Ganpat University, Kherva, Gujarat, India. He served as the Joint Commissioner of the Food and Drug Control Administration, Gujarat state, India. He earned his BPharm and MPharm from L.M. College of Pharmacy, Ahmedabad, India. He has delivered various lectures in industries and academics. His core area of interest is pharmaceutical technology of parenteral formulations.

DCAT PRESENTS

Conference & Pharma Expo

EXCIPIENT FEST® Americas

The Science... is the Fun!

Excipient Technology for Pharma Formulation, New Drug Application & Sourcing Strategies

April 16-17, 2008

The Grand Ballroom • PR Convention Center

San Juan, Puerto Rico

Platinum Sponsors

JRS PHARMA

BASF The Chemical Company

Media Sponsor

Drug Delivery Technology

Gold Sponsors

COVIDIEN Mallinckrodt

SPI Pharma

dowwolff CELLULOSICS

Pharmaceutical Technology

Aqualon

FMC

Mutchler Inc. PHARMACEUTICAL INGREDIENTS

degussa. Röhm Pharma Polymers

EMERSON RESOURCES INC

ROHM HAAS

HUBER

AsahiKASEI

ISP

DOBER GROUP

Colorcon

DMV-Fonterra Excipients The ingredients of success

PALATINIT

ROQUETTE

IPEC AMERICAS

excipientfest.com

DCAT/ExcipientFest: One Washington Blvd., Suite 7, Robbinsville, NJ 08691, USA
Tel (609) 448-1000 (800) 640-DCAT Fax (609) 448-1944 info@excipientfest.com

IN VITRO RELEASE TESTING

The Issues & Challenges Involved in In Vitro Release Testing for Semi-Solid Formulations

By: Qiuxi Fan, PhD; Mark Mitchnick, MD; and Andrew Loxley, PhD

INTRODUCTION

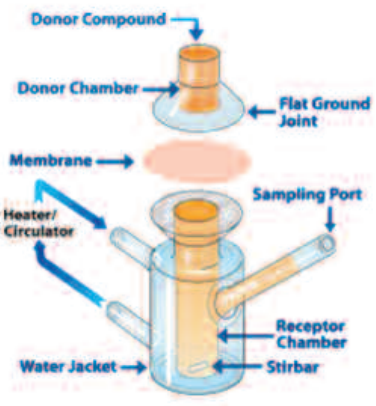
The use of an in vitro release test (IVRT) to evaluate drug release from semi-solid formulations has become the routine test for topical product development. Like the dissolution test for solid dosage forms, IVRT for semi-solid dosage has become increasingly important. As FDA Guidance puts it, "In vitro release is one of several standard methods that can be used to characterize performance characteristics of a finished topical dosage form (ie, semi-solids like creams, gels, and ointments)… A variety of physical and chemical tests commonly performed on semi-solid products and their components (eg, solubility, particle size, and crystalline form of the active component, viscosity, and homogeneity of the product) have historically provided reasonable evidence of consistent performance. More recently, IVRT has shown promise as a means to comprehensively ensure consistent delivery of the active component(s) from semi-solid products. An in vitro release rate can reflect the combined effect of several physical and chemical parameters, including solubility and particle size of the active ingredient and rheological properties of the dosage form. In most cases, in vitro release rate is a useful test to assess product sameness between pre-change and post-change products… Important changes in the characteristics of a drug product formula or the thermodynamic properties of the drug(s) it contains should show up as a difference in drug release."[1]

Based on FDA Guidance, the IVRT method for topical dosage products is built on an open chamber diffusion cell system like the Franz diffusion cell system (Figures 1 and 2) with a synthetic polymeric membrane.[2] The membrane separates the donor part containing test product from the receptor part filled with medium (usually PBS buffer). Diffusion of drug from the topical product to and across the membrane is monitored by assay of sequentially collected samples of the receptor medium. At predetermined time points, an aliquot of medium is removed from the receptor part for drug content analysis either by high pressure liquid chromatography (HPLC) or other analytical technique, and the same amount of fresh medium is refilled into the receptor to keep constant volume. Theoretically, release is proportional to the square root of time, ie, a straight line in the release profile.[1]

This paper discusses different IVRT set-ups for different systems (one-phase and two-phase systems) of topical products and their respective release profiles, as well as highlighting the challenges involved in collecting useful data and how to overcome them.

FIGURE 1

Franz Diffusion Cell



ONE-PHASE SYSTEM

There are two one-phase systems to be discussed: a water-based system, such as hydroxyethyl cellulose (HEC) gel with peptide as the API, and oil-based systems, such as 1-octanol solution or light mineral oil suspension of either antibiotic or low molecular weight agents like lidocaine or caffeine as the API.

Water-Based System

Two HEC gels with different concentrations of a peptide API, and a poloxamer gel with the same peptide, all containing Transcutol® as a penetration enhancer have been tested

using the IVRT method at Particle Sciences Inc. Because of the relative simplicity of the water-based formulations, IVRT was carried out without modification from the FDA Guidance, using the experimental configuration presented in Table 1, and the release profiles obtained from the three formulations are shown in Figure 3.

It is obvious that for water-based one-phase systems, the regular IVRT method works well with no need for modification, and differences between formulation types and API loading within a formulation type are clearly observed.

Oil-Based System

Fan et al investigated the controlled release of an antibiotic drug (doxycycline HCl) from its solution/suspension in an organic solvent through a porous membrane.[3] When formulated as a simple system of API solution/suspension in 1-octanol/light mineral oil, IVRT results were also dependent on API concentration in the formulations: 5 mg/ml (Sol. 1) or 10 mg/ml (Sol. 2). A similar IVRT procedure was performed as for the water-based formulations, except that a hydrophilized polyvinylidene fluoride (PVDF) membrane (Millipore, 0.1-micron pore size) was used instead of a nylon one. Table 2 shows the permeation data, and Figure 4 presents the release profiles.[3]

From these two IVRT examples of different one-phase semi-solid systems, it is not difficult to observe that one-phase systems pose little challenge for the IVRT method mainly because (as the name "one phase" indicates) either a simple diffusion or partitioning is the major mechanism for API transport through the polymeric membrane. Therefore, different formulations are easily distinguished.

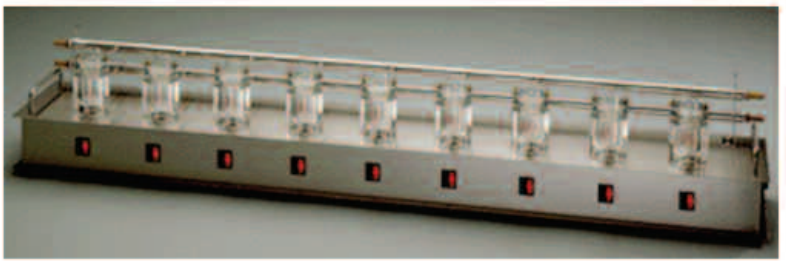
TABLE 1

IVRT Configuration

Diffusion cell	PermeGear®9-station Franz cell stirrer
Weight of sample gel	~ 0.3 grams
Membrane	GE®, Megna, Nylon membrane, 0.45-micron pore size
Receptor medium	PBS
Sampling aliquot	300 microliters
Sampling time	0.5, 1, 2, 4, 6, and 24 hrs

FIGURE 2

9-Station Franz Cell Stirrer



TWO-PHASE SYSTEM

Two-phase systems are more complex than one-phase systems because many more factors are involved, such as API solubility in the two phases, API partitioning between the two phases, interactions within the system and between the emulsion, and membrane interface. And these factors might pose challenges for IVRT to differentiate formulations or even to achieve a reliable release profile.

Oil-in-Water (O/W) System

The O/W emulsion is the most widely applied system in semi-solid dosage products because of its fast API release, and its relative stability and ease of application to the skin. In most cases, because the API is dissolved in the aqueous continuous phase, there is no major barrier to the API's transport through the formulation and into and through the polymeric membrane during the IVRT experiment.

At Particle Sciences Inc., several formulations containing the oil propylene glycol (PG), water, and a low molecular weight microbicide as the API have been tested using regular IVRT conditions. The same IVRT configuration was used except that the receptor medium was a mixture of PBS and ethanol because of this particular API's low solubility in PBS alone. As shown in Figure 5, formulations of the same concentration of API dissolved/dispersed in different phases were easily distinguished from their IVRT release profiles.

Water-in-Oil (W/O) System Using Peptide as the API

In addition to the O/W system, IVRT of water-in-oil emulsions using a higher molecular weight peptide as the API has also been performed at Particle Sciences Inc. Compared to the O/W system, the peptide emulsion system presented the following several challenges for IVRT:

- The high molecular weight of the peptide (close to 2000 Daltons), high solubility in water, and much lower solubility in the continuous oil phase mean that partitioning from the aqueous internal phase into the non-aqueous continuous phase may not be a strong enough driving force for the peptide to diffuse through the membrane.

- The W/O formulation contains a large volume fraction of aqueous phase to dissolve the API, with a relatively small amount of oil-phase components surrounding it as a continuous phase. Within such a tightly bound structure, the peptide may not diffuse from the water phase through the continuous oil phase and release to the medium.

- If negligible release is observed, the IVRT configuration would need to be changed or reformulation with another selection of oil phase and/or emulsifier be carried out.

TABLE 2

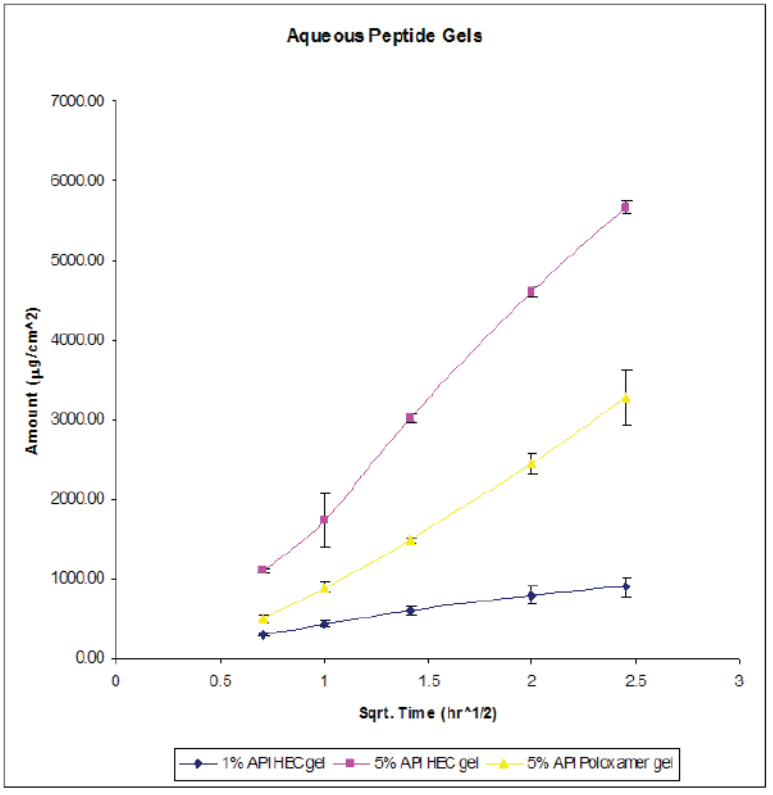
Permeation Data Using 1-Octanol as an Oil-Based System[3]

Diffusion System	Permeability (cm/hr)	Flux µg/cm² hr)	*Q_{24} (µg/cm²)
Sol. 1	0.015 ± 0.003	72.8 ± 12.2	516 ± 146
Sol. 2	0.015 ± 0.002	149.7 ± 21.8	2521 ± 538

*Q_{24}, receptor concentration after 24 hrs.

FIGURE 3

IVRT Release Profiles of Water-Based One-Phase System



Initial IVRT was carried out by the routine se-tup shown in Table 1. As expected, zero release was observed after 24 hrs, which illustrated the challenges previously outlined. Other research groups also indicated that a solubilized drug's delivery from emulsion systems, such as creams, lotions, or ointments, relies on this API's initial concentration, diffusion coefficient in the external oil phase, and partitioning coefficient between the internal water phase and the external oil phase.[4] As for the W/O emulsion system, the preferred partitioning toward the internal water phase would keep the API rarely available in the external oil phase. At the same time, for the API going through the membrane into the aqueous medium, diffusion occurs through the membrane pores filled with medium and is influenced by the partitioning coefficient of the API between the bulk solvent (ie, the continuous oil phase) and the aqueous solvent in the membrane pores.[5] In this case, as this high molecular weight peptide API has much higher solubility in water (> 100 mg/ml) than in the oil phase (< 10 mg/ml), not surprisingly, partitioning was always favored toward the water phase; therefore, diffusion through the continuous oil phase into the aqueous medium generally was not observed. The major challenge here is that if the continuous phase is different from the aqueous phase containing the API, it would be very difficult for the API to transport through the interface between the carrier fluid and the formulation by diffusion and/or partitioning. In another case, if the API is in a dispersed phase whose continuous phase has a sharp interface with the collection medium, then release will be even lower due to reduction in the diffusion of API through the oil phase, and the fact that the whole formulation will not pass through the membrane.

In order to overcome this delivery challenge, a modified IVRT

configuration was proposed to achieve a measurable release profile from the W/O emulsion system:

- Use a larger pore size (0.8 microns, 1.0 micron) and/or hydrophobic membrane (Celgard® membrane, PTFE membrane) to facilitate the emulsion transportation.
- Increase the concentration of API in the emulsion.
- Add organic component to the receptor medium, such as ethanol, to improve wetting the membrane.[6]

After implementing the new set-up, distinguishable release profiles were observed from different W/O emulsion systems.

SUMMARY

In the topical pharmaceutical arena, the application of IVRT to investigate drug release rates from emulsion formulations has received increased attention throughout the past decade. This paper analyzed the issues/challenges related to the use of IVRT for different emulsion systems: a one-phase (either oil or water) system and a two-phase (O/W, W/O) system, and whether IVRT can differentiate formulations. One-phase systems and O/W two-phase systems with the API in the aqueous phase (or in the dispersed oil phase but with a non-zero solubility in the aqueous phase) pose little challenge for IVRT with a wide range of membrane choice and medium selection based on API properties. On the other hand, for W/O two-phase systems, the challenges for IVRT are significant and stem from the API solubility issue in the two phases, the API partitioning between the two phases, oil phase membrane-wetting

FIGURE 4

IVRT Release Profiles of Oil-Based One-Phase System

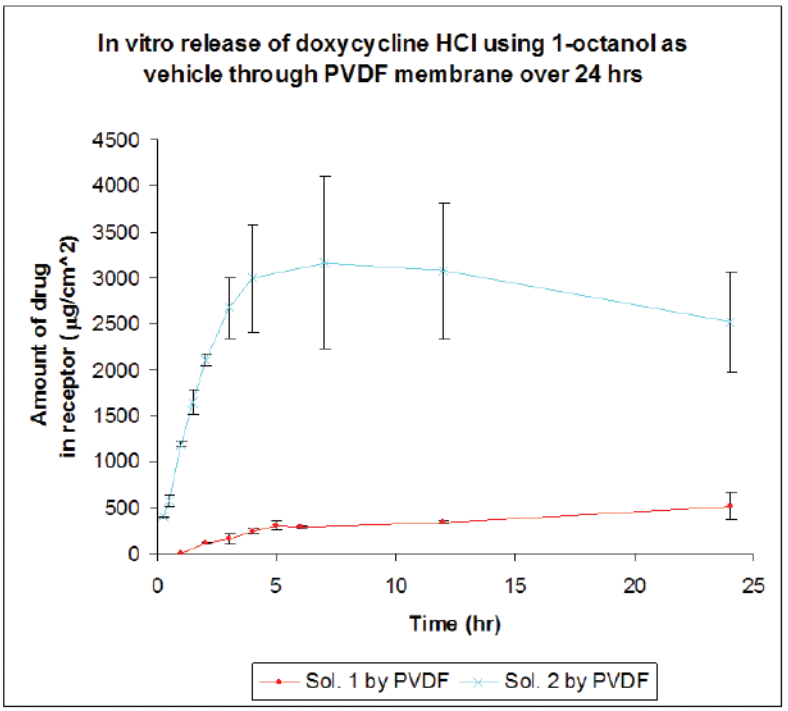


FIGURE 5

IVRT Release Profiles of O/W System

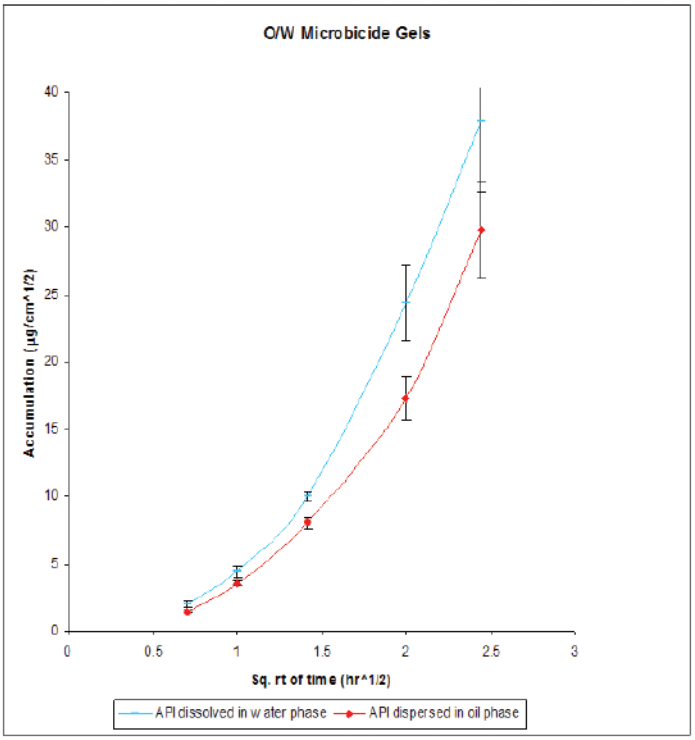
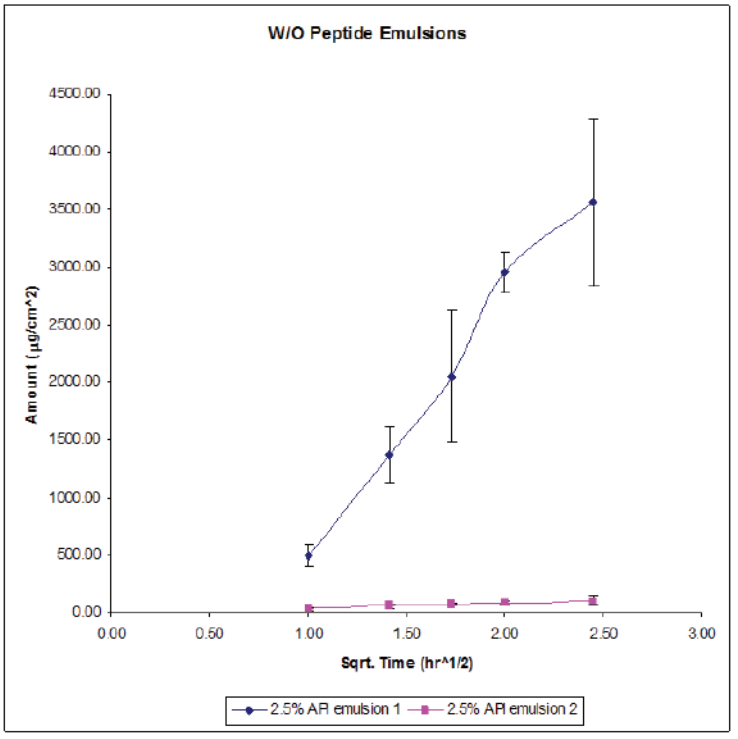


FIGURE 6

IVRT Release Profiles of W/O System



issue, and slow release issue. In the case of O/W/O and W/O/W systems, they behave similarly to W/O and O/W systems, with an additional complicating phase.

