Drug Development & Delivery

October 2011 Vol 11 No 8 www.drug-dev.com

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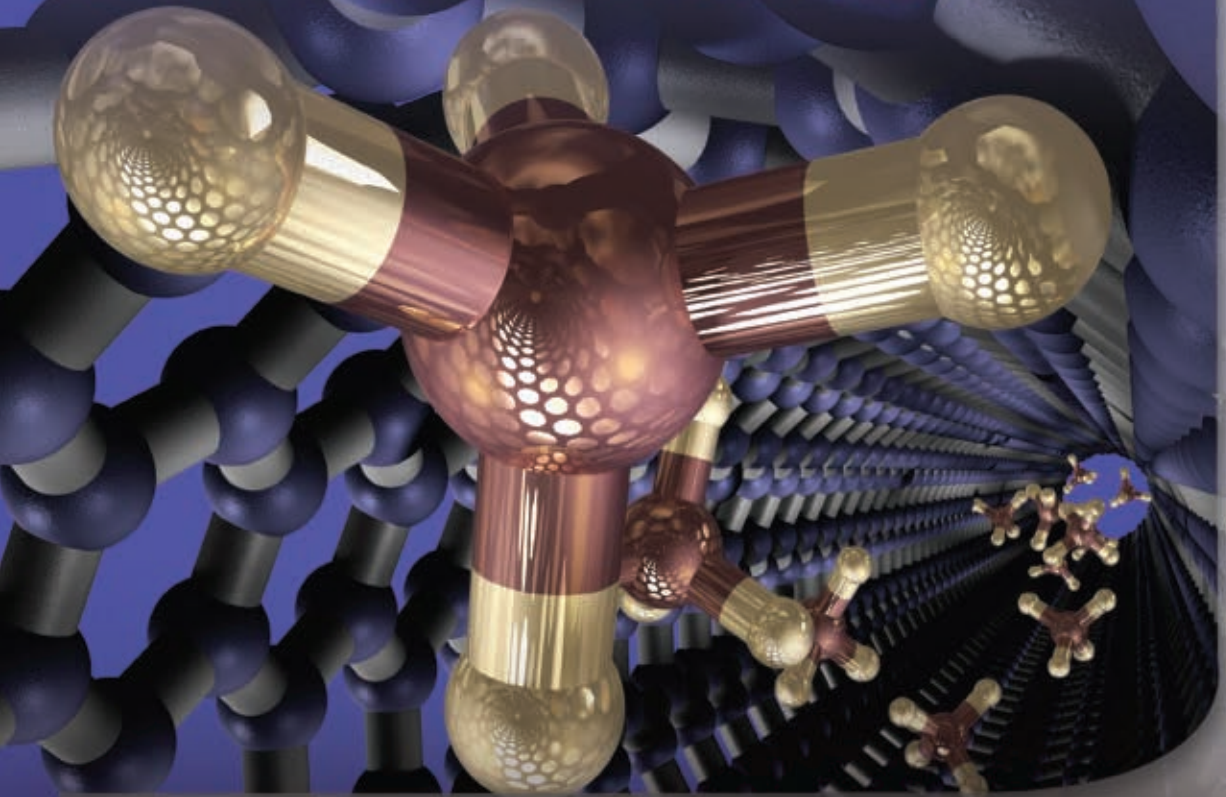

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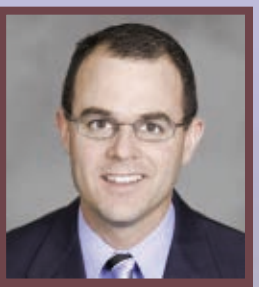

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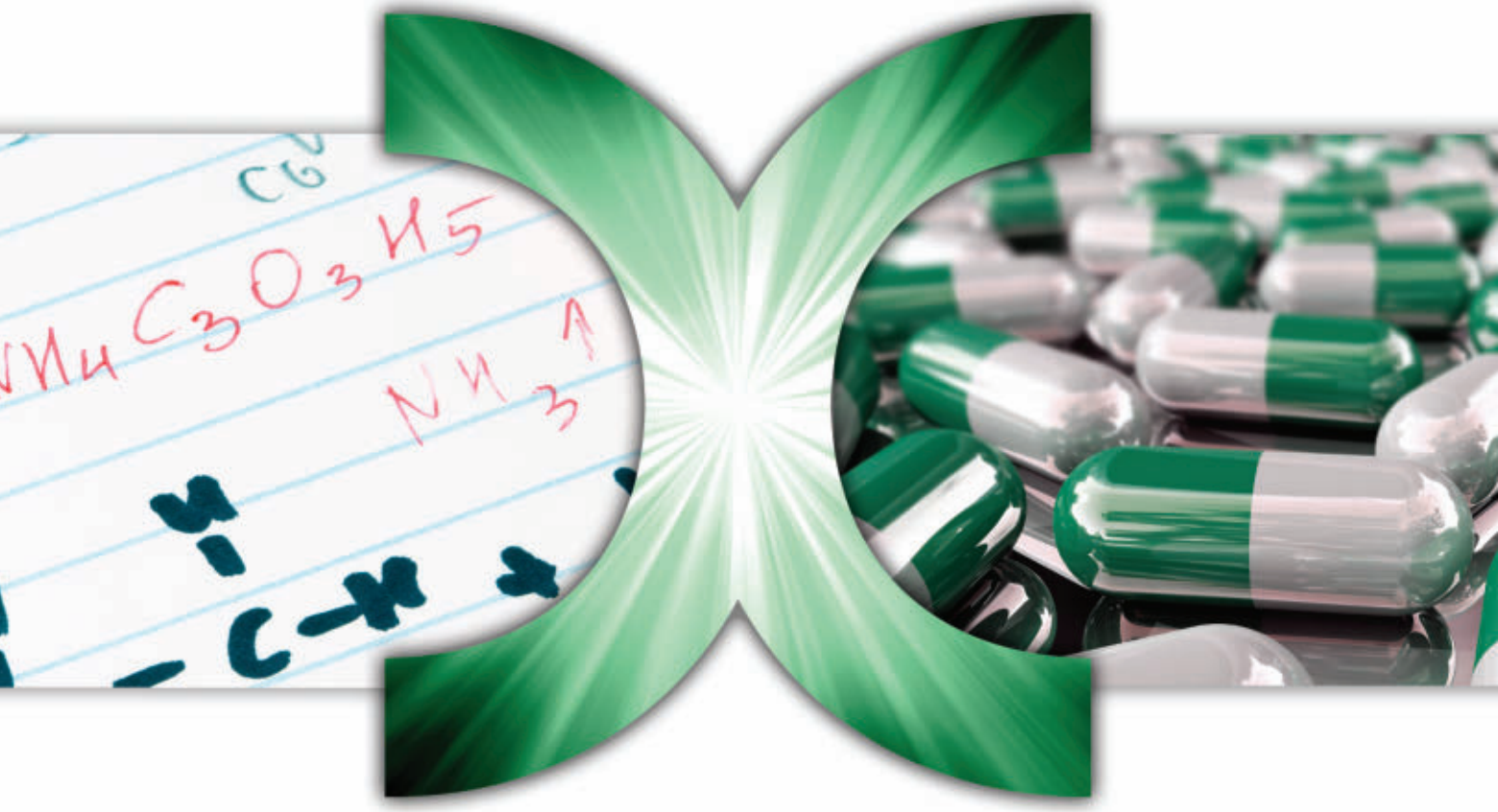

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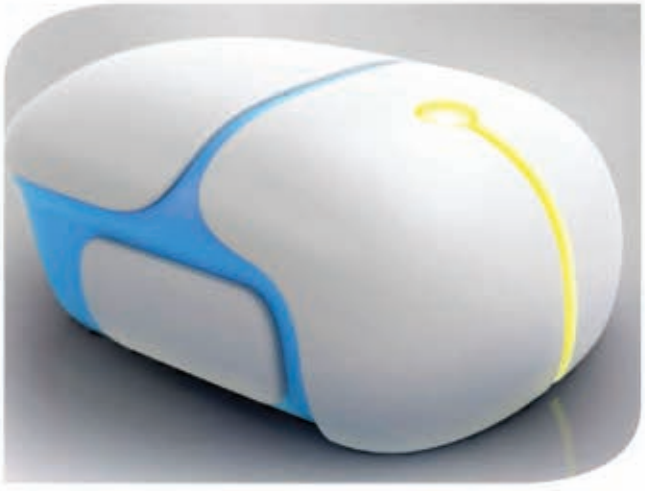