Differing from case to case, the regular IVRT set-up may need to be modified to meet the requirements of different emulsion systems as well as different APIs. The present paper used a high molecular weight peptide API in a water-in-oil formulation as an example of how to overcome these challenges.

It is evident that the regular IVRT procedure needs to be modified to meet the requirements of different emulsion systems as well as APIs. The present paper used a large MW peptide as an example of how to overcome those challenges based on our successful IVRT experiences for different emulsion systems here at Particle Sciences Inc. Now that IVRT can be adapted to evaluate all types of formulations, the next challenge is the correlation between in vitro and in vivo release results, which is currently under intense investigation at the company.

REFERENCES

1. FDA Guidance for Industry: Nonsterile Semi-solid Dosage Forms: Scale-Up and Postapproval Chanes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation, May 1997, SUPAC-SS CMC 7.
2. Website: http://permegear.com/.
3. Fan Q, Sirkar KK, Wang Y, Michniak B. In vitro delivery of doxycycline hydrochloride based on a porous membrane-based aqueous-organic partitioning system. J Controlled Rel. 2004;98:355-365.
4. Clement P, Laugel C, Marty J-P. Influence of three synthetic membranes on the release of caffeine from concentrated W/O emulsions. J Controlled Rel. 2000;66:243-254.
5. Ong JTH, Manoukian E. Release of lonapalene from two-phase emulsion-type ointment systems. Pharm Res. 1988;5:16-20.
6. Ferreira LAM, Seiller M, Grossiord JL, Marty JP, Wepierre J. Vehicle influence on in vitro release of glucose: w/o, w/o/w, and o/w systems compared. J Controlled Rel. 1995;33:349-356.

BIOGRAPHIES

Dr. Qiuxi Fan joined Particle Sciences, Inc. in 2006 as a Chemist focusing on preformulation and IVRT areas with over 10 years experience in both industrial and academic environments of pharmaceutics and cosmetics. In 2005, Dr. Fan worked at Dermik Labs as a Scientist, the dermatology division of Sanofi-Aventis. He published several papers on a variety of topics from passive transdermal/topical delivery to active iontophoretic delivery to applying intelligent polymers (ie, temperature-sensitive gels for transdermal delivery of antibiotics) in the Journal of Controlled Release, Pharmaceutical Research, etc. He is also the inventor of two pending US patents related to transdermal/topical drug delivery. Dr. Fan earned his PhD from New Jersey Institute of Technology.

Dr. Mark Mitchnick is the CEO of Particle Sciences. Dr. Mitchnick holds approximately 20 issued and pending US and international patents related to nanoparticle production, skin care formulations, self-sterilizing catheters, and encapsulation and stabilization of active ingredients. Dr. Mitchnick earned his BSc in Animal Sciences from Purdue University and his MD from Georgetown University Medical School. He was trained in Paediatrics at The New York Hospital, Cornell Medical Center.

Dr. Andrew Loxley is Manager of Special Projects at Particles Sciences Inc., a contract research organization in Bethlehem, PA, specializing in pharmaceutical formulation development. He leads a variety of projects, many based on novel and proprietary nanotechnologies, in fields from HIV vaccine and microbicide development to gene-silencing SiRNA delivery. Prior to joining Particles Sciences, he worked as a researcher in the nanotechnology space. British-born, he earned his BSc in Chemistry from the University of Sussex and his PhD in Physical Chemistry focusing on Microencapsulation from the University of Bristol.

PALATABLE FORMULATIONS

Oral Drug Delivery Technology – Delivering on Patient Expectations

By: Jeffrey H. Worthington, MBA, and David A. Tisi, MS

INTRODUCTION

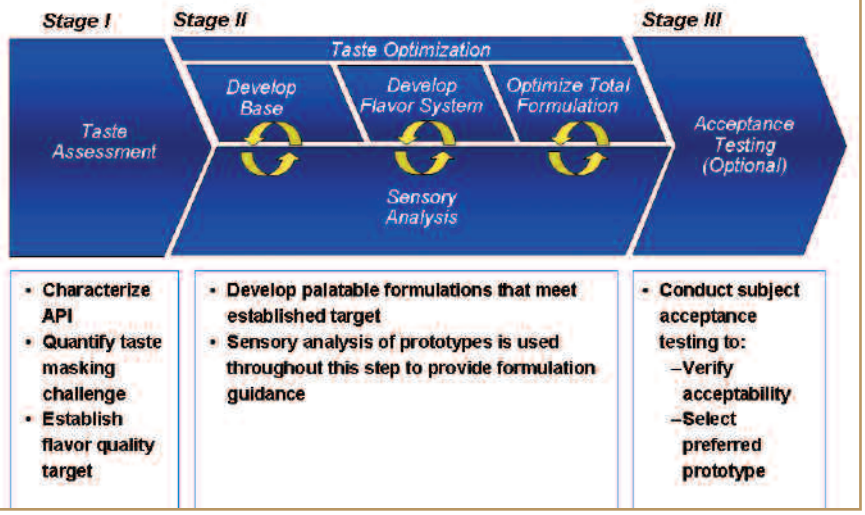
Today, most pharmaceuticals are developed and promoted exclusively on their medical benefits – superior efficacy, fewer side effects, faster on-set of action, or longer lasting (reduced dosing frequency) – many of which have been enabled by advances in drug delivery technology. While these medical benefits are of paramount importance, the product's aesthetics (appearance, aroma, flavor, texture, and mouthfeel) can have a significant effect on patient compliance. Unfortunately, drug products' aesthetic characteristics are under-considered and underutilized by many companies. This often leads to the launch of drugs that are unacceptable to many patients, despite their medical benefits. When medication compliance is compromised, health outcomes suffer and drugs fail to realize their sales potential. A properly formulated drug product that considers the aesthetic dimensions of patient acceptability will better serve the patient over the long-term and generate greater sales for the manufacturer and technology holder alike.

SENSORY ANALYSIS OF DRUG PRODUCTS

For the food and beverage industry, optimizing the sensory attributes of products is the top priority in the heated competition for "share of stomach." The mission of pharma companies on the other hand is to promote dosing compliance, not product consumption. Fortunately, patients have comparatively modest expectations of their medication. Most are looking for an "acceptable" tasting medicine – one that can be easily swallowed without gagging (odor), pain (trigeminal effects), or suffering (taste). This translates to a drug product with moderate sensory characteristics – not too bitter, not to odorous, not too irritating, not too gritty. Whether the formulation is orange, grape, bubblegum, chocolate, or mint flavored is of much lower importance to the lack of these negative sensory attributes.

FIGURE 1

Sensory-Directed Development Process



Regardless of whether the objective is to develop a "great-tasting" food or beverage or a "palatable" pharmaceutical, sensory analysis is required to effectively guide formulation development. There are two major classifications of sensory tests: affective and analytical. Affective tests determine customer (patient/consumer) response to products and are generally used by market research to test product concepts (eg, focus group), determine product preference, or to determine product acceptance (eg, degree of liking). Analytical tests are used to identify and quantify products' perceived sensory characteristics under controlled laboratory conditions. There are several types of analytical tests, including discrimination tests (used in quality control), grading tests (used in product quality labeling), and descriptive methods. The descriptive methods find the greatest application in formulation development and are discussed further herein. The reader is directed to the references for additional information on sensory analysis methods.

The descriptive methods provide complete characterizations of the sensory attributes of a product – appearance, aroma, flavor, texture, and mouthfeel. All descriptive methods involve the detection (discrimination) and description of both the qualitative and quantitative sensory aspects of a product by trained panels of judges (panelists or subjects). The qualitative factors are the individual perceived sensory aspects that define the product and are referred to by various terms, such as attributes, characteristics, character notes, or descriptors. The quantitative aspect of descriptive analysis expresses numerically the degree to which

each of the qualitative terms (attribute) is present, which is referred to as intensity. Use of reference standards for the qualitative terms and reference scales for intensity of different attributes ensures consistent application of the measurements across panelists and reproducibility across evaluations.

PROCESS FOR DEVELOPING PALATABLE DRUG PRODUCTS

Consumer packaged goods companies have evolved highly sophisticated processes, tools, and techniques for developing products that appeal to our sense, where product attributes, such as appearance, aroma, flavor, mouthfeel, skin-feel, and sound, are key product differentiators in these highly competitive industries. Pharma's primary focus is the safety and efficacy of its products with comparatively little resources devoted to product aesthetics, as this has not been the historic base of competition, particularly for prescription drugs. The sensory-directed process shown in Figure 1 has been adapted from the consumer packaged goods industry and provides a framework for developing palatable oral pharmaceuticals.

Stage I is sensory analysis of the API and benchmarking of competing products. This should be conducted as early in clinical development as possible (Phase II). One of the primary objectives is to characterize the API to identify and quantify its critical sensory attributes, eg, bitter basic taste, odor, and trigeminal effects, such as tongue sting or throat burn. It is particularly important that this assessment include measures of the temporal effects of the critical sensory attributes, which can significantly impact the taste-masking challenge. Additionally, if there are important competing marketed products, then it's vital to assess the sensory quality of these to ensure that the new drug product's aesthetics are as good as or better than the alternatives. The net result is the establishment of a sensory target for the drug product.

Stage II is the actual development of a series of palatable formulations that meet the sensory target established in Stage I. The development process consists of three discrete steps, beginning with the unflavored base and then the flavor system. One of greatest misconceptions in the pharma industry is the

FIGURE 2

Sensory Time/Intensity Profile of Marketed Drug Product Illustrating Complete Bitterness Coverage

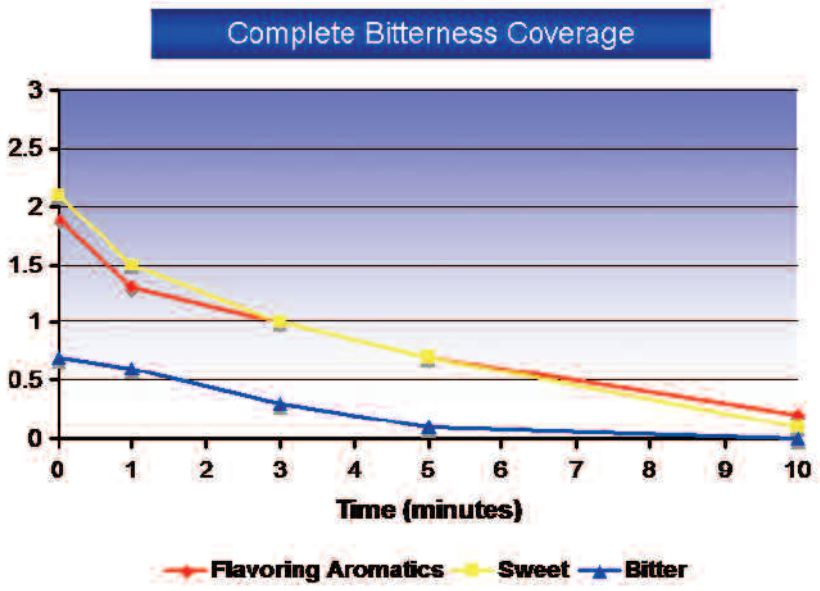


FIGURE 3

Sensory Time/Intensity Profile of Marketed Drug Product Illustrating Incomplete Bitterness Coverage

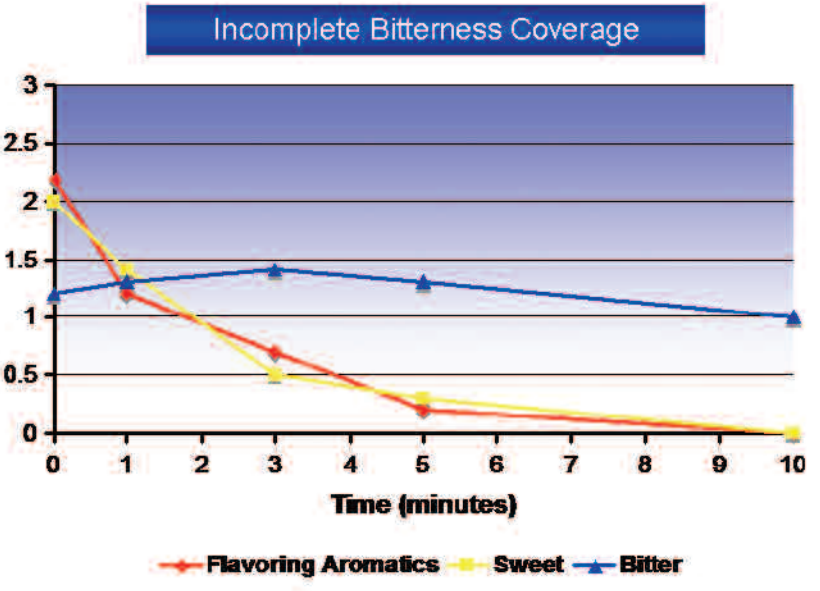


FIGURE 4

Sensory Time/Intensity Profile of Marketed Drug Product Illustrating No Bitterness Coverage

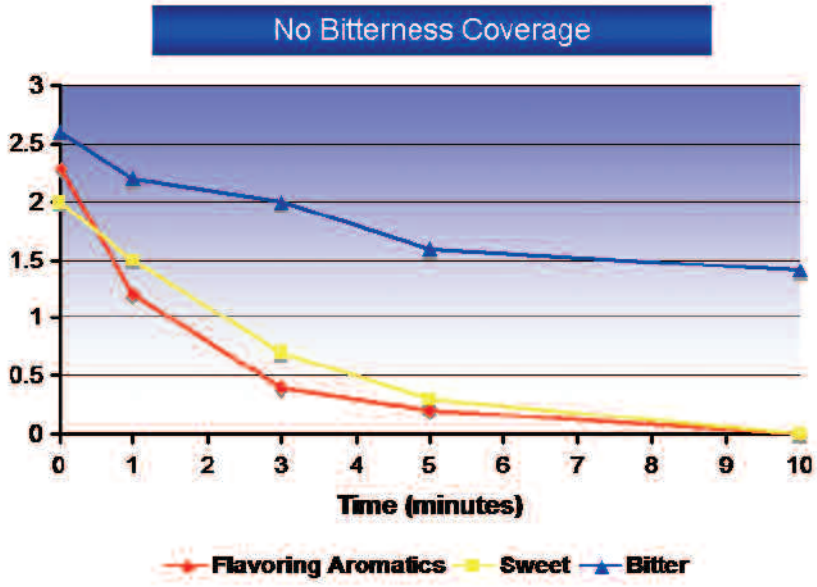
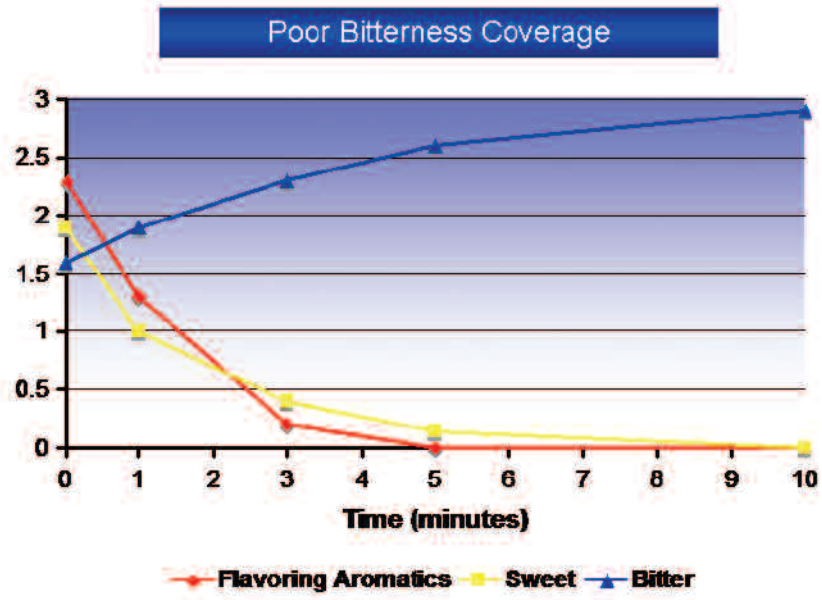


FIGURE 5

Sensory Time/Intensity Profile of Marketed Drug Product Illustrating Unique Bitterness Masking Challenge



belief that the key to bitter taste-masking is the selection of the appropriate flavoring material, eg, orange, grape, and strawberry. However, the anatomy and physiology of taste and odor perception are fundamentally different. Bitterness, like the other basic tastes (sweet, sour, and salty), is perceived through stimulation of the taste buds on the epithelium of the tongue. Flavoring materials are aromatics (odors) that are perceived through stimulation of the olfactory epithelium, which contains receptor cells and the free nerve endings of the trigeminal nerve. The olfactory receptor cells lie in the upper reaches of a small area of the nasal cavity, called the olfactory epithelium. Odors are perceived through two different routes — smelling directly through the nose (orthonasal) or during gustation when the volatile odorous molecules reach the olfactory center through the nasopharyngeal passage (retronasal). Understanding the differences in perception, one would not expect an aromatic flavoring material to mask a bitter or other basic taste. Stage II is structured in large part on an appreciation of the fundamental differences between taste and odor perception as will be discussed further.