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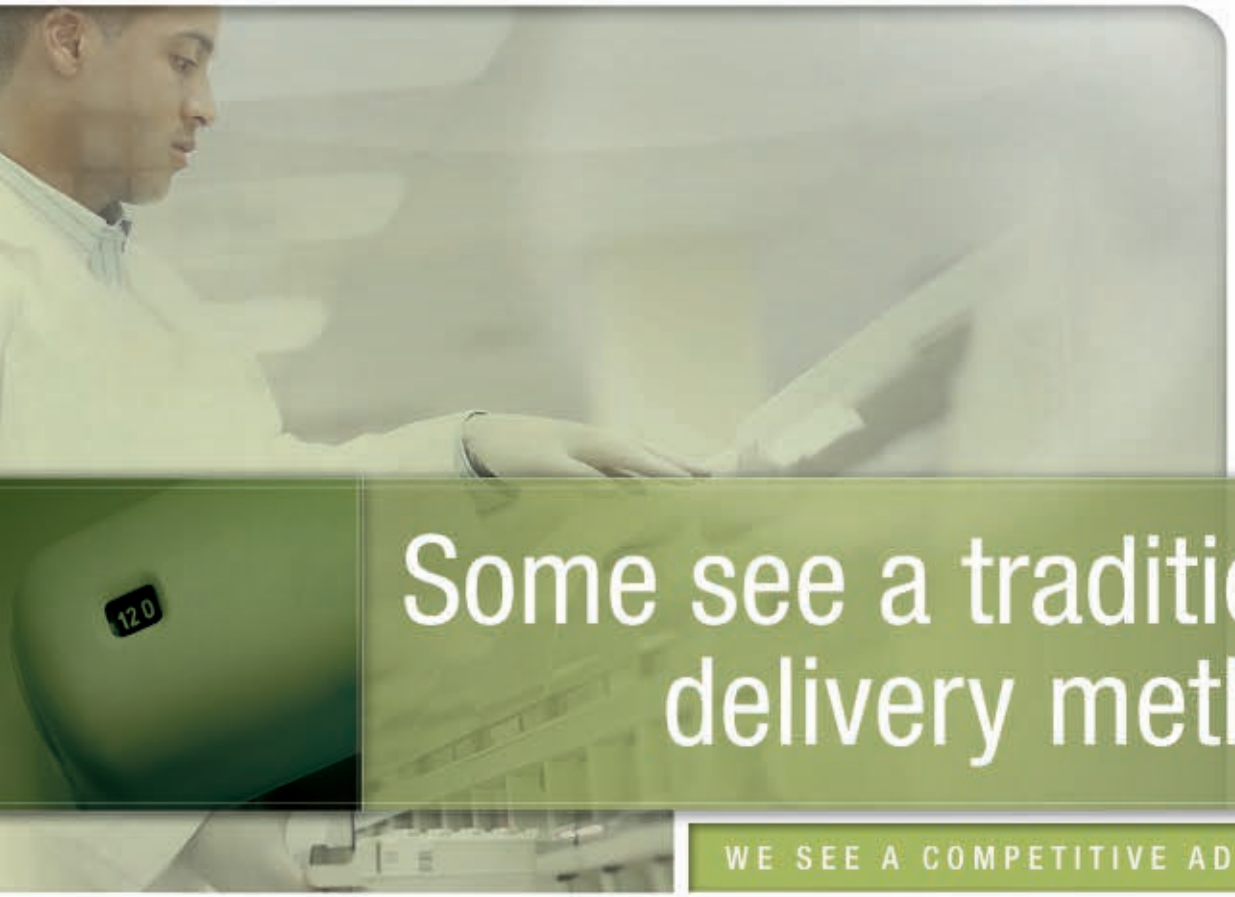

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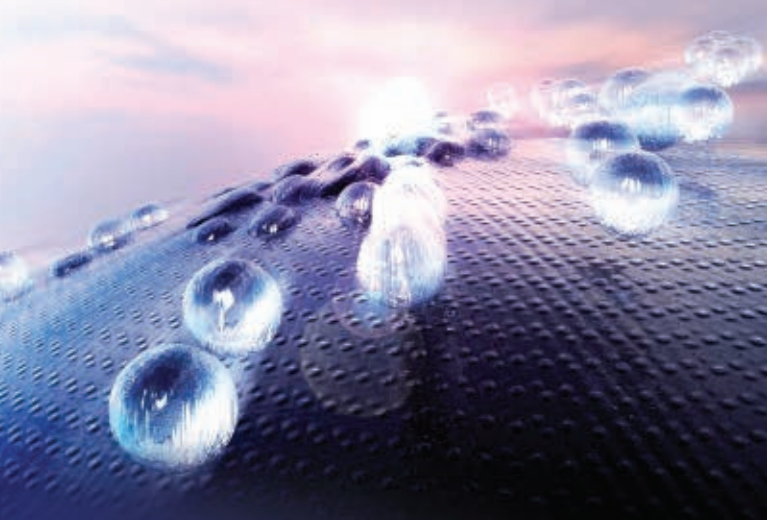

"NanOsmotic technology is a family of novel, closely related formulation and process approaches for the efficient and effective delivery of poorly water-soluble drugs by the oral route. The technology is a synergy of proprietary particle engineering technologies with widely available solubilization and osmotic controlled-release technologies that afford potential for significant improvement in drug product performance relative to more conventional formulations approaches or utilization of particle engineering technologies alone."

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36 *Injectable Drug Delivery - Easing the Pain With Technology*

Frost & Sullivan Analyst Debbie Toscano says innovation in injectable drug delivery system design is in a constant state of evolution as manufacturers strive to meet the ever-changing demand for safe, functional, and patient-friendly devices.

42 *Recent Trends in Drug Discovery & Drug Solubility: A Novel Hybrid Particle-Engineering Approach to Solving the Insoluble*

Gary G. Liversidge, PhD, indicates the NanOsmotic® technology offers a number of potential performance advantages over alternative technologies in the poorly water-soluble drug delivery space, including enhanced bioavailability, improved chemical and physical stability, higher drug loading, and the ability to achieve programmable release of drug for extended periods.

46 *Nose-to-Brain Drug Delivery: A Review*

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54 *Solid Dosage Forms for Biopharmaceutical Classification System Class II APIs*

Garry Gwozdz, Robert Gwozdz, and Robert W. Lee, PhD, focus on formulation of nanoparticulates via milling as well as solid solutions, as these are two of the most widely applicable of the available technologies. Conversion of nanoparticulates into solid oral dosage forms are also discussed.

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Nanoparticle Engineering

"There is no doubt that new technologies will be discovered to formulate APIs and NCEs with the intention of enhancing oral bioavailability. It will be of interest to see if there is a significant leap from the current repertoire of solid solutions, particle size reduction, amorphous materials, and permeation enhancers."

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The Best Chewing Out I Ever Received

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Avantor Performance Materials Expands Portfolio

Avantor Performance Materials recently announced it has expanded its portfolio by offering cGMP-manufactured Methylene Chloride and Acetone produced at its manufacturing facility in Phillipsburg, NJ.

The company's Macron brand NF-grade Methylene Chloride provides exceptional quality for pharmaceutical and cosmetic applications and is now available in 200-L containers, giving customers more options for ordering smaller quantities. Avantor is the only chemical manufacturer offering methylene chloride in drum-size packages.

In addition, Avantor's J.T.Baker brand of Multicompendial-, NF-, and FCC-grade Acetone are packaged in various container sizes. Acetone is used in a variety of pharmaceutical applications as a process intermediate. It is also widely used in medical, cosmetic, and food applications. Both chemicals are also available in larger quantities, up to bulk tanker deliveries.

"While bulk containers are readily available in the marketplace, there is a growing demand for smaller quantities of these popular performance chemistries from customers who cannot store and use large amounts cost effectively," said Executive Vice President, Global Pharmaceuticals and The Americas Paul Smaltz. "As customers strive to comply with more stringent FDA requirements, Avantor's ability to provide cGMP-manufactured chemicals in smaller containers gives pharmaceutical manufacturers a wider range of choices in selecting reliable, high-purity and high-quality solvents without having to purchase it by the tank wagon."

Avantor plans to expand its cGMP solvent manufacturing capability in the near future to meet ongoing customer needs for cGMP-manufactured chemicals in more convenient, custom package sizes. The company plans to make the J.T.Baker brand of FCC-grade Hexane available by the end of 2011. All Avantor cGMP solvents are available in the company's 100% reusable CYCLE-TAINER solvent delivery system containers.

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Marina Biotech Granted US Patent Related to Nucleic Acid-Peptide Drug Delivery Platform

Marina Biotech, Inc. recently announced the US Patent and Trademark Office (USPTO) has issued a Notice of Allowance for patent application US 11/955,207 with claims that cover a library of over 1x10(15) novel peptides. The patent application is part of the company's proprietary Trp Cage Library patent portfolio. This allowance strengthens the company's nucleic acid-peptide drug delivery platform, and further expands the company's patent protection for its comprehensive set of nucleic acid delivery technologies, which also include DiLA2, SMARTICLES, and the tkRNAi system.

"A primary advantage of this patented peptide library is the ability to rapidly screen and identify novel peptides that exhibit cell-specific targeting characteristics for directed delivery of nucleic acid therapeutics" said Barry Polisky, PhD, Chief Scientific Officer of Marina Biotech. "Delivery remains a significant challenge in the nucleic acid therapeutic space, and peptides with high affinity and specificity are expected to be a fundamental component to developing delivery approaches to a wide spectrum of tissues and cell types. In addition, the library may also be exploited to screen for peptides that function as specific antagonists, agonists, or generally exhibit drug-like properties."

The company's proprietary Trp Cage Phage Display Library is the subject of issued patents, US Patent No. 7,329,725; US Patent No. 7,704,953, and US Patent No. 7,772,189. The Trp Cage motif is highly structured allowing for the identification of peptides with high binding affinity for specific cell or tissue types, and avoids the limitations of low affinity and specificity often associated with linear peptide libraries. This technology is directly applicable to the company's DiLA2 and SMARTICLES delivery platforms as peptides are readily conjugated to the components of these delivery platforms. Peptides capable of directed delivery are expected to further improve the delivery efficiency of the company's UNA and CRN substituted nucleic acid constructs, which have demonstrated in vivo activity and efficacy against targets in both normal/healthy and disease models, respectively.

A Notice of Allowance confirms the substantive examination of a patent application and will result in a final issuance of a U.S. patent after an administrative process is completed.

Unilife Develops Multiple-Chamber Prefilled Syringes, Auto-Injectors & Infusion Devices

Unilife Corporation recently announced the development and patenting of the Unifill EZMix multiple-chamber ready-to-fill (prefilled) syringes. Unifill EZMix syringes have been developed in direct response to the unmet needs of pharmaceutical companies seeking an innovative and convenient delivery system for the reconstitution and administration of lyophilized drugs and vaccines. Unifill EZmix syringes feature two or more primary drug containers within a single glass barrel to store a combination of liquid stable or lyophilized drugs along with up to 1 mL of diluent for reconstitution.

In addition to being the world's first and only dual or multi-chamber prefilled syringes with automatic (passive) safety features fully integrated within the glass barrel, the Unifill EZMix syringe offers minimal steps of use for healthcare workers and patients alike. The end-user simply advances the plunger to mix the lyophilized powder with the diluent, before swirling the device to complete reconstitution. An audible, tactile click signals the injection of the full dose and the activation of a passive safety system that allows operators to control the speed of needle retraction directly from the body into the barrel.

Unilife also announced the development of a unique proprietary range of auto-injectors for the self-administration of injectable drugs by patients outside of healthcare facilities. Developed for use in conjunction with Unifill prefilled syringes, Unifill Auto-Injectors are compact in size and enable patients to inject a fixed dose of medication with the simple push of a button, without ever seeing the needle. Unlike conventional auto-injector technologies that are used with standard prefilled syringes, the incorporation of the Unifill syringe with its integrated safety features give Unifill Auto-Injectors several significant market advantages, including a small diameter, a true end-of-dose indicator, and automatic retraction of the needle from the skin after completion of the injection.

Unilife has developed its Unifill Auto-Injectors in single-use disposable and re-usable configurations for use across a wide spectrum of therapeutic drug classes. The Unifill self-injection systems can be customized to support a range of drug viscosities, patient dexterity, and visual acuity requirements. Injectable drugs are increasingly supplied in both prefilled syringe and auto-injector formats across a multitude of therapeutic classes. The availability of the Unifill syringe, either in a stand-alone format or supplied together with the Unifill Auto-Injector, can enable pharmaceutical companies to standardize their device platforms under the Unifill technology.

In addition, Unilife announced the development of its AutoInfusor portfolio of subcutaneous infusion systems for the patient self-administration of drugs in 3-, 5-, 7-, and 10-mL volumes. Unilife has developed its AutoInfusor technology to address the unmet needs of pharmaceutical and biotechnology companies with drugs that have complex formulations with higher viscosities and requiring large dose volumes. AutoInfusors are now available for supply to pharmaceutical companies for human clinical trials in either prefilled or fill-at-time-of-use formats.

Oxford BioTherapeutics Licenses Lonza's GS Gene Expression System

Oxford BioTherapeutics Ltd and Lonza recently announced a non-exclusive license agreement providing OBT with access to Lonza's GS Gene Expression System. The agreement covers the research, development, and commercial use of the GS System by OBT and contains standard payments and license fees that have not been disclosed. Licensing of the GS Gene Expression System expands OBT's access to world-class technologies for its maturing pipeline of therapeutic antibodies in oncology, and demonstrates its commitment to strengthening both antibody production and preclinical capabilities.

"We are delighted to have access to Lonza's GS Gene Expression System as an addition to our technology portfolio," said Tom Boone, who recently joined OBT as Senior Vice President, Protein Sciences following 28 years at Amgen. "The speed and ease of use of the GS System will aid the rapid selection of high-producing cell lines and accelerate the production and development of our most promising anticancer agents."

"We are proud to have our GS Gene Expression System contribute to Oxford BioTherapeutics innovation in cancer research," said Janet White, Head of Development Services. "We look forward to supporting OBT's efforts to expand and develop its pipeline of promising new oncology drugs."

The GS Gene Expression System, which is owned and licensed by Lonza, is used for the production of therapeutic recombinant proteins and monoclonal antibodies. Nearly 100 biotechnology and pharmaceutical companies and over 75 academic laboratories worldwide are successfully using the GS Gene Expression System, which has established itself as the industry standard. This system is characterized by its speed and ease of use. In addition, the higher yielding cell lines provide cost-efficient production of therapeutic proteins.

The Oxford Genome Anatomy Project (OGAP) database represents the world's largest proprietary collection of disease-associated proteins. OGAP oncology contains proteomic data on 5,000 cancer membrane proteins combined with their genomic and clinical information derived from human blood and cancer tissue studies. OGAP contains proprietary target information on three quarters of the entire human proteome. Over 1 million human protein fragments have been sequenced in OGAP in 50 different human tissues representing 60 diseases, including 25 forms of cancer covering 17,000 different genes and over three quarters of all human proteins and genetic variants in over 8 million SNPs and haplotypes.

Foster Introduces Custom Drug Delivery Film & Rod

Foster Corporation, a PolyMedex Discovery Group company and leader in biomedical materials, recently announced it has introduced custom extruded film and rod from drug/polymer blends for implant, patch, and oral drug delivery applications. Working with customer-specified active pharmaceutical ingredients and a range of polymer formulations, including EVA, bioresorbable, and water-soluble polymers, Foster is able to support customers from formulation development through clinical production of advanced drug delivery systems.

Foster's dedicated business unit for highly regulated materials, Delivery Science, specializes in blending polymers and active pharmaceutical ingredients with twin screw extrusion technology in a cGMP clean room environment. Traditionally, the company provided custom blends in pellet form for conversion into shapes used for drug delivery. These shapes included film for mucosal and transdermal patches, and rods for implantable drug delivery. Foster now also offers a range of custom film and rod extrusions for these applications.

Foster's unique approach combines material blending with the direct extrusion shape forming process, which provides a significant advantage for polymers with active pharmaceutical ingredients.

"Many active pharmaceutical ingredients are temperature sensitive. Heat histories associated with multiple processes that risk degradation of the drug can severely limit a particular delivery platform," said Tony Listro, Delivery Science Managing Director. "Direct extrusion removes a heat history associated with independent processing of film or rod for pre-compounded pellets, reducing the risk of degradation to the drug. Performing the entire process in a single cGMP-controlled facility consolidates supply and regulatory logistics."

At the present time, Delivery Science can produce drug/polymer film in widths of 2 to 5.5 inches (50.8 to 139.7 mm) and thicknesses of 0.0012 to 0.0394 inches (0.03 to 1.00 mm), and solid rods ranging from 0.020 to 0.315 inches (0.508 to 8.0 mm).

Xcelience Expands CTS Manufacturing & Packaging

Xcelience, a leader in early drug development, has expanded clinical trial supplies manufacturing and packaging capabilities to include four new pieces of equipment and a new fully automated packaging line.

To complement existing expertise in matrix tablet delivery systems, Xcelience added a MG Futura (capsule-filling machine for powder and pellets), LCI Multi-granulator MG-55 (extruder), QJ-230T marumerizer (spheronizer), and wurster insert (bottom spray) to the existing Glatt GPCG-3 fluid bed processor. These new pieces enable production, coating, and encapsulation of MUDF delivery systems.

"The new MG Futura is a great example of our continued commitment to add state-of-the-art technology that delivers real value to our clients," explains Theodore Koontz, Director of Operations. "The MG Futura improves upon production times, increases overall capacity, and expands upon our existing capabilities for powders, pellets, and powder micro-dosing for inhalation systems."

In addition, Xcelience has added a fully automated packaging line (including ink-jet coding) for primary bottling of tablets and capsules. The new packaging line enhances the speed at which batches are packaged, shortens timelines, and enhances the ability to package larger batches of drug product.

Xcelience is a premier provider of formulation development and manufacturing solutions with a solid reputation for accelerating early phase development. The company's outstanding quality record, drug-development expertise, disciplined project management, and willingness to customize enables delivery of real advantages to pharmaceutical innovators focused on small-molecule development. Partnering with a specialist for early development can reduce product risk and accelerate development timelines. Since 1997, Xcelience has been renowned for reliably expediting drug development and reducing compound risk. Its scientists have considerable experience overcoming challenging physical and chemical properties while achieving improved solubility and compound bioavailability.

NanoSmart Begins Development of New Drug Delivery Platform for Cancer

NanoSmart Pharmaceuticals, Inc., a biopharmaceutical corporation developing novel cancer pharmaceuticals, has moved into its new corporate facility located in Laguna Hills, CA. The facility provides the administrative and laboratory work space necessary to begin formal development of its initial product pipeline.

"Our new location gives us a physical presence in Orange County, CA, and allows us to move forward with our strategic development goals," said Dr. Henry Smith, CEO of the company. "We are excited about the opportunity to develop our initial products and conduct formal, nonclinical studies leading toward our initial regulatory filings."

NanoSmart is developing a patented, novel anti-tumor-targeting platform based on fully human autoimmune antibodies. These antibodies target areas of necrosis found in many different types of cancer. NanoSmart's drug delivery system represents a versatile platform technology with many advantages, including improved localization of cancer therapeutics leading to increased safety and efficacy. By combining these antibodies with different cancer drugs, NanoSmart has the potential to develop a very large number of novel biopharmaceutical products.