Stage III is acceptance testing of one or more palatable prototype formulations developed in Stage II. This testing is most commonly conducted using healthy volunteers, but patients may be used as appropriate. The objective is to have the subjects select the preferred flavor type amongst a group of prototypes of similar flavor quality or to ensure that the prototypes meet the established target (eg, is liked the same or more than a competing product).

UNDERSTANDING PALATABILITY

Fundamentally, the flavor quality of a drug product is related to the perceived blend of the product's sensory characteristics. Many drug substances are bitter, and the perceived bitterness "stands out" from the other basic tastes (sweet, sour, salty). If the basic tastes are balanced through the proper selection and use of complementary excipients, then the bitterness of the drug substance will not be distinctly perceived, and consequently, the

drug product will be considered more palatable. The same concept applies to other basic tastes as well as trigeminal effects and odors; the key is to "blend away" the negative attributes. Importantly, patient acceptability of drug products is a function of both the initial flavor quality (ie, first 10 to 20 seconds following ingestion) and the aftertaste (ie, 1 to 10 or more minutes following ingestion). Get one of them wrong and palatability suffers. In general, this requires that the positive sensory attributes of the flavor system (specifically sweet basic taste and flavoring aromatics) be perceived at a stronger intensity than the negative sensory attributes (eg, bitterness) initially and throughout the aftertaste.

Time/intensity sensory profiles of four marketed prescription drug products will be used to illustrate the concept (Figures 2-5). Experienced pharmaceutical sensory panelists evaluated the four drug products using the Flavor Profile intensity scale, which ranges from none (0) to strong (3) and is defined with reference standards. For each drug product, the average intensity of the critical sensory attributes (bitter, sweet, and flavoring aromatics) is plotted as a function of time for 10 minutes. The area above a slight intensity (>1) has been shaded. In general, attributes at a slight intensity or greater can be readily perceived by most patients. Ideally, the negative attributes, in this case bitter, should be below a slight intensity, and the flavor system attributes (sweet basic taste and flavoring aromatics) should be greater than the perceived bitterness at each point in time.

The API shown in Figure 2 is not very bitter; most patients would not perceive the bitterness as it is well below a slight intensity. The flavor system (flavoring aromatics and sweet basic taste) provides complete coverage of the bitterness initially and throughout the aftertaste and will be readily perceptible to patients to about 5 minutes. This drug product is a pediatric antibiotic oral suspension and is widely considered by parents and pediatricians to be the "gold standard" of palatability based on ease-of-dose administration to children 2 years and older.

The API in the drug product illustrated in Figure 3 is more bitter than in the previous example but not extremely so. The problem is that the flavoring aromatics and sweetness decay quickly, exposing the bitterness, which remains above the "concern" intensity (>1) throughout the aftertaste. The challenge is to shift the sweetness and flavoring aromatics decay curves upward such that they are at or above the bitterness profile at each point in time. Fundamentally, this requires optimization of the flavor system to increase its initial impact and duration, a fairly straightforward exercise given the relatively low taste-masking challenge of this API.

The flavor system of the drug product shown in Figure 4 provides no coverage of the bitterness initially or at any point in the aftertaste. Unfortunately, the API is quite bitter with a relatively flat decay curve, which further exacerbates the problem. This API represents a difficult taste-masking challenge and would require complete reformulation of the excipient system in order to improve palatability. More specifically, this will require optimization of the sweetener system, necessitating the use of one or a combination of high-intensity sweeteners plus an underlying aromatic support system to extend the flavoring aromatics further into the aftertaste.

The drug product illustrated in Figure 5 represents an extremely difficult taste-making challenge. The flavoring aromatics and sweetness decay quickly, exposing the bitterness, which starts above the "concern" level (>1) and increases in intensity throughout the 10-minute aftertaste. In this case, the API is encapsulated, and the coated particles tend to get stuck between the teeth and under the gum line. As the coating dissolves, the extremely bitter API is continually released in the oral cavity where it binds strongly to the taste receptors. Food and beverages do little to ameliorate the bitterness of this drug product – a truly unpleasant dosing experience for patients of any age but particularly children. The flavor system of this product can certainly be improved; however, optimization of the coating system or another technology approach would be required to achieve a step-change improvement in palatability.

BUILDING A PALATABLE FORMULATION

Developing a palatable drug product is akin to building construction. As shown in Figure 1, the first step is to develop a solid foundation or base formulation. The base formulation consists of the API plus all of the excipients required for a commercial dosage form (buffers, preservatives, suspending agents, disintegrants, processing aids) plus the excipients added to improve palatability. The objective is to develop a "white" (unflavored) base. A "white" base exhibits balanced basic tastes (sweet, sour, salt, and bitter), which is the underpinning of taste-masking. The concept is to "blend away" the critical sensory attributes of the API, typically bitterness, through the selection and screening of appropriate excipients. It is particularly important at this stage to develop a robust sweetener system that produces a sweetness profile that closely matches the bitterness (or other critical attribute) profile of the API. Candidate excipients are selected based on knowledge of their sensory characteristics in the dosage form of interest. Screening experiments are then conducted to determine the applicability of the candidate excipients and to establish preliminary usage levels. To minimize human exposure of drug substances, it is often desirable to work with a Generally Recognized as Safe (GRAS) mimetic or surrogate for the API during the development process. In these situations, a preliminary step is required wherein an appropriate mimetic is identified and its usage level established to match as closely as possible the critical sensory attribute(s) of the API.

The next step is to develop the flavor system. The objective is to improve the coverage of the critical sensory attributes in the initial flavor and aftertaste by building a well-blended and full-bodied flavor. A structured approach is followed to select flavoring ingredients. To begin, reputable flavor suppliers that serve the pharmaceutical industry are asked to submit samples based on a description of the projects technical requirements. Experienced sensory panelists screen the

aroma of candidate flavorings to eliminate those with a low or inappropriate aromatic identity or the presence of off-notes, eg, solventy, soapy, aldehydic characteristics.

Flavoring materials that pass the initial aroma screening are then formulated into the pre-optimized (mimetic) base from the previous step. The flavor quality of the resulting prototypes is evaluated by the sensory panelists for key attributes, such as aromatic identity and intensity, balance (blend) and fullness (complexity), lingering flavor aromatics and sweetness, bitterness masking, mouthfeel characteristics, and off-notes. Often, multiple flavoring materials are required to provide the required degree of coverage.

The final step is to combine the most promising excipients from the previous two steps and optimize the usage levels of all excipients. No new excipients are introduced during this step; however, individual excipients may be dropped if their contribution to the overall palatability of the formulation is determined to be limited. Designed experiments may be employed to efficiently optimize the formulations, with the sensory panels evaluating the resulting prototypes for the aforementioned attributes.

BEYOND THE BENCHTOP

When a series of palatable flavored formulations have been developed, acceptance testing may be conducted to down-select to the subject-preferred (patient or healthy volunteer) prototype (Stage III). Most companies elect to advance a primary and back-up flavored formulation in the unlikely event of a compatibility issue with one of the flavor system excipients. In addition, manufacturers are advised to measure and monitor the sensory quality of the prototypes during manufacturing process development and scale-up to ensure that the flavor quality does not deviate from the original specification. Finally, sensory evaluation of stability samples is often conducted to ensure the flavor quality of the drug product is acceptable not just upon manufacture but also at its expiry date.

OPPORTUNITY

Advances in oral drug delivery technology continue to yield important medical benefits ranging from faster onset of action and improved side-effect profiles to more convenient dosage forms. However, many of these technologies have their own sensory challenges that will need to be addressed in order to fulfill their promise. While in vitro techniques, such as the "electronic tongue" are available, these techniques are of limited value to developers, particularly in the absence of correlations between human taste panel and instrumental responses for the specific API of interest. Additionally, advances in our understanding of the biochemistry of taste and odor perception may one day result in the discovery of new chemical entities that ameliorate the negative sensory attributes of many drug substances. In the meantime, drug developers would be well served by mining the food science and technology literature for information on quantitative sensory analysis, flavor construction, and the sensory characteristics of ingredients (excipients) in various formulation systems, all which are critical to developing palatable drug formulations. Palatable drug formulations improve the prospects for patient dosing compliance, which translates to improved health outcomes and increased product sales.

REFERENCES

1. Meilgarrd MC, Civille GV, Carr BT. Thomas. Sensory Evaluation Technique. 3rd ed. Boca Roton, FL: CRC Press;1999.

2. Neilson AJ, Ferguson VB, Kendall DA. Profile methods: Flavor profile and profile attribute analysis. In: Moskowitz H, ed. Applied Sensory Analysis of Foods. Vol. 1. Boca Raton, FL: CRC Pre3ss;1988.

BIOGRAPHIES

Mr. Jeffrey H. Worthington is Founder and President of Senopsys LLC, a specialty services firm dedicated to the development of palatable pharmaceuticals. He has more than 20 years of experience in taste assessment and optimization and has contributed to the development of numerous prescription and over-the-counter medications. Mr. Worthington is a frequent author and speaker on the subject of developing palatable pharmaceuticals and serves on the National Institutes of Health's Best Pharmaceuticals for Children Act – Pediatric Formulation Initiative. Prior to founding Senopsys, Mr. Worthington was Vice President of Pharmaceutical Technology at Arthur D. Little, Inc. He earned his BS in Chemistry from Northeastern University and his MBA from Babson College.

Mr. David A. Tisi is Technical Director at Senopsys LLC. Mr. Tisi is a trained descriptive sensory panelist and formulator with experience developing palatable foods and pharmaceuticals. Having spent his career at the intersection of food and pharmaceutical technology, he has particular expertise in applying food technology to the development of novel pharmaceutical dosage forms. Prior to joining Senopsys, Mr. Tisi was a Scientist at TIAX LLC, where he managed and executed projects to improve the sensory quality of food and drug products. He earned his MS in Food Science from Cornell University.

DRUG DELIVERY Catalent Executive

CATALENT PHARMA SOLUTIONS: A WORLD LEADING PROVIDER OF ADVANCED DRUG DELIVERY TECHNOLOGIES & SERVICES

Mr. David Heyens
Senior Vice President, Global Sales
Catalent Pharma Solutions

"Because of our experience, world-class experts, technologies, and extensive customer base, we fully understand the challenges our customers face. And we're here to help solve them. We believe we can deliver more effective solutions for our branded drug partners, more quickly, and help generate higher value results than anyone else."

Catalent Pharma Solutions is a leading provider of advanced dose form and packaging technologies as well as drug development, manufacturing, and packaging services for pharmaceutical, biotechnology, and consumer health companies in nearly 100 countries. Formerly known as Cardinal Health's Pharmaceutical Technologies and Services segment, Catalent Pharma Solutions recently became an independent company. Catalent is the world's leading drug delivery technology provider with more than 70 years of formulation and manufacturing expertise. Drug Delivery Technology recently interviewed Catalent's David Heyens, Senior Vice President, Global Sales, to learn more about the company and how Catalent helps companies find solutions to some of the key challenges facing the industry today.

Q: Can you provide a brief overview of Catalent's drug delivery technologies and services?

A: We have a long history in advancing the delivery of drugs, through the use of advanced dose forms, advanced drug formations, and advanced packaging technology. We offer product development expertise for virtually every route of administration, including oral, injectable, respiratory, nasal, topical, ophthalmic, otic, and other routes. We also hold more than 1,000 patents and patent applications covering advanced dose forms, formulations, and packaging, and a network of more than 1,000 scientists globally.

Catalent commercialized softgel capsule

technology, developed the advanced Liqui-Gel® technology, created the "fast-dissolve" dosage form with Zydis®, and introduced the vegetable-based capsule VegiCaps® Soft. We offer a range of advanced controlled-release technologies, including EnCirc™ for higher drug loading and EnSolv™ for improved dissolution, plus conventional CR formulation expertise. We also have an advanced protein expression technology, GPEx®, which is being used to create advanced biologics. Supporting all of this, we provide analytical chemistry services, clinical supplies production and management, regulatory consulting, and commercial-scale manufacturing and packaging.

Q: How has your company's recent introduction as Catalent Pharma Solutions affected the services it offers to the industry?

A: Although we now operate as an independent company with a new name, all of our world-class drug delivery and development services, production, customer service, and quality operations remain the same. We remain committed to our business and to serving our customers.

Q: What do you see as the key industry trends and issues that will impact the pharma and biotech markets throughout the next 5 years?

A: With more sparse near-term branded pipelines, greater reimbursement challenges, and fewer blockbuster drugs, companies of all sizes are seeking better solutions to make every single molecule as successful as possible. Big pharma no longer chooses only the most likely molecules to develop, but tries to develop every one that has the potential for success, or licenses them out to another company. Molecules are increasingly more targeted and specialized, therapeutic indications are focusing more on niche treatments, and compounds are more often posing formulation and clinical challenges. As a result, advanced dose forms and formulations have become even more critical in helping to solve many current industry issues, and the industry seems more willing to go outside to find technology solutions. Another major trend is the need to balance globalization with the need to understand and shape products for local markets, payors, and consumers. Companies must design products that can provably add value to support favorable formulary access and pricing for prescription drugs. In the consumer health arena, local market understanding and rapid, proactive innovation will determine who wins and who loses. Choosing the right delivery technology and outsourcing partner – one like Catalent who understands the impact that every development stage choice can have on ultimate outcomes – will be critical for future success. Finally, one of the growing issues facing the industry today is the growth of drug counterfeiting worldwide. The problem affects drug makers and patients in virtually every country around the globe to some degree. Catalent is taking a

leadership role here, both for prevention and detection of counterfeit drugs. Advanced dose form and packaging technology can play a role in combating counterfeit products.

Q: In this challenging environment, how does Catalent help companies find solutions and bring value to the industry?

A: We help companies increase the productivity of their pipeline with advanced dosage forms and formulations, and with innovative packaging technologies, that enable them to consistently produce products with more value, measured by improved clinical and market outcomes. Catalent's experts can help customers get maximum productivity from their pipeline and improve the odds of the clinical success of their compounds. Branded companies choose our expertise and technology platforms not just for product differentiation, but mainly to improve patient outcomes, which ultimately drives product success.

With our vast global knowledge and local expertise in nearly all parts of the world, we intimately understand and are well equipped to deal with the global challenges our customers face. Our worldwide network of quality and regulatory professionals helps ensure regulatory compliance through every step.

For years, Catalent has been planning and implementing leading-edge technologies to combat counterfeiting. Our anti-counterfeiting capabilities include leading techniques available today – overt and covert packaging technologies, advanced dose forms that are difficult to counterfeit, e-Pedigree programs with RFID and 2D bar codes, and forensic analytic science expertise for detection.

Finally, one of the most important things we offer our customers, whether they are large or small, is reliable solutions, consistently delivered. We believe this ultimately has led to a high degree of confidence from our customers in our ability to deliver. All the advanced technology in the world is of little value if the technology partner is not dependable. Because we have been serving this industry for so long, in so many ways, we have learned what to expect, ask, and anticipate, and we try to use all of that experience for the benefit of our customers.

Q: How does Catalent help companies develop products with improved outcomes and achieve favorable reimbursement status?

A: The value of any drug delivery technology to customers today lies first and foremost in how well it can help enhance the therapeutic effectiveness of drugs that use it. This is a bit different than a decade ago, when advanced delivery technologies were most frequently used to provide simple-line extension differentiation. In today's challenging reimbursement environment, with many "me too" type drugs competing for the same patient share, customers are looking to exploit every path to differentiate based on outcomes, including through the dose form they use.