NanoSmart Pharmaceuticals, Inc., is a privately held company engaged in developing novel methods to treat cancer and other diseases. The company is focused on using its patented tumor-targeting antibodies to develop a variety of biopharmaceuticals to treat many different types of cancer.

Jennerex's Virus-Based Drug Targets & Infects Tumors

Jennerex, Inc. recently announced the publication of clinical data on its lead product JX-594. For the first time in humans, an oncolytic virus was shown to reproducibly infect, replicate, and express transgene products within cancer tissue after intravenous infusion. Normal tissues were not significantly affected clinically, underscoring the designed selectivity of JX594 for malignant tissue and safety of the product.

JX-594 replication and engineered transgene expression within solid tumors was evaluated on a Phase I dose-escalation trial of intravenous infusion of JX-594. Twenty-three patients with advanced, treatment-refractory solid tumors were enrolled in one of six cohorts. Safety, antitumor activity, and pharmacokinetic parameters were also evaluated. JX-594 was generally well-tolerated, and dose escalation proceeded without dose-limiting toxicities. The most common treatment-related adverse events consisted of Grade 1-2 flu-like symptoms lasting up to 24 hours. Cancer-selective and dose-related JX-594 delivery and replication in tumors were demonstrated in biopsies obtained 8 to 10 days following infusion. In patients receiving higher doses whose tumor biopsies were evaluable for analysis, 87% exhibited JX-594 positivity, whereas JX-594 was not detected in biopsies collected from patients receiving lower doses.

JX-594 is a proprietary, engineered oncolytic virus that is designed to selectively target and destroy cancer cells. JX-594 is designed to attack cancer through three diverse mechanisms of action: 1) the lysis of cancer cells through viral replication, 2) the reduction of the blood supply to tumors through vascular targeting and destruction, and 3) the stimulation of the body's immune response against cancer cells, ie, active immunotherapy. Phase I and Phase II clinical trials in multiple cancer types to date have shown that JX-594, delivered either directly into tumors or systemically, induces tumor shrinkage and/or necrosis and is well-tolerated by patients (over 100 treated to date). Objective tumor responses have been demonstrated in a variety of cancers, including liver, colon, kidney, lung, and melanoma. JX-594 has a favorable safety profile with predictable and generally mild side effects that typically include flu-like symptoms that resolve in 48 to 72 hours.

The vaccinia poxvirus strain backbone of JX-594 has been used safely in millions of people as part of a worldwide vaccination program. This strain naturally targets cancer cells due to common genetic defects in cancer cells. JX-594 was engineered to enhance this natural safety and cancer-selectivity by deleting its thymidine kinase (TK) gene, thus making it dependent on the cellular TK expressed at persistently high levels in cancer cells. To enhance product efficacy, JX-594 is also engineered to express the GM-CSF protein. GM-CSF complements the cancer cell lysis work of the product candidate, leading to a cascade of events resulting in tumor necrosis, tumor vasculature shutdown, and an anti-tumoral immune attack.

Transgene, a biopharmaceutical company specialized in the development of immunotherapeutic products, holds an exclusive license to develop and commercialize JX-594 in Europe and neighboring countries. Green Cross Corporation, a leading company in the development, manufacturing, and commercialization of viral vaccines and other biological products, holds an exclusive license to develop and commercialize JX-594 in South Korea, and Lee's Pharmaceutical Ltd. holds an exclusive license to develop and commercialize JX-594 in China.

F-Star & Merck Serono to Collaborate on Novel Targeted Biologics

F-Star GmbH recently announced that a research, license, and commercialization agreement was signed with Merck Serono, a division of Merck KGaA, Darmstadt, Germany, for the discovery of new antibody-derived therapeutics against inflammatory disease targets using F-Star's Modular Antibody Technology.

Under the terms of the agreement, Merck Serono will nominate up to three therapeutic targets, and the parties will collaborate to jointly discover mono-specific Fc-based targeted biologics (Fcabs) and bi-specific IgG-based targeted biologics (mAb2) for which Merck KGaA will have exclusive worldwide development and commercialization rights. F-Star will receive an initial technology access fee and research-based funding and is eligible to receive additional license fees, development, regulatory, and commercialization milestones, which in aggregate, could reach $673 million, as well as undisclosed tiered royalties on product sales. Further details of the agreement were not disclosed.

"We are very pleased to have completed this agreement with Merck Serono," said Dr. Kevin FitzGerald, Chief Executive Officer of F-Star. "Merck Serono Ventures has proved to be a supportive venture investor in F-Star, and we are now excited to expand the relationship to include collaborative discovery and development projects. F-Star has developed novel technology for the discovery of targeted biologics that offer significant improvements over conventional antibodies. This agreement builds on F-Star's strategy to develop and demonstrate the therapeutic potential of our proprietary technology through advancing our own pipeline as well as through a limited number of very selective research collaborations."

"We are very pleased to see our investment in F-Star through Merck Serono Ventures mature into a strategic collaboration, which reinforces our commitment to deliver innovative treatments in the area of inflammatory diseases," said Susan Herbert, Head of Portfolio Development at Merck Serono. "We believe that F-Star's Modular Antibody Technology has the potential to offer important functional advantages over conventional antibodies and will potentially allow us to generate highly differentiated drugs for patients with so far unmet medical needs."

F-Star is an antibody-engineering company based in Vienna, Austria, and Cambridge, UK. The company develops improved therapeutic antibodies and antibody fragments based on its Modular Antibody Technology, which allows the introduction of additional antigen-binding sites into antibodies and antibody fragments by engineering the non-CDR loops of antibody domains.

Recovery Strategies

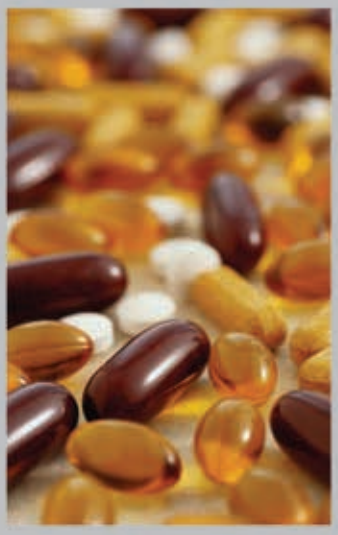
Karma in Clinical Trials: India Versus America

Part 6 of a 6-part series on how not to blow the recovery.

By: Derek Hennecke, President & CEO Xcelience LLC

FUNCTIONAL EXCIPIENTS





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In 2006, 2.5 million people participated in clinical trials across the US. The last reported death I can find was in 2008. The odds of dying as a result of a clinical trial then are abysmally small; less than 1 in 2.5 million, assuming the average trial of 1 year (Phase Is are shorter; Phase IIIs are longer).

By comparison, the odds of dying in a plane crash in a given year are 1 in 400,000. The 1-year odds of dying while walking across the street are 1 in 48,500. The odds of dying in a car crash are 1 in 6,500 (Don't Be Terrorized. reason.com;August 2006).

Volunteering for a clinical trial is therefore considerably safer than the trip to and from the lab, whether you fly, drive, or walk.

So why aren't people signing up to participate? A recent study in Annals of Surgery (September 2011;254(3):438-443), for example, said only 6 in every 1,000 patients who had cancer surgery in a California registry of cancer patients participated in a clinical trial. This is significant -cancer drugs account for 40% of all INDs.

Are American patients unwilling to take part? Or is it just easier and cheaper for companies to launch studies abroad? These are two of the reasons clinical trials have been moving to places like India, where the government facilitates clinical research with little or no oversight, participants are easily come by, and the cost of the clinical trial is about half of what it would be in the US.

In India, clinical trials are a booming industry, and while the monetary costs are minimal, the costs are of a different kind. In 2007, 132 deaths were attributed to clinical trials in India. The following year, that figure rose to 288; then 637. In 2009, 668 Indians died in clinical trials, according to the India Tribune, August 8, 2011.

Even these shocking numbers are probably far below the actual number of deaths. The system is designed to minimize reporting. In India, the trial investigator - hired by the firm conducting the trial - is solely responsible for determining the subjects' cause of death. That's like having a cop stumble in on his own son in a crime scene and expecting him to impartially report his findings. No trial investigator wants the clinical trial drug to be the blame. It's much easier to assume the subject died of a prior disease. To make matters worse, there's no system of independent auditors to investigate the cause of death and very little recourse even when the trial is found to be at fault. The government deemed only 22 of the 668 deaths this past year worthy of compensation. Compensation for five of those families was $300 to $600.

Dr. Chandra Gulhati, a medical practitioner who led several UK clinical trials, told the India Tribune he investigated a case in which 800 pages of protocol were submitted to the Drug Controller in India for approval, and

SIDEBAR

The Explosion in Outsourcing

While biking down the Tampa Bay Trail in August, a jogger swerved into my lane and sent me flying over the handlebars. The ambulance attendants peeled me off the pavement and took me to the hospital, where I learned I'd broken my collarbone in four places.

When I followed up with my orthopedic surgeon the next business day, he informed me that I needed a plate and a dozen screws to line the fragments back up. He had operated the previous year on my wrist after a hockey accident, so I was surprised when he told me he couldn't do the operation. He does wrists. He could give me the name of a doctor who does collarbones. A few days later, I lay on that other doctor's operating table.