There is substantial research showing that every choice about

dose form and packaging configuration made in the drug development process can impact patient outcomes. Our research with physicians, pharmacists, payors, and patients indicates that medication compliance – patients taking the drugs the way they are supposed to – can be influenced by seemingly small things, like dose form color or size, or by packaging confirmation. We help customers make dose form and packaging decisions that can help improve outcomes every step of the way. We also recommend that customers build outcome optimization thinking earlier into clinical strategy, incorporating advanced dose forms and packaging into clinicals in order to drive differentiated results.

Q: What are the most common reasons companies choose to partner with Catalent?

A: Above all – for our technologies, our expertise, and our global reach. In 2008, we will celebrate 75 years of experience in providing the high degree of consistent performance and regulatory assurance customers in pharma and consumer health need. Our depth of knowledge and breadth of resources is unparalleled, as is our track-record of making the difficult possible by bringing even the most challenging molecules to market.

Companies also choose Catalent because our experts partner with them in a collaborative way for solutions. With so many available options, we can often recommend and implement the most efficient, most effective pathway to clinical and commercial success. Customers can benefit from working with a single, reliable, experienced supplier who understands their needs, which makes their job easier. And by working with a single supply source, customers save considerable time from screening and managing individual suppliers, with multiple hand-offs and multiple failure points.

Finally, Catalent's track-record for quality, regulatory compliance, and consistent performance over decades is a key reason why customers of all sizes come to us. We understand that our customers are placing some of their most important assets into our care — at times a specific project's success may determine the future prospects for an entire company, and hundreds of employees. We approach our customers' projects and products with the same care, creativity, and quality as if they were our own.

Q: Please explain how you work with customers.

A: We build strong relationships with our customers. We discuss their needs and concerns, help them develop ideas for new products and strategies for bringing their product to market in the most advantageous way, considering competitive threats, costs, dose form, and packaging to ensure patient compliance.

Q: Tell us about your sales force. How do you make sure your reps truly understand a customer's needs and offer relevant solutions?

A: First and foremost, we believe our sales team has the broadest experience base in the industry. We have pharmacists and PhDs, inventors and drug marketers, regulatory experts, and formulators, all properly trained and engaging with customers every day. Because our sales team understands our customers' issues, they can more readily help resolve them. Also, we provide our sales team the skills and market-based training they need, and access to comprehensive market intelligence resources to help them fully understand the challenges our customers face.

Second, we have taken a close look at our customer base, and segmented it to ensure the right alignment of sales resources and customers, based on the customer's current and future strategy and needs.

Finally, we have a hybrid structure that combines integrated account executives, who represent all of our offerings and solutions; strategic account executives, who focus on our largest customers; and technical sales specialists, who bring a depth of experience with one delivery system or service to a customer's specific need.

Q: Why did you choose the name "Catalent"?

A: The name was created to combine the ideas embodied in catalyst and talent – what we do for our customers, and how we do it. Catalent serves as a catalyst for our customers' success, enabling them to make the most of their product. Talent focuses on our people – the unique breadth and depth of scientific, operational, regulatory, and both global and local market expertise.

Q: What are the key messages you want to convey to DDT readers?

A: Because of our experience, our world-class experts, our technologies, and our extensive customer base, we fully understand the challenges our customers face. And we're here to help solve them. We believe we can deliver more effective solutions for our branded drug partners, more quickly, and help generate higher value results than anyone else. And, the earlier we're involved during a product's development, the better those results are likely to be, because nearly every single choice made can impact a product's future value. We're ready to help – give us a call. ◆

Technology Showcase

Dose by Dose Counter

The 3M™ Integrated Dose by Dose Counter provides an accurate, customizable, patient-friendly solution to guidance issued by the Food and Drug Administration (FDA) requiring dose counters for pressurized Metered Dose Inhalers (pMDIs). The robust design eliminates over- and under-counting, while the familiar look and clear display allows patients to use the device with no additional training. It's compatible with most valves and can be modified to fit your needs. By combining the 3M™ Integrated Dose by Dose Counter with our global regulatory experience, 3M can help smooth the integration process to add a dose counter to your programs. For more information, contact 3M Drug Delivery Systems at (800) 643-8086 or visit **www.3m.com/dds.**

Liquid Silicone Rubbers

Dow Corning® S Series liquid silicone rubbers are designed, tested, and supported for implants of 29 days or less. They also are appropriate for disposable applications in IV sets and catheters and for a variety of components, including valves and O-rings. The chemistry of the S Series LSRs is similar to that of Dow Corning's existing LSRs and is consistent across the three new products — Dow Corning® S40 Liquid Silicone Rubber, Dow Corning® S50 Liquid Silicone Rubber, and Dow Corning® S70 Liquid Silicone Rubber. The framework of this chemistry set incorporates most of the same polymers but now optimizes the chemistry from a molecular level, resulting in a stronger, more consistent material. S Series LSRs reach their ultimate physical properties upon initial cure with no drift. For more information, contact Dow Corning Healthcare Solutions at (989) 496-4000 or visit **www.dowcorning.com/healthcare.**

Development & Manufacturing

Coating Place, Inc. is a privately owned drug delivery systems development and manufacturing company specializing in Wurster fluid bed microencapsulation of powders, granules, crystals, and beads. Other coating capabilities include softgels, hard shell capsules, and tablets. Our services include contract formulation development, technology transfer, scale-up, and commercial manufacturing in a GMP environment with analytical support. Applications include controlled oral delivery, such as enteric, delayed, or sustained release, moisture or oxygen barrier and taste-masking applications for Rx, OTC, and controlled substance products. Our facilities process solvent, aqueous, and hot melt formulations. Our creative and innovative staff is ready to take on your toughest projects. For more information, contact Coating Place, Inc. at (608) 845 9521 or visit **www.encap.com.**

Packaging Solutions

Bilcare™
Pharma Packaging + Solutions

Bilcare is a global provider of innovative packaging materials and solutions for the pharmaceutical industry. We partner with our customers and support them with a broad portfolio of film- and foil-based packaging materials to provide their drugs with the optimum protection and shelf-life as well as with specialty materials and solutions for brand protection and enhancement of brand identity. We provide research services that enable our clients to develop the optimum package by quantitatively determining the failure mode of new and existing applications using an innovative stability evaluation protocol that reduces time, cost, and resource loading. For more information, contact Remco van Weeren, PhD, at Bilcare, Inc. at (610) 935-4300 or visit **www.bilcare.com.**

Technology Showcase

Orally Disintegrating Tablets

AdvaTab® is a new generation of ODT technology that offers distinct advantages and unique applications – unparalleled taste, flexible dosing, modified release, and a robust tablet. AdvaTab can be combined with Eurand's leading Microcaps® taste-masking technology to provide an ODT with superior taste and mouth-feel. AdvaTab tablets dissolve rapidly in the mouth within 15 to 30 seconds, and the smooth mixture of carrier excipients and taste-masked drug granules is suitable for delivering high drug doses. Modified-release drug granules can also be incorporated into the AdvaTab dosage form to provide a fast-dissolve tablet with sustained-release properties. AdvaTab tablets can be packaged in either bottles or push-through blisters. For more information, contact Eurand at (937) 898-9669 or at **bizdev@eurand.com.**

Pharma Development Services

It is critical for a service provider to meet the technical, financial, and timing demands of projects and offer clients first-class expertise and capabilities throughout the world. The Glatt Group has been supplying solid dosage technology, equipment, integrated systems, and processing expertise to the global pharmaceutical industry for the past 50 years along with the highest level of support and commitment possible. Glatt uses this extensive experience to provide solutions to partners from the initial concepts in product and formulation development through process scale-up to commercial manufacturing of solid dosage products. With facilities in New Jersey, Germany, and Switzerland, Glatt is uniquely positioned to apply its considerable solid dosage development and manufacturing assets to major markets within the industry. For more information, contact Glatt Pharmaceutical Services at (201) 825-8700 or visit **www.glattpharmaceuticals.com.**

Airless Bottle

LABLABO's new EasyFoil bottle is fitted with a pouch consisting of an aluminum multilayer film rolled up and welded around a superior ring and an inferior cup, both produced in a thick plastic material. The film is composed of an exterior PET layer and an interior PP or PE layer wrapping a central aluminum layer of 12 microns in thickness. Depending on the nature of the product used, the internal layer choice will be PP or PE, the ring and cup being produced in the same material with a sufficient thickness to provide a perfect barrier, especially against oxygen or UV. EasyFoil accepts the most viscous products (> 100.000 cps) and the most fluid (alcohol) and offers excellent restitution, the bottle could be used upside-down, precise dosage delivery, or containment of the pouch at a stand still position, an ideal packaging for transdermal applications. For more information, visit Lablabo at **www.lablabo.com**, or e-mail l.khoury@lablabo.fr.

Controlled Delivery Platform

SCOLR Pharma applies its patented CDT® Controlled Delivery Technologies to develop formulations for companies with pharmaceutical, OTC, and nutraceutical products. These elegantly simple technologies can be used for controlled-release periods for up to 24 hours and can be manufactured using readily available standard materials and conventional production equipment. SCOLR Pharma partners with companies under contractual arrangements that include licensing fees, royalties, manufacturing contracts, or other mutually agreed upon financial arrangements. SCOLR Pharma's CDT® has the many distinct advantages, including highly programmable (capable of a wide range of release profiles), easy to manufacture (employs conventional manufacturing equipment), cost effective (utilizes standard tableting excipients), higher payload (when compared to other technologies), and strong patent protection (full patent life and easy enforcement). For more information, visit SCOLR Pharma at **www.scolr.com.**

Technology Showcase

Transdermal Delivery

Aveva is a leader in transdermal drug delivery systems with global resources and operations that make it a quality company to partner with. Featuring a state-of-the-art facility (over 117,000 sq. ft.) located in Miramar, Florida, Aveva offers a full range of services, including a core competency in global research and development, along with fully equipped blending, coating, and packaging capabilities. Aveva has an excellent record of regulatory compliance and comprehensive quality systems. Aveva's qualified team includes Nitto Denko's global subsidiaries that can make a tremendous impact on your projects in a timely manner. For more information, contact Robert Bloder at (954) 624-1374 or visit **www.avevadds.com.**

Pharmaceutical Product Development

Licensing opportunities for PharmaForm's patented transdermal and transmucosal delivery systems are available. PharmaForm's proprietary delivery platform is a versatile polymeric delivery system that can be applied to many drug candidates and product applications. The company's Drug Delivery Technology team is integrated with formulation development, analytical, materials, and manufacturing groups to develop and optimize transdermal systems. The Formulation and Product Development and Analytical groups work closely to plan and execute the numerous facets of system development activities. After formulation development, clinical assessment, and final formulation selection is complete, PharmaForm can scale-up your product for commercial manufacture. PharmaForm will combine its pharmaceutical expertise, formulation chemistry, and long history of know-how to develop a high-quality transdermal drug delivery system for your market application. For more information, contact PharmaForm at (512) 834-0449 or visit **www.pharmaform.com.**

Spray & Dispensing Systems

Ing. Erich Pfeiffer GmbH, based in Southern Germany, is a leading manufacturer of pharmaceutical spray and dispensing systems. The Pfeiffer product range is extremely versatile and offers dispensers for nasal, oral, and topical drug administration. Specific user needs are met by a choice of mechanical or electronic devices for multidose, unitdose, and bidose applications. More than 5 decades of experience, dedicated innovation, and an uncompromising commitment to quality are behind the Pfeiffer dispensing systems, which are supplied to customers across all five continents. Customer requirements are integrated into the development process from the very early stages to ensure that user needs for safe, easy, and effective drug administration are met. Building on these strong foundations, Pfeiffer is committed to researching new systems for future therapies and applications. For more information, contact Pfeiffer of America at (609) 987-0223 or visit **www.pfeiffer-group.com**.

Cyclo Olefin Polymers

Zeon Chemicals L.P. is a wholly owned subsidiary of Zeon Corporation of Tokyo, Japan, a world leader in specialty elastomers, polymers, and specialty chemicals. Zeon Corporation is one of the top producers of polymers in the world with plants in Asia, North America, and Europe, and Research and Development laboratories in Kawasaki (Japan), Louisville (KY, US) and Barry (UK). Zeon Chemicals, headquartered in Louisville, offers ZEONEX® Cyclo Olefin Polymers (COPs), which are designed to protect the world's most valuable protein-based drugs and contrast media. Pure and exceedingly clear, ZEONEX can even be steam sterilized. When you need superior quality, demand nothing less. For more information, contact Zeon Chemicals at (877) 275-9366 or visit **www.zeonchemicals.com/medical2.**

Technology Showcase

Innovative Dosage Forms

CAPSUGEL®
Quality
People and Products Working Together™

Capsugel® is the world's leading supplier of two-piece capsules. With over 140 years of production experience, Capsugel offers formulation services, patented dosage delivery technology, and liquid and precision powder-filling equipment. The new Xcelodose® system creates clinical trial batches in precisely dispensed amounts as low as 100 micrograms. With Xcelodose, capsules can be filled with drug substances alone, eliminating the need for excipient compatibility and preformulation activities. Capsugel supports clinical development with the CFS 1200™ capsule liquid-filling and sealing bench top machine for R&D Labs as well as 100- and 300-hole benchtop fillers. Products include two-piece capsules in gelatin, pullulan, and HPMC; Licaps® liquid capsules; softgels; PCcaps® for preclinical animal studies; and DBcaps® for double-blind comparator trials. For more information, visit Capsugel at **www.capsugel.com**.

Oral Delivery

EUDRACOL® provides targeted drug delivery direct to the colon, with delayed and uniform drug release. The system consists of several layers. At the center is a core containing the active, which is enclosed in several layers of EUDRAGIT®. The first layer allows the tablet to pass through the stomach intact and be conveyed via the small intestine to the beginning of the colon. The switch from the acid environment of the stomach to the alkaline environment of the intestine causes the outer protective layer to dissolve. During further passage through the colon, the next layer becomes permeable due to the basic pH value and the presence of fluid. Water can then penetrate this layer, causing the drug to diffuse from the core and be absorbed by the intestinal wall. For more information, visit **www.pharma-polymers.com** or call (732) 981-5383 or +49-6151-18-4810.

Liposome Preparation

The LIPEX Extruder™ was introduced in 1985, and it quickly became the standard for the preparation of laboratory-scale liposome formulations. The 10-mL unit was supplemented with 100- and 800-mL units to facilitate scale-up and GMP production. NLI introduced the 142- and 293-mm filter-holders, which were designed for large-scale (10 to 100 L) liposome production. The company now develops and produces custom-designed equipment for large-scale manufacturing. An ever-expanding customer base has made LIPEX™ technology the equipment of choice that provides seamless scale-up from research to clinical manufacturing. For more information, contact Northern Lipids, Inc. at (604) 222-2548 or visit **www.northernlipids.com**.

Central Lab Services

P·B·I

Pacific Biometrics, Inc. (PBI) is announcing new Clinical Biomarker Services, which are designed primarily to support clinical development of biotherapeutics. These include validation of ligand-binding assays for immunogenicity testing by ELISA and MSD and multiplexing for novel biomarkers, in a regulatory-compliant environment. Established in 1989, PBI is a Specialty Central Laboratory with an established reputation as the premier lab with scientific expertise, reliable results, and outstanding client services for cardiovascular risk, diabetes, osteoporosis, arthritis, and inflammatory diseases. For more information, contact Pacific Biometrics, Inc. at (800) 767-9151 or visit **www.pacbio.com.**

DRUG DELIVERY Executive

DOW CORNING

DOW CORNING: GOING BEYOND THE SILICONE MOLECULE

With more than 40 years of experience in the healthcare industry, Dow Corning Corp. provides a range of materials that includes soft filling elastomers, high-consistency rubbers and liquid silicone rubbers, bonding, pressure-sensitive and soft skin adhesives, medical-grade tubing, polyurethane potting compounds, fluids, emulsions, and dispersions. Headquartered in Midland, Michigan, Dow Corning is equally owned by The Dow Chemical Company and Corning Incorporated. More than half of Dow Corning's annual sales are outside the United States. Drug Delivery Technology recently interviewed Scott Fuson, Vice President for Specialty Chemicals, and Global Executive Director for the Life Sciences Industry for Dow Corning. He shared how his company is going beyond silicon-based technology, where it is the industry leader, to being a customer-focused partner, innovator, and solutions provider.

Mr. Scott Fuson
Vice President for Specialty Chemicals
Global Executive Director for the Life Sciences Industry
Dow Corning Corp.

"Offering solutions requires deep customer relationships, based on trust and confidence. Also, customers must be certain that you are truly prepared and capable of addressing a wider range of their needs. Our sales staff listens to what the customer is trying to achieve and offers recommendations in areas where our expertise and experience can support their goals."

Q: Please explain how you are going beyond silicones?

A: We've always been good at perfecting science at the molecular level. Now, in addition to making the molecule better, we're using our technology and expertise to make our entire offering better by strengthening our customers' offerings. We've broken away from the notion that innovation means "new products." This doesn't mean we're deemphasizing products, because that's what we make and sell. It's really more about augmenting our product concepts and existing products by finding additional ways to innovate to serve the customer.

To do that, we take an outside-in approach. This involves first working to understand the needs and challenges of customers and identifying any emerging or unmet needs. Then we consider ways we can help customers deliver on their own brand promises, as defined by the market and the customer.

Offering solutions requires deep customer relationships, based on trust and

confidence. Also, customers must be certain that you are truly prepared and capable of addressing a wider range of their needs. Our sales staff listens to what the customer is trying to achieve and offers recommendations in areas where our expertise and experience can support their goals. We also learn about opportunities by talking with others inside and outside of customer companies to gain a better understanding and perspective of the macro issues they face.