I felt a great deal of confidence going under on the table of that doctor. He does nothing but operations like mine from dawn till dusk. That's the kind of confidence I want my customers to have when they come to see me. It reinforced a decision I made earlier this year.

Xcelience does formulation and manufacturing of clinical trial materials. Like my doctor, we're specialized. We take pride in being the best at what we do and going the extra mile. Like my orthopedic surgeon, I often get happy customers asking me if I could do one more thing for them. Lately I've received several requests for spray-drying and hot-melt extrusion.

I could've purchased some equipment and announced that Xcelience now does spray-drying and hot-melt extrusion. But that would have been akin to my orthopedic surgeon announcing that he now does collarbones as well as wrists. I'm not sure I want the generalist. I have more confidence in the specialist.

In August, we announced a partnership with Bend Research, an established industry leader in solubilization technologies, such as spray-dried dispersions and hot-melt extrusion formulations. Bend Research has been working with these technologies for over a decade, though their history includes more than 30 years of application engineering and physical chemistry in non-pharmaceutical industries.

Xcelience will continue to oversee the project through that phase if the customer asks us to, but Bend Research consistently delivers a level of spray-drying and HME expertise we could only aspire to. Through this partnership, we can now deliver that same level of science.

But it's not just about Xcelience. We are one small part of a much larger trend. Outsourcing in general is exploding. In fact, a recent report from Visiongain forecasts revenue from contract manufacturing will hit $64 billion by 2016, more than doubling between now and 2021.

Manufacturing of finished dosage forms will be leading this growth with compounded annual growth of 8.7% between now and 2016. Production of APIs accounted for 71% of the total contract manufacturing industry worldwide last year.

The US was responsible for 42% of contract manufacturing and demand for CMOs is expected to continue to come from drug makers in developed countries as they ramp up their R&D, but also increasingly from biotech.

Industry employment statistics are also ticking up, albeit modestly. We may rejoice that our industry no longer tops the list of industries laying off. The most recent study by Challenger Gray and Christmas showed a 50% drop in layoffs through August. Just 122 positions were eliminated that month, while drug makers said they planned to add another 433 jobs.

the green light was given four days later. If the same project had been submitted to him, he says it would've taken him a month to understand it. Dr. Gulhati is now investigating the cause of 81 deaths due to recent clinical trials.

Do participants willingly consent to such massive risks? The evidence suggests that at least in some cases they do not. In addition to using poor and illiterate trial volunteers, the concept of achieving consent forms is loosely interpreted. An HPV vaccine trial, which was later cleared in the case of six deaths, highlighted a number of deficiencies. Consent forms were signed by the wardens of the hostels where the participants lived, rather than by the participants themselves. There was no proper procedure to monitor the health of the participants for adverse effects, no uniform system for reporting Adverse Events, and no follow-on health insurance for treatment in case they fell ill during the trial.

The study also found more than 20% of study participants were from India's small tribal groups even though the law specifically bars the use of people from tribes unless the drug is of specific benefit to them. The report called these "minor deficiencies" but here in the US and Europe, we would take them more seriously.

This is a situation that will change as India becomes a developed country. At India's current rate of growth, it will have a real GDP per capita of $15,000 in 2030. That might not sound like much (in the US it was $46,000 in 2009), but it will move most of the population above the poverty line. It's just a matter of time until either the Indian people or international humanitarian organizations start moving ahead of the curve.

So far, stirrings of discontent come mostly from NGOs, rather than the Indian citizens themselves, and the focus of concern is not the humanitarian issue, but whether or not the trial drugs themselves are beneficial enough to Indians to justify the trials. The NGO PATH says India should only conduct tests for medical conditions like diarrhea and malaria, which are Indian-specific. Cancer is not specifically an Indian disease, so foreign researchers should conduct their research at home, it says.

FDA LOOKING TO ADD TWO MORE MONTHS TO APPROVAL PROCESS

One way to improve the quality of trials in India would be it equips the FDA with the capability of reviewing the torrents of data coming out of trials in that country. Instead, we have an over-worked under-funded agency struggling to meet its 10-month PDUFA deadlines.

But this too may soon change if the FDA is granted the wish it brought to Congress this summer - an additional 60-day filing period to the drug approval process and a fee increase.

The FDA's goal is to shorten the approval process by lengthening it. It's not as counter-intuitive as it sounds. Right now, the average Prescription Drug User Fee Act (PDUFA) process takes 10 months, which many say isn't long enough for a thorough review. The response that comes out of that 10-month pipeline indicates whether or not the drug is likely to be approved, and requires the company to take specific actions toward approval. Some companies argue the FDA is under too much strain to produce an outcome in that time-frame, and the result is a response that really isn't predictive of whether or not the drug will actually be approved.

The combination of the extra time with the FDA's request for increased funding may be the right prescription. The FDA collects one third of its funds, or $922 million of a $3.28-billion 2010 budget, from the companies seeking FDA approval. The agency wants to raise this user fee another 6% over 2012 levels to bring in an additional $713 million in 2013. The fee in 2012 for applications requiring clinical data are currently $1,841,500.

Right now, funds generated go directly into the reviews with nothing left over. The new money is destined for drug safety, rare diseases, and training in new technologies and science. The agency contends that by increasing the science, it'll be able to approve drugs faster in the long run.

I agree with the FDA that rushing to judgment to meet a department goal is foolhardy; and I can't argue against investing in more training for any organization. The question is, how do we know that the extra two months and the additional fees will result in better drugs delivered quicker? Tell me on LinkedIn what you think. ◆

BIOGRAPHY

Derek G. Hennecke is a Founding Member, CEO, and President of Xcelience. He has a long history of growing strong businesses around the world. Blending a scientific and business background, he has nearly 2 decades of international experience in the healthcare industry and a track record as a highly successful international turn-around manager in the global drug development community. Xcelience is the first company Mr. Hennecke has managed as an owner, having launched a management buy-out from MDS Pharma Services in 2006. The newly-formed company immediately embarked on a robust pattern of growth. Before founding Xcelience, Mr. Hennecke spent more than 10 years abroad working for the Dutch-based conglomerate DSM. In Montreal, he was GM of a 250-staff Biologics plant for more than 2 years. In Cairo, Egypt, as GM, he oversaw a turn-around in an anti-infectives plant that had been slated for closure. He spent 2 years in Holland developing new Pharma intermediates, and two years in Mexico as Commercial Director covering Central and South America. He also worked for Roche, both in Canada and Germany. Mr. Hennecke has a BSc in Microbiology from the University of Alberta and an MBA from the Erasmus University in The Netherlands.

The Challenges in Developing Today's Pharmaceutical Drug Delivery Devices

By: Geralt Williams, PhD

The challenges of developing a new pharmaceutical drug delivery device that will be a robust, user-friendly, and cost-effective commercial product are becoming ever more complex. It requires the input of multiple disciplines in areas such as design verification and control, risk management, process design verification, and compliance with the ever evolving regulatory standards and not forgetting the key element of unit cost in the current economic climate.

Ultimately, any device used with a drug product can only help patients if it is approved by regulators, prescribed by healthcare professionals, is efficacious and robust, is administered correctly by the users or patients, and has an acceptable cost to the healthcare system. This discussion examines some of the key elements involved in developing such a device using a pharmaceutical dry powder inhaler (DPI), particularly the Prohaler® DPI device from Aptar Pharma.

USER-FOCUSED DESIGN STUDIES

The starting point for any device that will be handled and used directly by patients in order to self administer their therapy, for example asthma treatment, is a user-focused design study. The aim is to create a simple device that is logical to use and gives effective feedback and reassurance to the user. The designers begin with a blank piece of paper and create the best user sequence and assess the potential areas of risk. Proof-of-principle models are then made with a range of different actuation formats, size, and shape influenced by thoughts on mechanical components. Subsequently user trails are conducted to test the aforementioned theories and gain insight into device preferences through naive eyes using a panel composed of asthmatic patients, non-asthmatics, nurses, and primary care physicians who are unfamiliar with the new device. This leads to the selection of an optimal design that is then verified by a further set of user research qualitative studies looking at areas such as intuitiveness and ease of use, size, ergonomics, etc (Figure 1). In addition, various inputs are collected with regard to various misuse scenarios, user