Q: How do you prepare your team to "go beyond"?

A: We ensure that employees know we're all responsible for innovation. It's not only the responsibility of our R&D staff. We recently conducted a survey of our customers across the globe, and asked them who in their companies is responsible for innovation. Thirty-seven percent indicated that all employees are responsible for innovation. We certainly agree. In a similar poll at Dow Corning, almost 100% of our employees believe they are responsible for innovation. This response is indicative of our corporate culture of encouraging new ideas and collaboration.

It's important for companies to build on their own unique strengths and competencies and to continuously reinvent themselves, even when they are successful. This requires commitment, flexibility, and a hard look at your offerings in light of emerging customer needs and market opportunities. This approach has made us think differently about our business challenges and to constantly seek innovations that benefit our customers – and our customers' customers.

When combined with our global business structure that promotes the sharing of innovative thinking between geographies and business units, this mindset offers several advantages. One, we are positioned to take a big-picture view of the challenges and opportunities our customers face. Two, we're able to respond with a diverse range of solutions. And finally, employees are rewarded for their contributions to innovation and are therefore more loyal and engaged.

Q: How do you ensure that all interactions with a customer are consistent with the corporate brand promise?

A: First and foremost, you have to understand that you can't "failsafe" this. Over-controlling customer interactions can be detrimental. A good place to start is by defining the attributes and drivers associated with your brand. It's important to analyze all touch-points, or instances in which customers have an experience with your employees, products, business partners, or communications/advertisements, to ensure you're providing customers with experiences that match their exact needs. Most importantly, employees have to be engaged and committed, because they are the strongest advocates of delivering the brand promise. We make it clear to our employees that everyone is "customer-facing" – and therefore, an internal understanding of our brand is essential to delivering the brand promise.

Q: How do you know if the experience you offer customers matches each of their needs and wants?

A: The answer is to listen. You need to listen not only to what customers tell you in interactions and on surveys but also to the types of questions they're asking you. Customers are more loyal if you're capable of offering them robust, flexible options that meet their needs exactly. This requires employees who assess customer needs to be quick and nimble – and prepared to offer recommendations based on their experience and expertise.

Everyone associated with your brand, including business and channel partners, needs to understand the importance of his or her interactions with customers. At Dow Corning, we've worked hard to understand how to create customer value, and our corporate culture appreciates that our customers' success is our success. Understanding the "voice of the customer" gives us an "outside-in" perspective on what customers value. We also communicate customer successes throughout the company by sharing stories from the field to build confidence and understanding within our team.

Q: Does innovation success automatically translate into increased revenue?

A: That's a natural goal; however, I would add that margin growth, even if it does not immediately translate into revenue growth, is also an important outcome of innovation. Typically, when this happens, revenue builds over time; it's not automatic. The most common types of margin-boosting innovations are those targeted at reducing costs and opening new markets for products. For this reason, at Dow Corning, innovation extends far beyond research and development to how we do business, and sustained revenue and margin growth are our priority objectives.

Q: What systems can companies use to measure their innovation levels?

A: All companies need to have systems in place to evaluate the impact of their innovation activities across a number of areas. These range from new business models, brands, or products to financial offerings or processes. In many cases, these activities are incremental, not radical changes, so they don't necessarily require the creation of entirely new processes or business models. As such, a company can afford to take on a number of incremental innovations at one time. Due to the broad scope of innovations often included in a company's portfolio, systems to track and evaluate activities are critical. Monitoring progress and return on investment is necessary to ensure that the innovation portfolio is balanced.

Q: How can an organization's structure contribute to (or detract from) innovation competence?

A: The structure and culture of innovation must stem from the top of the organization, with the CEO. Innovation needs to be viewed as an important part of the company's overall growth portfolio. This sets the tone and can prevent potential concerns within an organization. Unfortunately, radical and disruptive innovation can be prematurely hindered by the actions of management and the corporate culture if the company is not structured with innovation in mind. This requires keeping a barrier between innovations and the current business to ensure the company delivers on its promises,

and customers' needs are met. At Dow Corning, we've established a business and technology incubator, creating an environment for these types of innovation to nurture. There are instances in which innovation needs to occur closer to the current business to ensure the project is adding value to the product, and it meets necessary time requirements.

Q: What criteria best evaluate the performance of one particular innovation?

A: I believe that three criteria work for understanding the performance of innovation activities. The first is "impact," which is measured by revenue and margin growth. The second is "return," which we measure as return on investment in terms of revenue and margin years after the innovation starts to produce revenue. The third is "success rate," which involves evaluating the portfolio and activities and gauging the actual impact versus predictions made at different points throughout the project's evolution process. This is more of a real options look, not a net present value analysis of the portfolio.

Q: How do you view partnerships as a way to "go beyond"?

A: A partner brings something that we don't have – a technology, a position in the value chain, or expertise that would take too long for us to learn. We know a little about that – Dow Corning was formed 60-plus years ago when The Dow Chemical Company and Corning, Inc. agreed to a 50/50 joint venture and shared the risk. We look at partnerships the same way. We enter them when we can't get the same value by ourselves. We work closely with a number of business partners and customers who want to invent state-of-the-art products, create advanced technologies, or develop new markets. Like us, they seek advances, even breakthroughs, in the creation of technical or market positions that currently don't exist.

It's important to have relationships with companies that have similar cultures and values. It is often more productive to work together on joint development rather than separately, so we seek collaborations with business partners and customers as models for how innovation can be moved forward.

In many cases, we share the learnings and value generated through the partnership between the two companies. We determine the value of selling our products as well as the value for our customers or partners in selling their products or advancing our joint business activity. We don't necessarily share the value of the final product or put everything into one pot, because, when it's a brand new application or market, you have no reference point.

Q: How do you help customers establish a robust quality system?

A: As a result of global initiatives, pharmaceutical manufacturing is currently transitioning from an art to a science. Also, pharmaceutical product suppliers increasingly are being asked to design quality into their products. As a global supplier of healthcare materials, Dow Corning works closely with customers to ensure these end-users have access to a wealth of technical expertise, technical data, and bio-safety information. Opportunities for exchange of information with our customers facilitates the qualification process and helps end-users ensure they are using the optimal products for their applications. Our industry offering includes adhesives, excipients, silicone

tubing, biopharmaceutical, and pharmaceutical products.

With additional regulatory and quality requirements for active and inactive pharmaceutical ingredients, it's increasingly important for suppliers to stay abreast of regulatory trends while partnering with pharmaceutical manufacturers to understand and meet their product needs.

Emerging regulatory trends for pharmaceutical products continue to focus on topics, such as global harmonization, process analytical technology (PAT), good manufacturing practices (GMPs), quality by design, science-based regulations, and risk-based pharmaceutical assessments. These initiatives challenge healthcare manufacturers to build quality and safety into their products from initial development and design through manufacture, launch and post launch surveillance. As a result, pharmaceutical manufacturers continue to place high expectations for improved raw material quality and safety on their suppliers. They are asking them to help define and build the proper level of controls into their manufacturing and distribution operations.

Q: What role do Good Manufacturing Practices play in today's global marketplace?

A: It is important to select products from a manufacturer that follows appropriate good manufacturing practices (GMPs) so that users can meet their requirements for safety, identity, quality, and purity. Appropriate GMP elements should be implemented for the entire manufacturing and packaging process — in our case, from silicon to silicone. If safety, quality, or purity comes into question, manufacturers should be able to easily and fully document the integrity of the materials from the supplier.

To ensure that these are maintained as pharmaceutical products become more numerous and complex, regulatory agencies around the world are systematically reappraising their approaches and are moving more toward risk-based decisions, science-based policies, and standards. They are also seeking integrated quality systems, international harmonization, and strong public protections.

At the same time, greater attention is being paid to guidelines, standards, and specifications and their role as blueprints for producing quality products that perform a specific function and ensure both efficacy and safety for patients. Although the ISO 9000 family of quality management standards has earned a worldwide reputation as a quality management system and delivers a valuable framework for quality, the standards mainly focus on the "what" rather than the "how" and the end result. In today's environment, it is essential for the healthcare industry to be able to manage and trace materials used in products throughout the entire supply chain.

For example, Dow Corning is unique as a supplier because of our integrated supply chain. We produce both silicone elastomers and silicone tubing at a site registered and audited by the United States Food and Drug Administration. This approach provides complete traceability from polymer compounding through tubing manufacture, under a quality system based on both ISO 9001:2000 and critical principles of GMPs. ◆

SPECIALTY PHARMA
Strategies For Business Development

Therapeutic Focus

Intranasal Insulin – A Potential New Treatment Modality for Diabetes Mellitus

By: **Robert M. Stote, MD, FACP**
Senior Vice President & Chief Medical Officer, and
Fred Feldman, PhD
Vice President of R&D, Bentley Pharmaceuticals, Inc.

Introduction

Diabetes mellitus is fast emerging as one of the most serious health problems facing society today.[1] As the United Nations' World Diabetes Day approaches on November 14, governments worldwide are acknowledging that, for the first time, a non-infectious disorder may now pose as serious a threat to global human health as major infectious diseases.

Diabetes results from the loss of the body's natural ability to produce and use insulin to maintain normal levels of blood glucose. Either the body produces no or insufficient insulin (type 1 diabetes), or the body cannot use the insulin it produces effectively (type 2 diabetes). The vast majority of cases (greater than 90%) are type 2. According to International Diabetes Federation estimates, roughly 246 million adults worldwide have diabetes. This number is projected to reach 380 million by 2025, representing more than 7% of the world's adult population.[2]

In the United States, it is estimated that nearly 21 million adults have diabetes. Of the total number of US adult diabetics, approximately 15 million have been diagnosed with the disease. The remaining 6 million adults face its potentially devastating effects, but have not been diagnosed and are not being treated.[3] Equally alarming is the fact that approximately 54 million people in the United States have pre-diabetes, a condition that raises the risk of an individual developing type 2 diabetes, heart disease, and stroke.[4] Some people with pre-diabetes have blood glucose levels higher than normal but not high enough to be classified as diabetics. This, combined with the nearly 21 million Americans who already have diabetes, means that approximately 25% of the US population is at risk for diabetes-related complications.[5]

Conventional Treatment

Because diabetes stems from problems with the production and supply of insulin in the body, insulin — delivered externally through subcutaneous needle injection — has been a primary means of maintaining blood glucose control since its discovery in 1922. The use of insulin is also very important for type 2 patients who are not adequately controlled on oral diabetes medications alone.

Insulin injection therapy aims to deliver through external intervention what a non-diabetic body produces on its own. Delivering the right amount of insulin at the right time maintains blood glucose levels at near normal levels, limiting severe long-term complications, such as blindness, kidney failure, and decreased wound healing. An excess of insulin, however, lowers glucose levels too rapidly, which may lead to hypoglycemia, a potentially dangerous short-term condition that can leave patients disoriented and at risk for seizure, coma, and death.[6]

Treatment is further complicated by psychological barriers that cause patients either to not begin or not adhere to their insulin regimens, including concerns about weight gain, hypoglycemia, and needle/injection phobia. Collectively, the reluctance to begin or maintain a lifetime insulin injection regimen has been termed "psychological insulin resistance."[7]

Current treatment progression typical for a type 2 diabetic includes the introduction of lifestyle modifications followed by the use of oral antidiabetic drugs, and then insulin injection therapy as a final step. Because of the time required to implement this stepwise approach, many patients will have had the disease for years and may have already developed complications.[8]

And although numerous studies have indicated that more effective glycemic control can significantly delay the progress of diabetes complications, approximately 50% of type 2 patients are not adequately controlled using a single oral therapy alone.[9-13] Many of these patients could benefit from a shift to insulin at this point in their treatment. However, they resist initiating a potentially valuable therapy and/or become non-compliant because of their aversion to injections.[14-16] A non-invasive delivery modality that avoids the anxiety of injections and encourages earlier adoption of insulin therapy has the potential to result in better blood glucose control and more favorable long-term outlooks.

The Alternative Insulin Delivery Landscape

Finding alternatives to insulin injection has been a major focus for the drug delivery industry. While transdermal insulin systems have shown promise and true oral delivery remains an area of significant interest, pulmonary delivery has moved ahead most aggressively with pharmaceutical development efforts.

Interest in delivering insulin via inhalation dates back to the 1920s, based on the lung being a large microvascular organ with a well-perfused surface for absorption as a potential target for delivery of therapeutics.[17] Several major pharmaceutical companies began developing inhaled insulin delivery systems.

Only one of these products has reached commercialization so far — the Exubera® Pulmonary Insulin Delivery System (Pfizer Pharmaceuticals and Nektar Therapeutics), which delivers insulin as a granulated powder to the deep lung and was approved by the FDA in 2006 for use in adults with both type 1 and type 2 diabetes. Observations of pulmonary lung function effects raised questions about long-term chronic pulmonary impacts, and patients entering enrollment require lung function testing with recommended periodic monitoring. Recent reports indicate that abnormal lung function effects disappear when use of the product is discontinued, but return when pulmonary treatment resumes.[18,19]

Several other products targeting pulmonary delivery are in Phase III trials and include the AIR® Inhaled Insulin System (Eli Lilly and Co. and Alkermes Inc.), the AERx® Insulin Diabetes Management System (Novo-Nordisk and Aradigm Corp), and Technosphere® Insulin (MannKind Corp.). All of these products consist of specifically formulated insulin delivered in a custom-designed inhaled delivery device.

The Intranasal Approach to Insulin Delivery

Since the 1980s, there has been a great deal of interest in the prospect of delivering insulin via the nasal mucosa. Drugs entering the nasal cavity are readily absorbed across the highly vascularized nasal mucosa directly into the circulatory system, avoiding hepatic first-pass metabolism and completely bypassing the lungs. For many drugs, intranasal delivery can provide for a fast rate of absorption and a rapid onset of action. Intranasal delivery is especially attractive for compounds, such as proteins and peptides, which would normally have to be injected.

With these evident benefits, the nasal mode of insulin delivery could be a more reliable method of maintaining glycemic control. It could also prove to be more convenient to use compared with larger sized inhalation devices and as a result, could improve compliance, particularly with adolescent patients.

The initial development of a clinically useful formulation was hampered by the generally poor bioavailability (1% to 2%) of this route of delivery, primarily due to the large size (5800 Daltons) of the insulin molecule, and by local irritation caused by these early formulations.[18-20]

Permeation Enhancement to Improve Bioavailability

In the past 2 decades, a number of agents were investigated for use as absorption enhancers to improve bioavailability in the development of intranasal insulin formulations. Without these absorption-enhancing agents, bioavailability was poor (1% to 2%). Following the addition of absorption enhancers to the formulation, bioavailability improved, with studies indicating systemic absorption as high as 10% to 15%.[21] However, the agents employed at the time — bile salts and derivatives, surfactants, fatty acids and derivatives, and various bioadhesive excipients — caused significant nasal irritation and compromised chronic use.[22-25]

An alternative permeation enhancer explored by Bentley Pharmaceuticals, Inc. was cyclopentadecalactone (CPE-215®), a compound that occurs naturally in plants (Angelica archangelica). CPE-215 has been a common additive in the food and cosmetic industries and is considered by the FDA to be a GRAS (generally recognized as safe) reagent for use in food and cosmetics. It appears to be significantly different from other compounds tested and does not appear to irritate the epithelial tissue of the nasal passage. This permeation enhancement technology was initially validated with small molecules, specifically testosterone, in a gel formulation that incorporates Bentley's CPE-215 excipient. The product, Testim®, was licensed to Auxilium Pharmaceuticals, Inc. It demonstrated significant improvement in testosterone dermal delivery and was approved for clinical use in the United States in early 2003. Testim has also been approved for clinical use in Canada and 15 EU countries.

Additional studies indicated that the technology could be extended beyond this small-molecule application to improve drug delivery of more complex higher-molecular-weight (greater than 1000 Daltons) compounds, especially therapeutic peptides for treatment of chronic diseases.

Studies on Nasulin™ Intranasal Spray Formulation

Early development work and animal studies on the insulin peptide (51 amino acids and a molecular weight of 5800 Daltons) conducted by Bentley indicated that CPE-215 allowed increased migration of insulin through the nasal mucosa.[26] Bentley's intranasal insulin formulation, Nasulin, is an oil-in-water emulsion formulation of regular short-acting human recombinant insulin dissolved in sterile water in combination with CPE-215 with mild non-ionic surfactants. CPE-215 enables the insulin in this formulation to pass more quickly through the nasal mucosa, delivering a larger payload than has previously been realized by other delivery systems, but without the nasal membrane irritation liabilities historically incurred by other methods. It is stable under refrigerated conditions for up to 2 years and stable at room temperatures for 1 month or more. This intranasal insulin formulation is administered in a multi-dose APF (Advanced Preservative Free) 100-microliter dose per spray device that is compact and easily transportable.

Animal toxicological studies conducted by Bentley in two animal species with three times per day nasal dosing for 3 months revealed no evidence of irritation or other pathology in the nasal mucosa with CPE-215 alone and in combination with insulin.[27] In a study performed in 2003, the Bentley intranasal insulin formulation was administered to eight healthy volunteers in the fasted state.[28] Plasma insulin levels peaked rapidly after approximately 10 to 20 minutes. Plasma glucose began to fall after 10 minutes, and reached a nadir 40 minutes

Global Clinical Supplies + Services. Integrated.

Our Promise

With Bilcare you will:

Work with an experienced and innovative business partner who shares your dedication, commitment and demand for excellence.

Receive clinical services that raise the standards of the industry.

Experience project management that delivers peace of mind.

+ **Clinical Supplies Project Management**
+ **Formulation Development**
+ **Analytical Research Services**
+ **Clinical Manufacturing, Packaging and Labeling**
+ **IVRS/IWRS**
+ **Global Logistics and Distribution**

Visit us at **AAPS Booth #128** to learn more about Bilcare Global Clinical Services

Bilcare™
Global Clinical Services

Americas + Europe + Asia

Your partner of choice for clinical supplies solutions worldwide

Call 800-310-4445, Email direct-gcs@bilcare.com or visit BilcareGCS.com today.

after dosing. A total of 11 doses of 25 IU were given to the eight subjects; the mean percent fall in glucose for this dose was 20.5%. This is comparable with the fall that might be expected following a subcutaneous injection of approximately 4 IU of insulin.[29] These results were consistent with an estimated relative bioavailability for the formulation of between 10% and 20%.

Similar results were obtained in a subsequent dose escalation study in patients with type 1 diabetes, using subcutaneous insulin or placebo as a comparator.[30] The relative bioavailability of intranasal insulin compared with subcutaneous regular insulin was 16.6% to 19.8% over 2 hours and 14.0% to 19.8% over 5 hours. At doses of 25 IU and above, a rise in serum insulin levels accompanied by a decrease in plasma glucose was seen. Peak insulin levels were again generally attained in 15 to 20 minutes and remained elevated for approximately 1 hour; the resultant effect upon glucose peaked at 40 minutes and waned 1.5 to 2 hours post-dosing. This intranasal formulation was generally well tolerated, and relatively well absorbed as demonstrated by a rapid rise in serum insulin level and concomitant reduction of plasma glucose levels.

Most recently, in a placebo-controlled Phase II pharmacokinetic study in patients with type 1 diabetes presented at the American Diabetes Association 67th Scientific Sessions in Chicago in June 2007, 12 patients receiving Nasulin demonstrated a more rapid onset of action than when they received either regular or fast-acting injectable insulins.[31] In addition, blood sugar levels for 2 hours after eating in patients treated with Nasulin were similar to those who received both injectable insulin formulations.

Researchers also presented results from additional Bentley-sponsored studies to determine if potential lung function parameters in smokers had any effect on the absorption of Nasulin (normal male smokers versus non-smokers). Nasulin was absorbed equally in a study of 18 smokers and 18 non-smokers, demonstrating more rapid onset of action than Humalog.[32]

Another study explored if there were any absorption differences due to the normal nasal cycles that occur between nostrils (alternating levels of mild congestion). When Nasulin was administered to different nostrils in 12 healthy male subjects, no significant differences in absorption were noted, although there was a slight trend in favor of the mildly congested nostril.[33] However, researchers concluded this difference is unlikely to be clinically important, and noted if nostrils are totally blocked, they should be cleared with gentle nose blowing before administration.

Adverse events reported in the smoking/non-smoking and dominant nostril studies included a total of four episodes of hypoglycemia in subjects receiving the investigational drug. In addition, some volunteers experienced transient, mild nasal irritation and/or watery eyes, which resolved rapidly. These transient findings were not consistently present with each dose, and were generally resolved within 15 to 20 minutes. None of these adverse events were deemed serious.

Onset of action with Nasulin was again favorable. In the type 1 diabetes study, patients' plasma insulin levels peaked sooner with Nasulin than with the very rapid acting Humalog and Humulin R (20 versus 53 versus 81 minutes). Compared with Humalog, Nasulin resulted in a greater decrease in plasma glucose concentration (AUC) in the first hour, with Humalog being slightly better in the second hour.

Bioavailability is a key consideration in assessing the efficacy of non-injected formulations of insulin, and the studies indicated that Nasulin performed well in this area. When administered to type 1 diabetes patients, the relative bioavailability of Nasulin versus Humalog was 17.0% over 1 hour and 8.7% over 2 hours. The relative bioavailability of Nasulin versus Humulin R was 26.5% over 2 hours. In addition, the absorption of Nasulin was not affected by smoking in the study of normal male smokers and non-smokers.

The encouraging results of these clinical studies demonstrate the positive pharmacokinetic, glucodynamic, and bioavailability properties of nasal administration (Nasulin compared with injected insulin).

Summary

For more than 2 decades, the medical community has been searching for a less-invasive and patient friendly method for treating diabetes. Intranasal delivery of insulin has the potential for significantly better patient compliance than a routine of insulin injections and may facilitate earlier entry into therapeutic regimens for patients reluctant to administer insulin by injection, potentially resulting in delayed onset of diabetes complications. Beyond diabetes treatment, this technology has the potential to extend delivery of a number of other complex molecules that address a wide variety of metabolic, neurological, and other serious medical problems. The technology has now been granted patent coverage, both for diabetes applications as well as for intranasal drug delivery of pharmaceutically active peptides, peptidominetics, and proteins. ■

References

1. Diabetes Atlas, third edition, International Diabetes Federation, 2006.
2. Diabetes Atlas, third edition, International Diabetes Federation, 2006.
3. 2001–2003 National Health Interview Survey (NHIS), National Center for Health Statistics, Centers for Disease Control and Prevention, estimates projected to 2005.
4. Cowie CC, Rust KF, Byrd-Holt DD, Eberhardt MS, Flegal KM, Engelgau MM, Saydah SH, Williams DE, Geiss LS, Gregg EW. Prevalence of diabetes and impaired fasting glucose in adults in the US population: National Health and Nutrition Examination Survey. 1999-2002. Diabetes Care. 2006;29:1263-1268.
5. U.S. Census Bureau: 2000 resident population estimates.
6. National Institute of Diabetes & Digestive & Kidney Disease (NIDDK): National Diabetes Information Clearinghouse (NDIC).
7. Korytkowski M. When oral agents fail: practical barriers to starting insulin. Int J Obes Relat Metab Disord. 2002;26 (Suppl 3):S18-S24.
8. Nathan DM. Clinical practice: initial management of glycemia in type 2 diabetes mellitus. N Engl J Med. 2002;347:1342-1349.
9. DCCT Research Group: The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the Diabetes Control and

Getting to market should feel like a sprint, not a marathon.

[And our skilled team will make every transition successful – from start to finish]

Global Manufacturing Services

- **Chemical**
- **Chiralitree®**
- **ResCom®**
- **Fermentation Technologies**
- **Finished Dosage Form**

That's why you need Team DSM. DSM Pharma Chemicals excels in seamless transitions from one stage of a product's development to the next. From our detailed cGMP workflow management systems to our self-auditing control procedures, DSM Pharma Chemicals is always aware of your product's status in the development and scaling-up process. So when you're a customer, rest assured that your product is fully documented and prepared on time, exactly as ordered, for manufacture (and a first place finish). But that's just part of the DSM package of solutions.

At DSM, we deliver comprehensive custom manufacturing services from start to finish for the entire spectrum of pharmaceutical companies throughout the industry. And that's the *real* value of working with DSM Pharma Chemicals.

So start with us and we're confident you'll stay with us.

VISIT US AT
CPhI
MILAN, ITALY OCT. 2 – 4
AAPS
SAN DIEGO NOV. 11 – 15

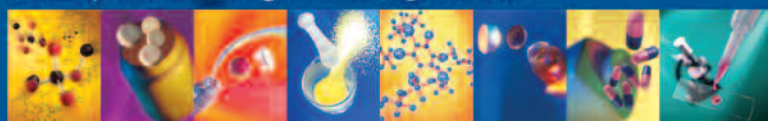
DSM Pharma Chemicals

PART OF DSM PHARMACEUTICAL PRODUCTS

DSM

www.dsmpharmaceuticals.com · telephone 973.257.8011
info.dsmpharmaceuticals@dsm.com

Relax, You're Right here **Right now**



Complications Trial. Diabetes. 1995;44:968-983.
10. Reichard P, Berglund B, Britz A, Cars I, Nilsson BY, Rosenqvist U. Intensified conventional insulin treatment retards the microvascular complications of insulin-dependent diabetes mellitus (IDDM). The Stockholm Diabetes Intervention Study (SDIS) after 5 years. J Intern Med. 1991;230:101-108.
11. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract. 1995;28:103-117.
12. UKPDS Group: Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998;352:837-853.
13. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus progressive requirement for multiple therapies. UKPDS Group: (UKPDS 49) JAMA.1999;281:2005-2012.
14. Zamanini A, Newson RB, Maisey M, Feher MD. Injection related anxiety in insulin treated diabetes. Diab Res Clin Pract. 1999;46:239-246.
15. Hunt LM, Valenzuela MA, Pugh JA. NIDDM patients' fears and hopes about insulin therapy: the basis of patient reluctance. Diabetes Care. 1997;20:292-298.
16. Gerber RA, Hauber AB, Bolinder B, Johnson FR. Diabetes patients' stated preference for insulin therapies: trading health for convenience. Diabetologia. 2004;47(suppl 1):A274.
17. Gansslen M. Uber Inhalation von insulin. Klin Wochenschr. 1925;4:71.
18. Moses AC, Gordon GS, Carey MC, Flier JS. Insulin administered intranasally as an insulin-bile salt aerosol: effectiveness and reproducibility in normal and diabetic subjects. Diabetes. 1983;32:1040-1047.
19. Salzman R, Manson JE, Griffing GT, Kimmerle R, Ruderman N, McCall A, Stoltz EI, Mullin C, Small D, Armstrong J. Intranasal aerosolized insulin: mixed meal studies and long-term use in type 1 diabetes. N Engl J Med. 1985;312:1078-1084.
20. Sinay IR, Schlimovich S, Damilano S, Cagide AL, Faingold MC, Facco EB, Gurfinkiel MS, Arias P. Intranasal insulin administration in insulin dependent diabetes: reproducibility of its absorption and effects. Horm Metab Res. 1990;22:307-308.
21. Hinchcliffe M, Illum L. Intranasal insulin delivery and therapy. Adv Drug Deliv Rev. 1999;35:199-234.
22. Duchateau GSMJE, Zuidema J, Merkus FWHM. Bile salts and intranasal drug absorption. Int J Pharm. 1986;31:193-199.
23. Ennis RD, Borden L, Lee WA. The effects of permeation enhancers on the surface morphology of the rat nasal mucosa: a scanning electron microscopy study. Pharm Res. 1990;7:468-475.
24. Merkus FWHM, Schipper NGM, Hermens WAJJ, Romeijn SG, Verhoef JC. Absorption of enhancers in nasal drug delivery, efficacy, safety. J Control Rel. 1993;24:201-208.
25. Agerholm C, Bastholm L, Johansen PB, Nielsen MH, Elling F. Epithelial transport and bioavailability of intranasally administered human growth hormone formulated with the absorption enhancers didecanoyl-L-a-phosphatidylcholine and a-cyclodextrin in rabbits. J Pharm Sci. 1994;83:1706-1711.
26. Bentley Pharmaceuticals, Inc. Data on file.
27. Bentley Pharmaceuticals, Inc. Data on file.
28. Leary AC, Stote RM, Breedt HJ, O'Brien J, Buckley B. Pharmacokinetics and pharmacodynamics of intranasal insulin administered to healthy subjects in escalating doses. Diabetes Technol Ther. 2005;7:124-130.
29. Drejer K, Vaag A, Bech K, Hansen P, Sorensen AR, Mygind N. Intranasal administration of insulin with phospholipid as absorption enhancer: pharmacokinetics in normal subjects. Diabet Med. 1992;9:335-340.
30. Leary AC, Stote RM, Cussen K, O'Brien J, Leary WP, Buckley B. Pharmokinetics and pharmocodynamics of intranasal insulin administered to patients with type 1 diabetes: a preliminary study. Diabetes Technol Ther. 2006;8(1):67-75.
31. Schwartz S, Ryan T, Carmichael C, Stote R. Interim results of a randomized, single-dose, 4-way crossover, pharmacokinetic study of intranasal insulin spray (Nasulin), injectable regular insulin (Humulin R), injectable fast-acting insulin (Humalog), and saline nasal spray in patients with type I diabetes mellitus. Oral presentation (abstract #36-OR) presented at the 67th Scientific Sessions of the American Diabetes Association, Chicago, IL, June 23-26, 2007.
32. Schwartz S, Ryan T, Carmichael C, Stote RM. Results of a randomized, single-dose, 2/3-way crossover comparison study of intranasal insulin spray (Nasulin) and injectable fast-acting insulin (Humalog) in normal nonsmoking and smoking subjects. Late-breaking presentation (abstract #02-LB) presented at the 67th Scientific Sessions of the American Diabetes Association, Chicago, IL, June 23-26, 2007.
33. Leary AC, Stote RM, Cussen K, O'Brien J, Leary WP, Buckley B. Intranasal insulin spray (Nasulin) in healthy subjects: choice of nostril. Poster presentation (abstract #467-P) at the 67th Scientific Sessions of the American Diabetes Association, Chicago, IL, June 23-26, 2007.

Robert M. Stote, MD, FACP

Senior Vice President & Chief Medical Officer
Bentley Pharmaceuticals, Inc.

Dr. Robert M. Stote became Senior Vice President and Chief Medical Officer of Bentley Pharmaceuticals, Inc. in March 1992 and served on the Board of Directors from 1993-2003. Prior to joining Bentley, Dr. Stote was employed for 20 years by SmithKline Beecham Corporation, serving in a variety of executive clinical research positions. Dr. Stote was Chief of Nephrology at Presbyterian Medical Center of Philadelphia from 1972 to 1989 and was Clinical Professor of Medicine at the University of Pennsylvania. Dr. Stote also serves as a Director of Datatrak International, Inc. and on the Scientific Advisory Board of NuPathe, Inc. He earned his Bachelor's degree in Pharmacy from the Albany College of Pharmacy and his doctorate in Medicine from Albany Medical College, and is Board Certified in Internal Medicine and Nephrology. He was a Fellow in Nephrology and Internal Medicine at the Mayo Clinic and is currently a Fellow of the American College of Physicians.

Fred Feldman, PhD

Vice President of Research & Development
Bentley Pharmaceuticals, Inc.

Dr. Fred Feldman joined Bentley Pharmaceuticals, Inc. in October 2005. He is an experienced life sciences researcher with more than 25 years of product development expertise. Dr. Feldman earned his Bachelor's degree in Biochemistry from the University of Chicago and his doctorate in Biochemistry from Purdue University. While Vice President of Pre-Clinical R&D at Armour Pharmaceutical Company and later at Rhone Poulenc Rorer after its acquisition of Armour, he developed new products and spearheaded registration activities in the United States and in international markets. He was a leader in the development of life-saving drugs for chronic diseases and replacement therapies that were registered and commercialized worldwide. Dr. Feldman went on to become Senior Vice President, Worldwide Head of Pre-Clinical R&D and Head of Biotechnology for Centeon, LLC and Aventis Behring, both Aventis Pharma subsidiaries, setting strategic scientific direction in such disciplines as gene therapy and therapeutic protein delivery. He has also been a high-level advisor to various venture capital investment organizations involved in a broad range of biotechnology and pharmaceutical applications.

Market Segment

Pharmaceuticals in India: A Business & Regulatory Outlook

By: Ames Gross, President, and John Minot, Associate, Pacific Bridge Medical

Introduction

Following decades of slow growth, India's economy is now advancing rapidly. From 1996 to 2006, its GDP grew at an average rate of 7% yearly, and this growth figure increased to 10% in 2006. It is expected to keep growing at 7% or higher throughout the next 5 years. With the fourth-largest economy in the world (as measured by purchasing power parity), India is finally coming into its own as a major world economy. Total medical spending in India is growing quickly, driven by better-off Indians willing to pay privately for modern care from private hospitals. This increased spending creates many opportunities for foreign pharmaceutical companies. India's $9-billion pharmaceutical market experienced 10% growth in 2006, and double-digit growth is predicted to continue through 2012. In addition, the country's low labor costs, large existing pharmaceutical manufacturing base, and sizable patient population make it an excellent location for Western companies to do contract manufacturing, clinical research, and R&D.

Demand

India's population, the second largest in the world, should not be described as one big pharmaceutical market. Most of its 1.1 billion citizens are rural or low-income and lack even basic access to Western medicines. The market, rather, is to be found in India's growing middle and upper-classes in urban areas, such as Mumbai, Kolkata, New Delhi, and Bangalore. If being in the middle class is measured by earning at least $1,000 per year, there may be as many as 100 million potential customers in India's major cities.

India is now going through a public health transition typical of rapidly developing countries. Once, ailments such as infectious diseases, malnutrition, and gastrointestinal disorders, were the predominant diseases requiring treatment. Today, however, with rising incomes, more and more Indians are able to drink, smoke, and lead more sedentary lives. As a result, "lifestyle" diseases, such as cancer and cardiovascular disease, are receiving more attention. Cases of cardiovascular disease, for example, are predicted to increase from 29 million in 2000 to 64 million in 2015, rising to 34% of all deaths.

Currently, the dominant drug types on the Indian market are still anti-infective and gastrointestinal. However, the greatest growth is predicted in coming years for cardiovascular, oncological, diabetes, and psychiatric drugs. Because Western companies have many new and innovative drugs in these types, which may not be available generically in India, they are prime areas of opportunity.