FIGURE 1

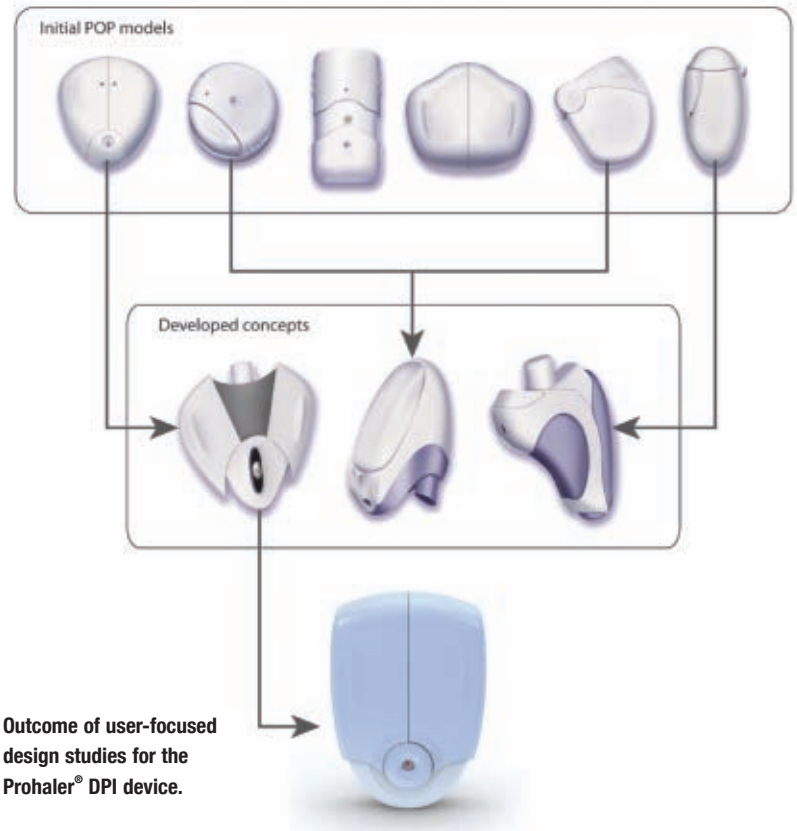

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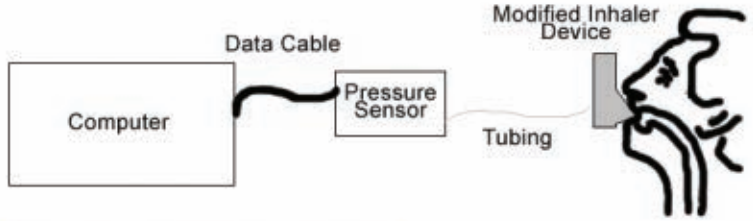
FIGURE 2

Equipment used to collect patient inhalation profiles.



-Recording every 20 msec of:

Inhaled Flow Rate (L/min)

Flow Acceleration (L/sec^2)

-Flow Integration to give:

Inhaled Volume (L)

preferences, and suggestions for improvements that are included into the design phase. At this stage, the preferred design concept is selected and moved forward into development.

Once such a device enters development, several other activities take over, including patient centric design, risk management, design for manufacture, and assurance that product performance meets all pharmacopeial standards and regulatory guidelines. Detailed documents giving guidance on the aforementioned aspects are available, for example, design verification and controls can be ascertained from ISO standards (Aerosol Drug Delivery Device Design Verification) and Code of Federal Regulation documents (Design Controls, title 21.820.30).[1,2] Guidance on risk management activites can be sought from the US FDA documents (Medical Device Use Safety: Incorporating Human Factors Engineering Into Risk Management) and ISO (International Standards Organization) standards (Application of Risk Management to Medical Devices) as well as ICH guidelines (Guidance for Industry, Q9 Quality Risk Assessment).[3-5] Several documents provide detailed instructions with regard to specific product development issues, such as ISO document 13485:2003 (Medical Devices - Requirements for Regulatory Purposes), ICH guidance for industry (Q8, Pharmaceutical Development), and FDA documents related to DPI development (Guidance for Industry CMC, 1998 and A Framework for Innovative Pharmaceutical Development, 2004).[6-9]

PATIENT-USE STUDIES

With all this information, it is possible to advance to the next stage where the product will be developed to pilot scale, and in-vitro product performance can be assessed. At this phase, the working prototype devices can then be included in further patient-use studies for the first time. For the Aptar Pharma Prohaler® device, some of the key elements that can directly influence the user are the airflow levels the patient is able to achieve when inhaling through the device in order to get the dose - the airflow needs to reach a certain level before the device triggers and releases the dose into the patients airstream and then on into the lungs. Given that patients with lung disease, such as asthma or COPD (chronic obstructive pulmonary disease), have compromised lung function, some may have difficulty in reaching the required airflow to trigger the device dosing mechanism. In addition, the resistance of the device needs to be assessed to see whether the patient senses any difficulty in inhaling through the device comfortably.

To address and optimize these key attributes of the device in accordance with the patients who will use it, a study was designed wherein patients could test out the new inhaler. In this study, inhalation profiles would be recorded, and key information would be gathered on the acceptability of the prototype devices to fine tune triggering airflow levels or device resistance. To record the patients' inhalation profiles, a specific kit was developed to record the inhalation profiles (Figure 2).

The system is able to measure differential pressure over time using the pressure sensor - to get useful data from inhalation profiles, it is necessary to measure flow rate over time as well. Based on the work of Ower & Pankhurst, the two parameters are related in the following (Equation 1), where ΔP = differential pressure, Rd = resistance of device, and Q = volumetric flow rate.[10]

Equation 1.

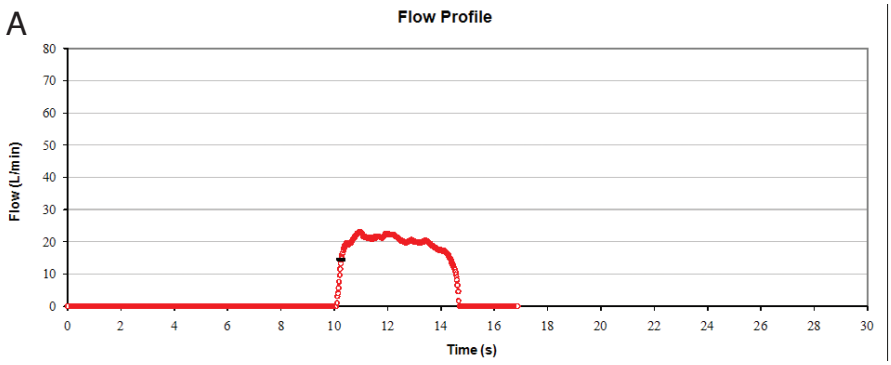
$$\Delta P0.5 = Rd \bullet Q$$

Experimental studies support this relationship for a range of marketed inhaler devices.[11] Once the resistance for the DPI device used in these studies had been established, it was then possible to convert the recorded differential pressure readings to flow rate readings using Equation 1.

Data were collected from various groups

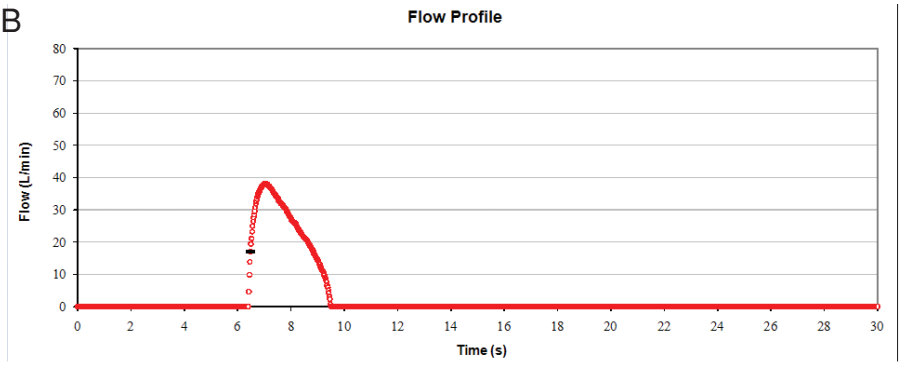
FIGURE 3 A&B

A



Inhaled Volume (Total)	1.45 L
Inhaled Volume (Real)	1.45 L
Peak Inhaled Flow Rate	23.1 L/min
Max. Flow Acceleration	1.70 L/s^2

B



Inhaled Volume (Total)	1.28 L
Inhaled Volume (Real)	1.28 L
Peak Inhaled Flow Rate	38.1 L/min
Max. Flow Acceleration	4.41 L/s^2

Typical patient inhalation profiles collected during the development phase of the device.

including healthy volunteers, both adult and pediatric asthmatic patients and COPD patients. Critical elements, such as inhalation volumes (in liters), peak inspiratory flow (in liters/minute), and airspeed velocity (in liters/second) were recorded. Examples of some of the inhalation profiles recorded from the patients during the clinical studies are provided in Figure 3A & 3B.

Using the data gathered during these clinical studies, it was then possible to adjust the triggering mechanism and airflow within the device to ensure all classes of patients could use the device efficiently and comfortably.

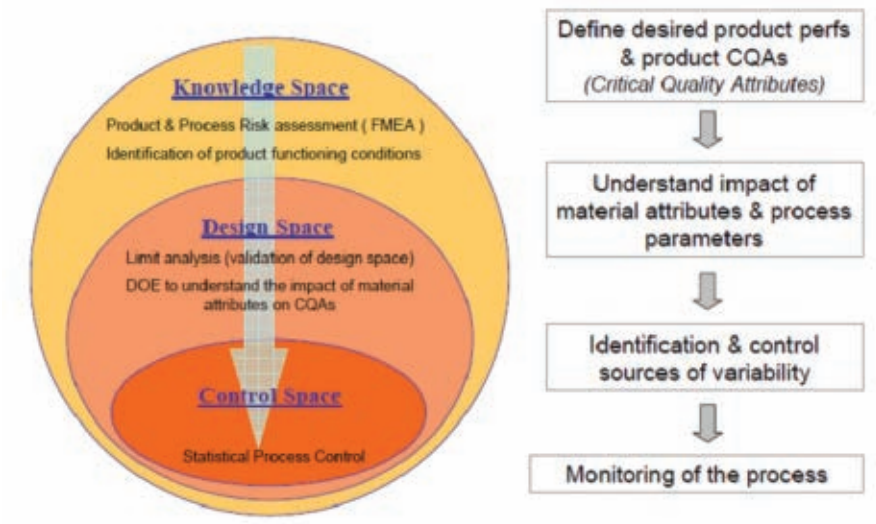
LINKING PATIENT STUDIES TO PRODUCT PERFORMANCE

In addition to using the patient inhalation profiles for making mechanical adjustments to optimize the device, the inhalation profiles were also used to develop the in-vitro pharmaceutical performance of the product. Performance attributes, such as emitted dose and fine particle dose, are key factors regarding the efficacy of a DPI inhaler. They ensure that the right amount of drug is delivered per dose (emitted dose) and that the emitted dry powder particles are fine enough to enter the lungs (fine particle dose < 5 microns). By using real patient inhalation profiles gathered in a clinical setting, it was possible to ascertain the in-vitro laboratory performance of the device in a representative way that the patient would use the device in a real-world setting. This assurance that critical performance attributes could be predicted in the laboratory offer high levels of confidence the device would work in a clinical setting. All this information helps define the design space for the device before it is scaled up to commercial levels.