Healthcare Providers

In theory, much healthcare is available for free in India. There is a large network of more than 160,000 public hospitals, clinics, and health centers at the national, state, and local levels. However, in practice, these providers are barely acceptable. Public facilities are overcrowded and poorly staffed and funded. Although services are supposed to be free, patients must often pay for supplies like bedsheets, bandages, and drugs. Bribes can also be necessary to get faster treatment. Almost always, when patients have the freedom to choose, they will opt for private hospitals over public.

For-profit private hospital chains, such as Apollo, Max, and Fortis, have come to flourish in India over the past 2 decades. Serving both well-off Indians and medical tourists from the West, they tend to offer

Leading the Way

We celebrate the approval of the first noninjectable insulin treatment approved in the US and the European Union.

Pioneered by Nektar Therapeutics, the breakthrough technology behind Inhaled Insulin is just one example of the vital role we play in realizing the full potential of medicine.

Join us in leading the way. Find out how at www.nektar.com

NEKTAR
Bringing Therapy to Life

much higher standards of treatment with better staff, training, and equipment. Their fees, while low by Western standards, are significant to Indian incomes. In total, the majority of medical costs in India are paid for privately and out-of-pocket. It is private spending, not public, that is the basis of future growth.

Industry

The Indian pharmaceutical industry has historically been characterized by a large number of small factories. There are more than 10,000 pharmaceutical plants, and only about 300 are large or medium size. However, parts of the pharmaceutical manufacturing sector have developed to become more competitive in foreign markets. The Indian API industry had sales of about $2 billion in 2005, making it the third-largest producer in the world. More than 90 Indian factories now have FDA approval. Global pharmaceutical companies, such as GlaxoSmithKline, Sanofi-Aventis, Pfizer, and Abbott, also have their own manufacturing facilities in India, making use of low local labor costs.

Despite the traditional focus on generics, original R&D is becoming a more practical option in India. This is partly due to the abundance of trained scientists in the country. For example, the Indian company Torrent Pharmaceuticals drew attention in 2004 when it licensed a new cardiovascular compound to Novartis. Large Indian firms are also players in R&D. GlaxoSmithKline has a wide-ranging drug discovery and development alliance with Ranbaxy.

Finally, India's low costs, availability of talent, and large population have made it a major site for international clinical trials. In 2002, the total clinical trial market in India was about $20 million. By 2005, this figure had risen to nearly $100 million. India is home to more than 100 CROs, as well as many clinical testing sites of foreign pharmaceutical companies.

Table 1. Asia Pharmaceutical Markets, 2006

Country	Market Size (US$)
Japan	$ 55 billion
China	$ 20 billion
India	$ 8.8 billion
Korea	$ 6.3 billion
Taiwan	$ 2.5 billion
Hong Kong	$ 1.5 billion
Thailand	$ 1.5 billion
Singapore	$ 400 million
Indonesia	$ 350 million
Philippines	$ 300 million
Malaysia	$ 210 million

Data compiled by Pacific Bridge Medical

Regulatory Structure

India has a federal form of government, and the medical regulatory structure is divided between national and state authorities. The principal national drug authority in New Delhi is the Central Drug Standards Control Organization (CDSCO). CDSCO is often referred to as the DCGI, which stands for Drug Controller General India, the title of its head official. There are also 35 state-level Food and Drug Administrations, one for each of India's states and territories.

The DCGI registers all imported drugs, new drugs, and drugs in selected categories. It also has responsibility for clinical trials and quality standards. The state FDAs register all other products, accredit manufacturing plants, and conduct the bulk of quality monitoring and inspections. The Indian cabinet has approved a plan that would bring all drugs under a new Central Drugs Authority, modeled on the US FDA. This may be approved by Parliament in a legislative session by the end of 2007, but if so, it will be phased in over time.

The DCGI has a shortage of reviewers, often relying on outside experts to provide opinions. To pursue regulatory approvals effectively, a company must use a regulatory professional with significant experience in applications for foreign companies. This professional must also be in a position to spend a significant amount of time in New Delhi (where the DCGI is located) following up on applications.

Most of India's pharmaceutical product policy is governed by the Drugs and Cosmetics Act (DCA). The DCA was first enacted in 1940 and has been amended many times since then.

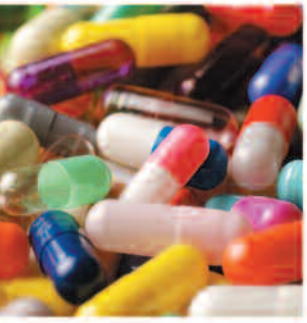
New Drug Registration

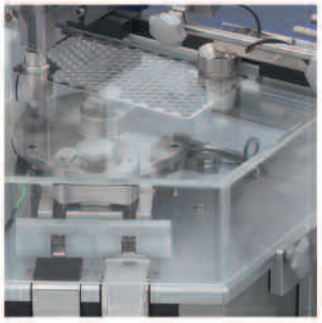
Drugs count as "new drugs" in India if they fall into one of the following categories: 1) drugs never marketed in India; 2) drugs with new therapeutic purposes or dosages that have not been marketed in India; 3) new fixed-dose combinations of two or more drugs; and 4) any drug that was first approved in India less than 4 years ago, unless it is included in the Indian Pharmacopoeia. Also, all vaccines are treated as new drugs, unless notified otherwise by the DCGI.

New drug registration is applied for officially in Form 44. The required attachments to the form vary depending on the type of new drug. All submissions require basic dosage and indication information, test specifications of active and inactive ingredients, listing of any applicable patents, and the raw material manufacturer.

Finished drugs with new active ingredients that have never been marketed in India require full preclinical and clinical testing information. These fall into the following categories: chemical and

Need to reduce the time-to-market for your latest drug?





Utilize capsules.

Pharmaceutical companies are taking months off the first-in-man timeline by micro-dosing API directly into capsules. But that's only one way capsules help gain time in the race to market. Capsule formulations require fewer processing steps, meaning less time for process optimization, documentation and equipment validation. And when early-phase clinical trials are conducted in capsules, there is no need for the time-consuming bioequivalence testing that would be needed to develop the commercial dose in a tablet. Finally, capsule formulations require fewer excipients than tablets, resulting in less time to select, evaluate, and validate raw materials.

This time saved during development translates directly into more selling time under patent protection, making the capsule dosage form decision not only simple, but smart.

For more information, visit **www.capsugel.com/simple**

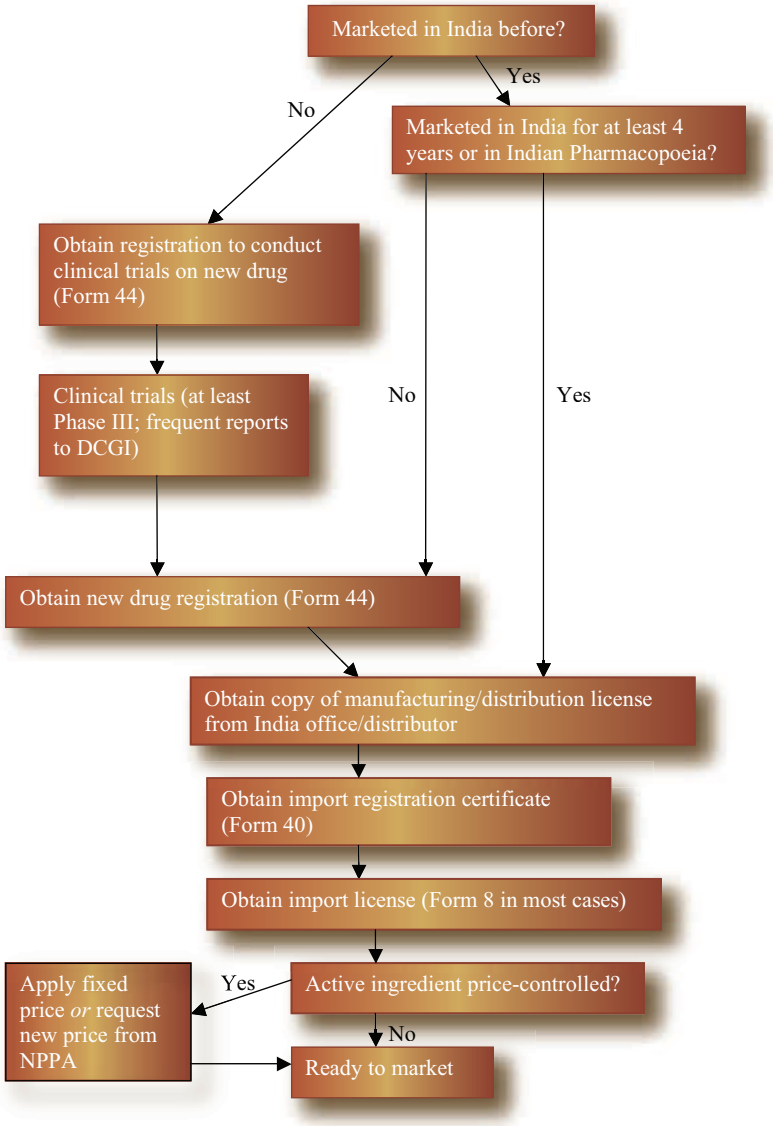
CAPSUGEL®
Quality
People and Products Working Together™

pharmaceutical information; animal pharmacology; animal toxicology; human clinical data from Phases I, II, and III; bioavailability and bioequivalence; and other special studies as appropriate. In addition to information on safety and efficacy, the DCA also requires comprehensive information on the marketing status of the drug in other countries. Information must be provided for any countries where the drug has marketing approval, investigational new drug approval, or has been withdrawn or rejected. Prescription information, samples, and testing protocols, and the proposed product monograph, labels, and cartons, must also be submitted.

It is possible to relax some of the requirements on a case-by-case basis, especially in the category of animal toxicology. This relaxation can be requested if a drug has been marketed for several years in other countries and its safety has been well-demonstrated. However, tests for animal pharmacology and animal toxicology are defined very closely in Schedule Y of the DCA, all the way down to the species and exact numbers of animals to be used in each test.

New fixed-dose combinations, new dosages and indications, new bulk drugs, and anything that was first approved less than 4 years previously, have significantly fewer requirements in the new drug process. They all require chemical and pharmaceutical information, including stability studies and testing specifications, as well as package inserts and labels. Anything taken orally requires bioavailability, bioequivalence, and comparative dissolution data. Anything taken by intravenous infusion or injection requires sub-acute animal toxicity data. New indications, dosages, or fixed-dose combinations require therapeutic justification that satisfies the DCGI of their safety, which can vary case by case and requires consultation and coordination. New drug registration has a fee of 50,000 rupees, or about $1,200. There is no fixed time frame in which the application has to be reviewed, but a typical range is about 12 to 18 months.

FLOWCHART: Importing Drugs



Clinical Trial Approval

Clinical trials are also applied for in Form 44, the same form used for new drug approval. Much of the same information as for new drug approval must be included, with the exception of reports on clinical trials that are still in the future. The Investigator's Brochure, study objectives and rationale, case record forms, informed consent documents, list of study locations, sponsor authorization letter, etc. must also be attached.

However, in late 2006, the government clarified additional information that should be submitted in the case of simultaneous global trials. In addition to normal Form 44 information, this includes a list of all worldwide trial sites and numbers of subjects at each site, all serious adverse events reported from other sites, and the status of the trials at other sites.

Phase III clinical testing generally must be conducted in India to receive new drug approval. This can only be waived in occasional cases, typically when the government is interested in a product for public health reasons and there is ample foreign data. A previous rule was that for drugs discovered in foreign countries, Phase I trials could not be conducted in India unless they were supplementary to Phase I trials that had been completed elsewhere. However, the new rules in late 2006 also allowed first-time Phase I trials in India as long as they are conducted simultaneously to other foreign Phase I trials.

Import Drug Registration

All drugs to be imported in India require their own import registration. This is independent from new drug registration. New drugs to be imported into India must first be registered as new drugs under Form 44 and then as imported drugs under Form 40.

The contents of Form 40 are fairly routine, but are still substantial. There is some overlap with the new drug application contents. Because clinical testing results are fully provided in new drug applications, they need only be summarized for form 40. However, information on regulatory status in other countries, GMP certification

"Partnering with Clients to Create Innovative Growth Strategies"

Comprehensive Market Coverage:

Medical Imaging

Medical Devices

Drug Discovery & Clinical Diagnostics

Healthcare IT/Life Sciences

Pharmaceuticals/Biotechnology

Patient Monitoring

Frost & Sullivan, a leader in global growth consulting for more than 40 years, offers unrivalled experience in the field of market analysis in all sectors of the Healthcare Industry. We leverage this comprehensive market expertise to serve an extensive clientele that includes Global 1000 companies, emerging companies, and the investment community. We help clients identify opportunities in the market and develop innovative strategies for growth through our exclusive market-engineering research and growth consulting services. We offer clients a balanced view of the market allowing them to make informed strategic decisions and achieve success in their industry.

FROST & SULLIVAN

Visit us on the Web at www.frost.com

For a detailed brochure, please email melina.trevino@frost.com

of the manufacturer, and items such as stability data, manufacturing methods, toxicity tests, bioavailability and bioequivalence, batch testing certificates, and inserts and labels must be included in full.

The process of receiving import registration can take up to a year, and it must be done after new drug registration. When import registration for a drug is available, a simple import license can be applied for, which is needed to actually let the drug in through customs.

Manufacturing

Most manufacturing is licensed by state FDAs, but new drugs, blood products, sera, and vaccines require approval from the DCGI. Manufacturing permission is fairly simple compared to new drug approval. In addition to basic information on the site, information must be furnished that the drug is being made to therapeutically justified specifications, and has new drug approval if appropriate. A GMP standard has also been recently implemented, under the name of "Schedule M." This may drive out many smaller drug manufacturers as it is enforced more strictly.

Intellectual Property Issues

Since 1970, in an effort to develop the local pharmaceutical industry, India's patent laws were changed to allow pharmaceutical processes to be patented, but not pharmaceutical substances. This made it completely legal to copy patented drugs, as long as they were made by a slightly different method. This led to the rapid development of small-scale bulk drug and formulation manufacturers in India. As a result, it became extremely difficult for Western pharmaceutical drug companies to succeed there.

However, when India joined the World Trade Organization in 1995, it committed itself to remedying its patent system to comply with international norms within 10 years. In 1999, a provisional system allowing marketing exclusivity was created, and finally, in 2005, the patent laws were amended to allow product patents as well.

Intellectual property rights are still comparatively weak in India, making it difficult to enforce patent protections. However, it is widely believed that a corner has been turned. India's large domestic companies, such as Nicholas Piramal, Ranbaxy, and Dr Reddy's Laboratories are increasing their research and development budgets in order to compete under the new patent regime. Global pharmaceutical firms have also been using the judicial system to prosecute infringers. The patent change has helped build confidence among Western companies that India is now worth the effort. For example, Bristol-Myers Squibb and Merck, which had terminated some of their Indian presence in the 1990s, returned in 2004 and 2005, respectively, citing the improved business and IP environment.

However, the new patent regime does not apply retroactively. Drugs discovered before 1995, even if patented elsewhere, are still copyable. Also, the new system only allows for the patenting of drugs discovered after 2005, when the system was implemented. New indications for drugs are not patentable, and neither are new chemical forms of existing substances unless they increase efficacy. This is why, if foreign pharmaceutical companies want to enter the Indian market with proprietary drugs, they should focus on bringing new drugs into India. These are the drugs that can be patented locally, brought first to market, and hopefully protected in court.

Summary

With a nontransparent regulatory system, fragmented geographic markets, and much local competition, India is not a place where easy success can be expected. However, its burgeoning economy, greater market openness, and the improved patent regime have altered the playing field. The potential of India for R&D, manufacturing, and sales now outweighs its drawbacks in many cases. Although India's business environment has improved greatly throughout the past decade, it is still a very complex country to operate in, and many obstacles can appear along the way. Due diligence and careful selection of regulatory professionals and business partners is essential to succeed there. ■

To learn more, please see PBM's India Pharmaceutical Regulatory Report at www.pacificbridgemedical.com.

Ames Gross

President & Founder
Pacific Bridge Medical

Mr. Ames Gross is President and Founder of Pacific Bridge Medical (PBM) and is recognized nationally and internationally as a leader in the Asian medical markets. Established in 1988, PBM is a consulting firm that assists medical companies with business development and regulatory issues in Asia. PBM has helped over 200 medical companies in Asia. Mr. Gross is a frequent contributor of articles on Asian medical issues for *Medical Device and Diagnostic Industry* (Los Angeles), *Clinica* (England), and other medically oriented journals. Mr. Gross is often a featured speaker at the Regulatory Affairs Professionals Society conferences, the Asian medical markets at the Medical Design and Manufacturing shows, the National Electrical Manufacturing Association meetings, and the Medtrade Home Health Care Exhibition, among others. Prior to establishing PBM, Mr. Gross gained broad experience, knowledge, and contacts in Asia while working at three major Wall Street firms. Mr. Gross earned a BA degree, *(Phi Beta Kappa)* from the University of Pennsylvania and an MBA from Columbia University. To purchase his comprehensive report on Orphan Drugs in Asia, please see the *Publications for Sale* section on his website (www.pacificbridgemedical.com).

John Minot

Associate
Pacific Bridge Medical

Mr. John Minot is an Associate at Pacific Bridge Medical. Mr. Minot has extensive experience working on research and writing projects focusing on various pharmaceutical market segments.