This type of approach was taken for several key functional attributes of the device and enters into what is termed a Quality by Design approach to device development. Quality by Design is a scientific risk-based approach in which there is a proactive design effort from conception through commercialization (Figure 4). It is important to fully understand how key product attributes and processes relate to final product performance. A design space is built around the product in which the multidimensional combination and interaction of input variables (eg, material attributes) and process parameters that have been demonstrated to provide assurance of quality are known. Once the design space has been established, by experiment or modeling, one can then be sure that working within this space will assure a product of known acceptable quality. Upstream risk analysis incorporating levels of gravity for functions directly related to any potential failure modes are used to identify the critical quality attributes (or functions) that will be managed in the Quality by Design process.

Taking the aforementioned approach, the device is then scaled up for commercial manufacture, where activities such as optimization of individual components can be achieved using suitable tolerance software (thus leading to optimal device components whether they are made of plastic, metal, or

FIGURE 4



Quality by Design methodology applied to the Prohaler® DPI device development.

elastomers). Consideration is also given to the final assembly of the device on a commercial scale to ensure it can be manufactured in large numbers to the right quality levels. Throughout this process, data collected during the aforementioned exercise allow for calculations to be made with regard to production costs. It is at this stage of building the commercial-scale manufacturing equipment that economies can be realized and attention can be given to make sure the unit cost of each component, as well as the assembly costs of the finished device, lead to a product matching the targeted unit cost.

DISCUSSION

The activities described in this article represent some of the key elements that need to be considered when developing a pharmaceutical dry powder inhaler device in today's evolving pharmaceutical technology market. With the starting point for any new treatment being an efficacious and safe drug, multi-disciplinary activities during development are essential for overall success, including not only the device but also drug formulation, clinical studies, filling and packaging, regulatory filing, etc – all of which will be critical for the commercial success of any new treatment. If all these challenges can be met, patients with respiratory ailments can be assured of efficacious, easy-to-use, affordable, and reliable high-quality therapies to improve their lives. ◆

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BIOGRAPHY

Dr. Gerallt Williams is Director, Scientific Affairs, Aptar Pharma, Prescription Division, France. After earning his PhD from the University of Wales, UK in 1985, he has held various industrial positions at Monsanto Inc. (UK), Fisons Ltd (UK), Valois (France), and Inhale/Nektar Therapeutics (USA). He is now in charge of scientific affairs for the Aptar Pharma Prescription division, Le Vaudreuil, France, and is engaged in the development of new devices for nasal and inhaled drug products.

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PERFORMANCE TRENDS

Generic DDEP Sales & Prescription Performance 2010

By: Josef Bossart, PhD

In last issue's article, we examined the sales and prescription performance of branded DDEPs (drug delivery enhanced pharmaceuticals) in 2010.1 This issue, we will look at how generic DDEPs performed in the same period. There is much talk about the outsized impact generics are making on the sales and profitability of the major pharmaceutical companies. The pain also extends to companies involved in developing and selling branded DDEPs.

Once again, it's important to define the qualifications and key references used for this month's analysis. Unless otherwise noted, sales and prescription data were sourced from SDI's Vector One® Top 200 reports published online by Drug Topics (www.drugtopics.com). These reports are updated annually and are available at no charge. The data in these reports refer to prescription pharmaceutical products sold in the US retail market and exclude hospital and institutional sales. Product sales figures are based on the average wholesale (AWP) or average selling (ASP) prices. The figures for generics are at best an order of magnitude estimate of sales. This is because the actual sales of generic pharmaceuticals are subject to contract bidding and heavy discounting at every level of the distribution system. There is a reason that Wal-Mart and other pharmacy chains can offer a 1-month prescription of a generic product for $4, including the dispensing fee. While discounting

is generally more limited for generic DDEP products because of fewer competing approved generics, there is still a discrepancy between actual sales and those estimated using AWP or ASP prices.

The products listed in the Top 200 retail generic prescription report represent about 88% of all prescription-dispensed generic pharmaceutical products at the US retail level. In terms of sales, the Top 200 products account for about 87% of all generic product dollar sales.

GENERIC DDEP SALES & PRESCRIPTIONS – 2010

Table 1 summarizes generic DDEP prescription and sales figures for 2009 and 2010. These numbers cover only the generic DDEP sincluded in the SDI's Vector One® Top 200 product lists for both of those years. Not every generic DDEP was included in both lists. A relatively low-volume (prescription) product with a high price could have made the Top 200 sales list but not the Top 200 prescription list. And a high-volume, low priced product would have had the opposite listing.

The products included in Table 1 do not include products that solely depend on simple formulation or delivery devices; formulation and device-enhanced pharmaceuticals (FDEPs). FDEPs incorporate formulation tools like enteric coating, and devices such as auto-injectors.

Prescriptions and sales for generic DDEPs were up in 2010. In the case of prescriptions, the increase, at almost 20%, was substantial. The slight increase in sales of 2.3% for the same period may well be real, or not. The rather large difference between prescription and sales growth is further evidenced by the substantial drop in price per prescription. This seems to be an issue of price erosion rather than a change in product mix.

In total, generic DDEPs accounted for about 4.3% of all generic prescriptions in 2010. In terms of sales, the figure is a much higher 11.9%. Although the sales figures are subject to critique in the absolute, in this case, they perhaps realistically reflect that generic DDEPs currently enjoy a substantial price premium relative to non-drug delivery enhanced products. This is evidenced by the fact that Wal-Mart and other pharmacy chains' discount prescription plans rarely, if ever, include generic DDEPs.

The sales and prescription market share of generic DDEPs relative to branded DDEPs in the US is presented in Figure 1.

LEADING GENERIC DDEPS – 2010

The leading retail generic DDEP products for 2010 in terms of prescriptions and sales are presented in Table 2. In a couple of cases, there are no prescription figures available for a product. In this case, the generic DDEPs made the Top 200 sales list but didn't hit the Top 200 prescription list. Each of these products had fewer than 2 million

TABLE 1

	2009	2010	Change Y/Y
Total DDEP Sales	$5,893,444,000	$6,030,806,000	+2.3%
Total DDEP Prescriptions	84,150,000	100,923,000	+19.9%
Implied Price per Prescription	$70.03	$59.76	

* Extracted from SDI's Vector One®: National 2009 & 2010 Top 200 Generic Drugs by Retail Dollars

Generic Sales & Prescriptions, Retail DDEP 2009 & 2010*

prescriptions in 2010.

In terms of prescriptions, the top generic DDEPs by far were the nasal fluticasone generics, topping 22 million prescriptions in 2010. The top dollar generic DDEP sales position was held by transdermal fentanyl (Note: in almost all cases, there are multiple generic suppliers for a particular generic DDEP; their sales and prescriptions were consolidated for this review).

TABLE 2

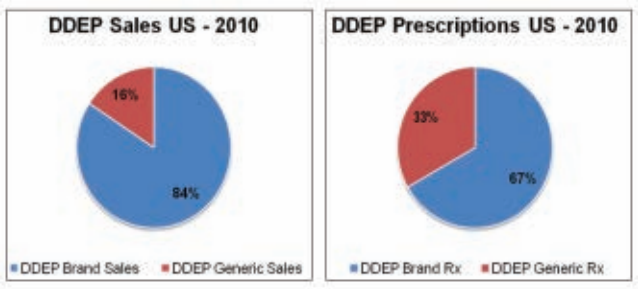
Product	2010 Prescriptions	Rx Chg. 2010/2009	2010 Sales	Sales Chg. 2010/2009	Implied $/Rx
Fluticasone (nasal)	22,448,000	+9%	$624,590,000	+57%	$27.82
Bupropion (once-daily)	10,440,000	+40%	$711,629,000	-27%	$68.16
Diltiazem (once-daily)	8,126,000	+5%	$319,505,000	+3%	$39.31
Diclofenac (once-daily)	6,052,000	+2%	$150,496,000	+2%	$24.87
Venlafaxine (once-daily)	5,526,000	+553%	$860,082,000	+673%	$155.64
Bupropion (twice-daily)	4,589,000	+25%	$208,158,000	-38%	$45.36
Nifedipine (once-daily)	4,072,000	-6%	$279,679,000	-6%	$68.68
Oxybutynin (once-daily)	2,325,000	+16%	$191,414,000	+11%	$81.73
Fentanyl (transdermal)	N/A	N/A	$940,980,000	-1%	N/A
Fentanyl (buccal)	N/A	N/A	$272,969,000	-21.4%	N/A
Total	63,578,000		$4,559,502,000		

* Extracted from SDI's Vector One®: National 2009 & 2010 Top 200 Branded Drugs by Retail Dollars

Leading Generic DDEP Retail Sales & Prescriptions, 2010

The majority of top-selling generic DDEPs were oral sustained-release formulations. This makes sense, as oral sustained-release formulation technology has been a part of most generic company

FIGURE 1



Branded & Generic DDEP US Market Shares, 2010, Sales & Prescriptions

formulation toolboxes since the late 1990s.