Executive Summary

Paul Grint, MD
Chief Medical Officer, Kalypsys

Richard Heyman, PhD
Senior Vice President, Drug Discovery Kalypsys

Kalypsys: Focusing on the Complexities of Diseases

By: Cindy H. Dubin, Contributor

Kalypsys is a drug discovery company formed in 2001 based on integrating an ultra-high throughput screening technology from the Genomics Institute of the Novartis Research Foundation with small-molecule discovery. Using the technology as a base, Kalypsys leaders built a drug discovery organization capable of taking an idea from target to clinical trials in a rapid and efficient manner without sacrificing quality. The company is supported by investors with interest in its long-term development, which is evidenced by a $100 million Series C financing in November 2006. Today, Kalypsys has clinical programs in metabolic diseases and pain and inflammation. Two of its programs, KD3010 and KD7040, are currently in Phase I trials for metabolic disease and neuropathic pain, respectively. Paul Grint, MD, Chief Medical Officer and Richard Heyman, PhD, Senior Vice President, Drug Discovery, Kalypsys, recently discussed with *Specialty Pharma* magazine that the company is focused on building value through advancing existing and new programs and on establishing strategic partnerships.

Q: ***What makes the company attractive as a potential partner or one in which to invest?***

Dr. Grint: We were able to raise $100 million in a Series C financing late last year, which solidified our financial position. Our current focus is to continue to advance our preclinical and clinical pipeline, as well as to find potential corporate partners that will bring long-term value. In 2006, we entered into a partnership with Alcon in the area of novel therapeutics for ophthalmology applications. We are looking to build upon this with a limited number of substantial, multi-product, multi-year collaborations with other pharmaceutical companies.

Dr. Heyman: Many pharma companies have big gaps in their pipelines because too few compounds have been taken into the clinic in a timely and cost-effective way. What makes Kalypsys unique is that we've built an organization that allows us to generate high-quality INDs in a very efficient, cost-effective way. We have all the pieces that a pharma company might have — a product pipeline that is very strong and investors who are willing to let us do what we're good at. Also, we're unique because we focus on therapeutic areas that are significant and large in terms of patient numbers: specifically, metabolic disease and pain and inflammation. These markets are very attractive to Big Pharma.

Q: ***How is the company unique from a technology perspective?***

Dr. Heyman: We're constantly trying to improve our technology, our competitive edge, and the entire drug discovery process. The ultra-high throughput screening Kalypsys systems that we use today have gone through many iterations of improvements since 2001. We have also sold these systems to organizations, including Merck, the National Institutes of Health, and The Los Alamos Labs. Of note, this provides us with revenue that we can use to fund our internal programs. To continue this evolutionary process, we recently partnered with Panasonic to develop the next generation of life science tools. It says a lot that a multi-billion dollar international company like Panasonic chose to partner with Kalypsys as Panasonic enters the life sciences field.

Dr. Grint: We have the technology and an infrastructure to fully integrate it into our discovery operations. We run many pieces of the process in parallel as opposed to in series and recruit people out of academia, biotech, and pharma who can utilize it in a very entrepreneurial and robust manner. We generate tremendous quantities of data and information that we use to make well-informed, data-driven decisions to advance or stop programs.

Q: ***What is Kalypsys' therapeutic focus?***

Dr. Heyman: We made a strategic decision to focus on therapeutic areas where there are unmet medical needs in large markets, namely metabolic diseases and the pain and inflammation space. Heart disease is the number one killer in Western society, and diabetes and obesity are considered pandemic diseases. If we don't change our lifestyle or come up with new treatments, children born today will have a lower life expectancy than their parents. There is a huge need for new and effective therapies and one of the unique things that we're trying to do with our drugs is to develop agents that target multiple risk factors — for example, in diabetes, obesity, and heart disease.

Dr. Grint: When we design clinical trials in metabolic diseases, we don't go after just cholesterol or glucose alone, but many aspects of these complex diseases as well. We're also going after diseases that impact the baby boomers. As the population ages, we believe we can have an impact in the area of acute and chronic pain and inflammation.

Q: ***Can you discuss for our readers the company's business model?***

Dr. Heyman: We have built a comprehensive infrastructure with preclinical and clinical discovery and development. This infrastructure can be scaled up and still maintain high efficiency and productivity. Therefore, having investors with a long-term vision has allowed us to build Kalypsys in a unique way. Sometimes a company can back itself into a corner and partner everything, but our investors are committed to building value and partnering smartly. The way that we have structured the company, we could almost have an exit for our investors by selling off or partnering a piece of the business and creating value without selling the entire lead asset or the company.

Dr. Grint: We've always talked about our desire as a company to drive our molecules to clinical proof-of-concept and get to a point at which we create value for potential partnerships. As we get closer, we've started to have discussions as a company about what's next. The ability to maintain a diverse pipeline will be a big component for our future.

Q: ***What has been the most difficult challenge in transitioning the drug discovery field?***

Dr. Heyman: From day one, we built an integrated drug discovery process on top of the screening technology. Additionally, we brought in (and continue to bring in) revenue by selling instrumentation on the systems business. We built a front end that rapidly and efficiently generates high-quality compounds and INDs. One challenge has been to balance the components in a manner that continues to generate revenue. That has been alleviated by investors who have long-term interests in the company and let us continue to focus on R&D instead of constantly traveling, looking for our next investment dollars.

Dr. Grint: Evolution is the best word for what we've gone through. We've always been a drug discovery company, and one of the most difficult challenges has been to not replicate the usual way that pharma and biotech companies operate. We have great tools and know how to maximize the output. We have been able to improve our operations in a rapid way that larger companies cannot easily achieve.

Q: ***Can you outline the business approaches that are being taken to enrich the company's pipeline?***

Dr. Grint: Our pipeline is entirely home grown, and there is no need to augment it through licensing at the present time. As I mentioned previously, we are looking for a limited number of substantial partnerships. By having a group of educated investors, we can enter into a shared risk, shared reward model.

Dr. Heyman: We're looking to create value both in the short- and long-term by building this type of business model. We want to share in the reward, and therefore, we're also willing to share in the risk. For this reason, we're open to creative business structures and looking to a limited number of deals that create value for both us and our partners.

Q: ***What is the status of product development and market potential?***

Dr. Grint: We have two Phase I clinical programs underway. The first, KD7040, is a topically administered inhibitor of inducible nitric oxide synthase (iNOS) being studied for treatment of neuropathic pain. The other, KD3010, is an oral agonist of peroxisome proliferator-activated receptor-delta (PPAR) that we're evaluating for treatment of metabolic diseases, such as lipid disorders and diabetes. Our plans are to advance KD7040 to Phase II in the fourth quarter of this year and KD3010 to Phase II in 2008.

Dr. Heyman: We also have plans to advance other programs into the clinic next year and keep our early-stage pipeline strong. We're looking for new programs that complement and balance with our existing portfolio in metabolic and pain and inflammation, where the market potential in both is big and growing.

Q: ***Please discuss your long-term goals/objectives for the company.***

Dr. Heyman: A key goal is to maintain our preclinical pipeline while advancing to the proof-of-concept stage with our current clinical pipeline. We'd also like to build a commercial piece and develop partnerships, both of which will create value and mitigate risk for Kalypsys.

Dr. Grint: In addition, we are advancing our technology in conjunction with Panasonic. We plan to introduce new screening systems as we continue to leap frog over past successes. Today, we have a robotics screening system that doesn't look like the one we had 3 years ago, and it's not going to be the same in 5 years' time. We believe the partnership with Panasonic is a significant way to help us stay on the cutting edge in the instrumentation arena.

Q: ***What is the one mistake you must avoid going forward?***

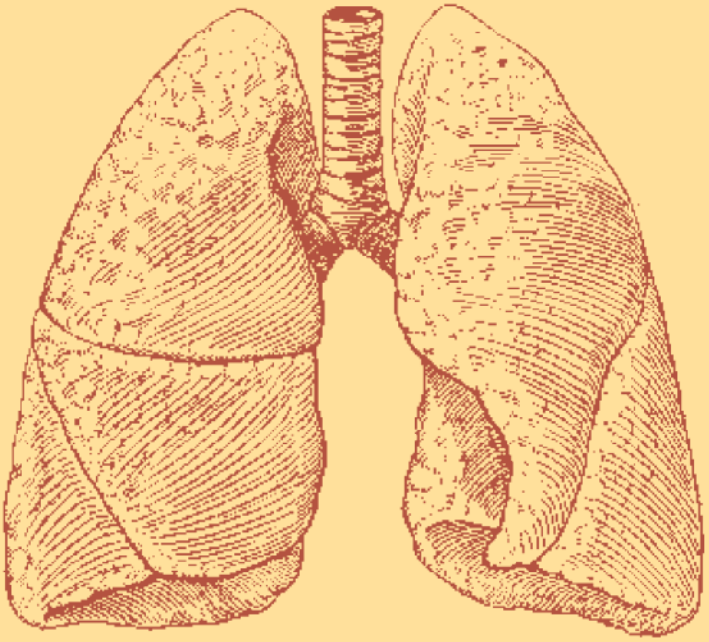
Dr. Heyman: To build a sustainable pipeline, we need the right people, investors, science, and technology. Drug discovery is an arduous journey, and we need to make sure we're not just good in one of those areas and bad in another. At the same time, we know not to stray from what we're good at and won't throw away our technology base.

Q: ***Does anything keep you awake at night?***

Dr. Grint: This is a risky business. To navigate it properly, a number of things need to occur in unison because there are many moving pieces, including great talent, investors, attention to detail, and execution in a cost-effective and timely manner.

Dr. Heyman: Keeping all of these pieces moving in unison is critical so that none become a rate-limiting step, but we've had success with it so far, and we're confident we will continue to do so. ■

RDD 2008 ARIZONA
Respiratory Drug Delivery



THE WESTIN KIERLAND
RESORT & SPA

SCOTTSDALE, ARIZONA, USA
MAY 11 - 15, 2008

POSTER ABSTRACT DEADLINE JANUARY 11, 2008

WWW.RDDONLINE.COM

Please Mark Your Calendars and Plan to Attend!

October 2007

Advertiser Index

Company	Pg	Phone	Web Site
3M Drug Delivery Systems	5	800-643-8086	www.3m.com/dds
Aveva DDS	55	954-624-1374	www.avevaDDS.com
Azopharma	4	954-433-7480	www.azopharma.com
BD	23	800-225-3310	www.bdpharma.com
Bilcare	25	610-935-4300	www.bilcare.com
Bilcare	89	800-310-4445	www.bilcare.com
Capsugel	15, 96		www.capsugel.com
Catalent Pharma Solutions Formerly known as Cardinal Health Pharmaceutical Technologies and Services	108	866-720-3148	www.catalent.com
Coating Place, Inc.	43	608-854-9521	www.encap.com
Degussa	13	732-981-5383	www.pharma-polymers.com
Dow Corning	2	989-496-4000	www.dowcorningnow.com
DPT Labs	107	1-866-CALL-DPT	www.dptlabs.com
Drug Delivery Partnerships	105		www.drugdeliverypartnerships.com
DSM Pharmaceuticals	91	973-257-8011	www.dsmpharmaceuticals.com
Eurand	9	937-898-9669	www.eurand.com
Excipientfest	61	787-746-5080	www.exceipientfest.com
Frost & Sullivan	98		www.frost.com
Genzyme Pharmaceuticals	45	800-868-8208	www.genzymepharmaceuticals.com
Glatt Pharmaceutical Services	51	201-825-8700	www.glattpharmaceuticals.com
Halozyme	47	858-794-8889	www.halozyme.com
Hospira	37	224-212-2267	www.hospira.com
InnerCap Technologies	3	813-837-0796	www.innercap.com
IOMED	27	801-975-1191	www.iomed.com
Lablablo	14		www.lablabo.com
Lipocine Therapeutics	17	801-994-7383	www.lipocine.com
Nektar Therapeutics	94		www.nektar.com
NOF Corporation	49	914-6819790	www.nof.co.jp/dds
Northern Lipids	20	604-222-2548	www.northernlipids.com
Pacific Bridge Medical	16	301-469-3400	www.pacificbridgemedical.com
Pacific Biometrics	35	206-298-0068	www.pacbio.com
Particle Sciences	4	610-861-4701	www.particlesciences.com
Penwest Pharmaceuticals	39	203-796-3700	www.penw.com
Pfeiffer	29	609-987-0223	www.pfeiffer-group.com
PharmaCircle	19	847-729-2960	www.pharmacircle.com
PharmaForm	11	512-834-0449 Ext 201	www.pharmaform.com
RDD (Respiratory Drug Delivery)	103		www.rddonline.com
Scolr Pharma, Inc	7	425-373-0171	www.scolr.com
Weiler Engineering	31	847-697-4900	www.weilerengineering.com
Zeon	21	1-877-ASK-Zeon	www.zeonchemicals.com/Medical2

SAVE THE DATE!!! January 21-23, 2008

12th Annual

Drug Delivery Partnerships™

The Event That Gets You One Step Closer to the Deal

Manchester Grand Hyatt • San Diego, CA

2008 Highlights

- Access to Over **500** of the Industry's Primary **Decision-Makers** Spanningthe Globe
- Carving Products Towards More **Payer-Friendly Outcomes**
- **Life Cycle Management Strategies**: How Will the KSR Ruling Impact Your Patents in the Future?
- **Stock Updates**, **Market Trends** & **Key Technologies** to Watch
- Drug Delivery Partnerships **2008 Trend Report**: The Top Deals Fueling Market Changes

Your Annual Stop for Industry News, Networking, and Deal-Making!

Don't Miss the Premier Drug Delivery Partnerships Event of the Year!

See you in San Diego!

Drug Delivery Technology Subscribers! Get 15% off the registration rate.
Mention code P1295DDTAD to get your discount!

www.drugdeliverypartnerships.com

EXTERNAL DELIVERY

Whose Job Is It Anyway?

By: John A. Bermingham

A few weeks ago, I was having lunch with Ralph Vitaro and Dan Marino, our Publisher/President and Executive Director, respectively. As usual, they made me pay for lunch. During our conversation, Dan brought up the point that his wife was a teacher. She had told Dan one evening that many teachers in her school today, when having trouble with students, send them down to see the principal or disciplinarian, and that more likely, teachers may not resolve issues with students directly or offer counseling. This sparked an interesting debate.

However, our conversation then migrated to business and whether the same situation exists in companies. The answer is yes! It is understandable that people naturally want to avoid confrontation and ugly issues. They do not want to confront their children much less an employee who has gone off track. However, just like with your children, you are doing a grave injustice to an employee who is going in the wrong direction or has unacceptable conduct issues by not quickly calling it to their attention. It is natural for you to not want to put the "hammer" on someone's head.

But when you accept the responsibility to manage others and have their careers in your hands, you must be able to praise in public and criticize in private. Same with your kids. I have found that in almost every instance in my career when I have had to call someone into my office to discuss a performance or conduct issue, they have been thankful for my calling it to their attention and discussing how to resolve it. One thing I always do to iensure success is to confront the situation, not the person.

As strange as this sounds, even though it is a personal/employee problem, you cannot confront the person. If you do that, the person you are talking to immediately goes on the defensive. It becomes your fault, someone else's fault, you don't understand the situation, the company is all screwed up, the devil made me do it. Yadda, yadda, yadda. But confronting the situation explicitly always has much different results. People are more likely to remain calm and be inclined to candidly discuss the issue pertaining to them rather than becoming defensive. I have had people in this scenario tell me how to best resolve their problem by making suggestions themselves. And usually, they have the correct solution. Strangely, in many situations, people did not realize that they were doing wrong.

You see, I think that it comes down to a matter of respect. In a disciplinary situation, you can get much further with a problem employee by showing firmness with respect rather than "beating" them up. You have the responsibility as a manager of people to act in this manner.

So I wonder how your employees would act if more superiors tried counseling and advising problem employees instead of simply banish them to the Human Resources Department for demotion and compensation reduction? There are exceptions though. Like the employee at a former company who was embezzling money from the company, and I caught him. He reacted in a surprising manner. He offered me a bribe to forget the whole thing. No counseling here, just immediate termination for cause. ◆

BIOGRAPHY

John A. Bermingham is currently the President & CEO of Lang Holdings, Inc., an innovative leader in the social sentiment and home décor industries. He was previously the President, Chairman, and CEO of Ampad, a leading manufacturer and distributor of office products. With more than 20 years of turnaround experience, Mr. Bermingham also held the positions of Chairman, President, and CEO of Centis, Inc., Smith Corona Corporation, and Rolodex Corporation. He turned around several business units of AT&T Consumer Products Group and served as the EVP of the Electronics Group and President of the Magnetic Products Group, Sony Corporation of America. Mr. Bermingham served three 3 in the U.S. Army Signal Corps with responsibility for Top Secret Cryptographic Codes and Top Secret Nuclear Release Codes, earned his BA in Business Administration from Saint Leo University, and completed the Harvard University Graduate School of Business Advanced Management Program.

Introducing

Catalent™

Catalent Pharma Solutions
The catalyst for your success

Discovering new treatments and successfully getting them to market is what drives the pharmaceutical, biotechnology, and consumer healthcare industry.

For years, many of the world's leading companies have turned to Cardinal Health Pharmaceutical Technologies and Services (PTS) for innovative solutions to the toughest challenges.

Now, as an independent company with a new name, Catalent Pharma Solutions continues to offer the same world-class service, reliably and on time.

We know that success, for you and us, requires constant innovation and operational excellence across the entire supply chain. From development to commercialization, Catalent has the technology, expertise, and global infrastructure to propel the development, manufacturing, and packaging of your products to new levels of success. Catalent Pharma Solutions. It's more than business as usual.

For more information, contact us at (866) 720 3148, email us at info@catalent.com, or visit www.catalent.com.

Reliable Solutions. Inspired Results.™

Catalent™