What aren't found in the top tier of generic DDEPs are generic inhalation products. This is a result of there being no simple, and cheap, regulatory pathway for generics, and the absence of low-cost generic metered dose or dry powder inhalation platforms. What was once a relatively low-cost metered dose inhalation platform based on CFC technology was discontinued at the end of 2008 when final CFC restrictions were imposed.

THE IMPACT OF GENERICS ON BRANDED DDEPS

It is a simple exercise to estimate the impact of generic drug delivery enabled pharmaceuticals on their brand name equivalents at the retail level. Multiplying the 100.9 million prescriptions for generic DDEPs in 2010 (Table 1) by the average price of a branded DDEP ($212, from last month's article), and rounding up for the full US market, we come up with a figure of $24 billion.[1]

REFLECTIONS

Generics are an integral part of the pharmaceutical ecosystem. Companies developing DDEPs need to figure out how to extend market exclusivity for their products if they hope to prosper. As it stands now, it's "3 and out;" that is 3 years and then a generic, for any DDEP that shows commercial promise, particularly any type of oral sustained-release, or buccal, pharmaceutical product.

Too many drug delivery technologies have become commodity items. To extend market exclusivity, the industry needs to raise the innovation bar. By developing new technologies that provide better therapeutic outcomes through unique delivery approaches for common medical conditions, the industry can recapture the value it delivers. The key to success in the drug delivery sector is not just new, but proprietary.

Inhalation products requiring a custom device or a unique formulation have a very strong position with respect to generics. In addition to having specific intellectual property related to their device, they are immune to substitutable generics in the US because there is no regulatory pathway for bioequivalence-only generics approval.

We have previously suggested that DDEPs be afforded some of the regulatory protection that is extended to Orphan drugs and Biologicals.[2] There would be real value in providing companies developing DDEPs a 7-year period of exclusivity with respect to ANDA equivalents. This would not prevent the approval of competitive products that secure approval through the NDA process, most typically 505(b)(2), but would eliminate for 7 years the threat of cheap-to-approve substitutable generics.

Hoping for a regulatory solution is hoping for a miracle. In the meantime, companies wanting to profit by developing DDEPs will need to come up with next-generation technology that not only provides next-generation therapeutic improvements but also comes with next-generation intellectual property protection. It can be done, but it won't be easy. ◆

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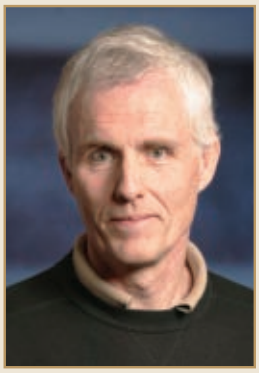
2. Bossart J. Two questions for drug delivery. Drug Development & Delivery. 2011;11(4):22-25.

BIOGRAPHY

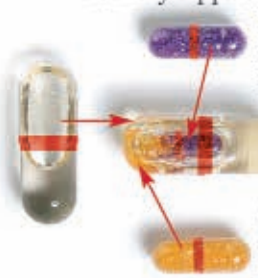


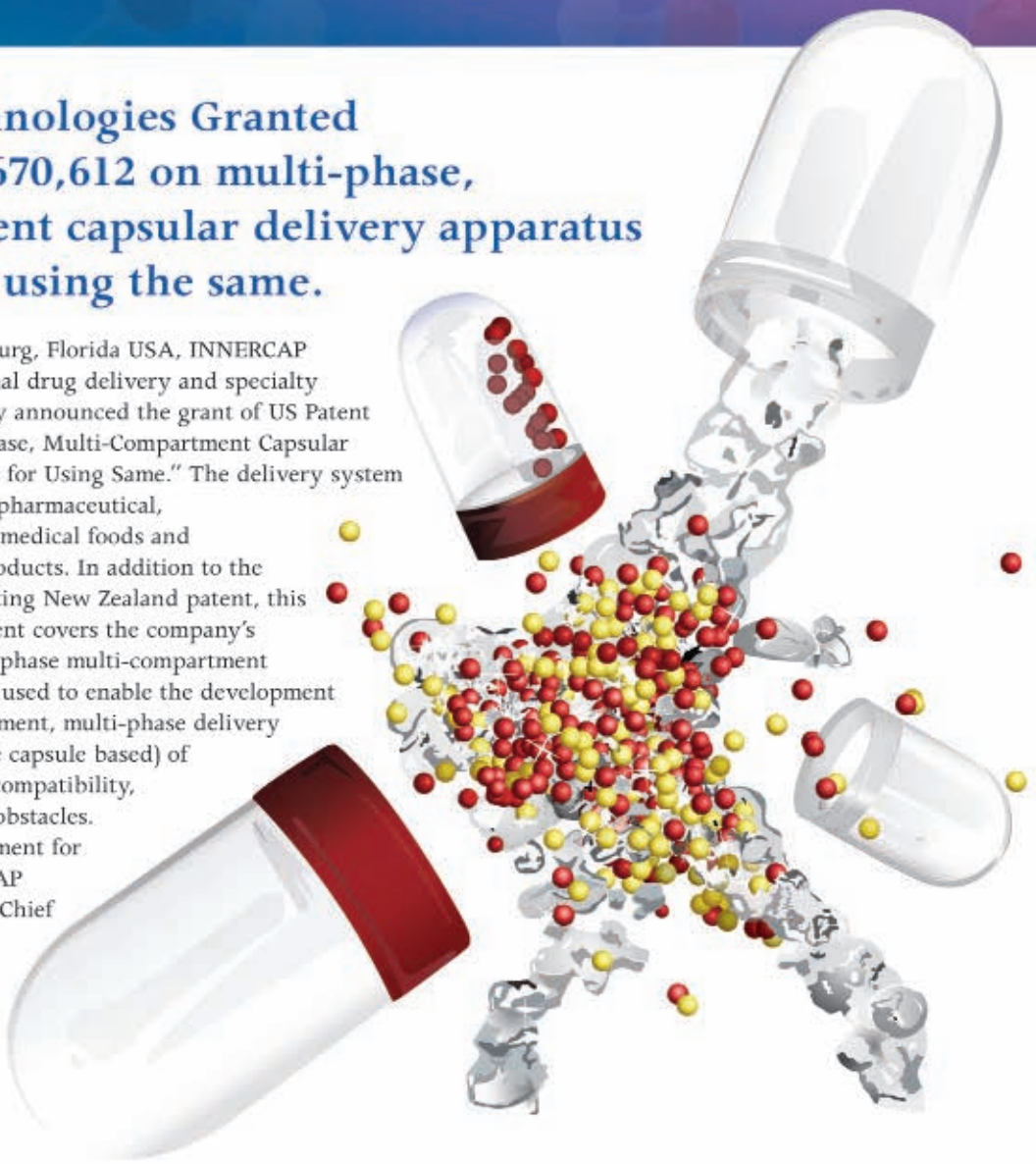
Dr. Josef Bossart is Managing Director of The Pharmanumbers Group, a boutique research and consulting group providing the biopharmaceutical industry with analysis and insights that improves business outcomes. In addition to issuing industry reports, such as DDEP2011 - Drug Delivery Product Success Rates, Development Times, Costs and Marketing Exclusivity, Pharmanumbers providesb strategy consulting and forecasting support for emerging and commercial-stage drug delivery companies. Dr. Bossart has more than 3 decades of experience in the biopharmaceutical sector, including senior sales, marketing, business development, and management positions with Enzon Pharmaceuticals, GeneMedicine, US Ethicals, and Rhône-Poulenc Rorer. Dr. Bossart earned his PhD in Medicinal Chemistry from The Ohio State University, College of Pharmacy.

THE ADVANTAGES

OF MULTI-PHASE, MULTI-COMPARTMENT CAPSULES ARE CLEAR

INNERCAP® Technologies Granted US Patent No. 7,670,612 on multi-phase, multi-compartment capsular delivery apparatus and methods for using the same.





March 23, 2010, Saint Petersburg, Florida USA, INNERCAP Technologies, Inc., an international drug delivery and specialty pharmaceutical company, recently announced the grant of US Patent No. 7,670,612 entitled "Multi-Phase, Multi-Compartment Capsular Delivery Apparatus and Methods for Using Same." The delivery system has uses for bio-pharmaceutical, pharmaceutical, medical foods and nutraceutical products. In addition to the existing New Zealand patent, this patent covers the company's multiphase multi-compartment delivery system used to enable the development of multicompartment, multi-phase delivery forms (two piece capsule based) of combination products that have compatibility, formulation or targeted delivery obstacles.

"This is a significant development for INNERCAP Technologies NOVACAP technology," said Fred H. Miller, Chief Executive Officer at INNERCAP. "The continued growth of our patent portfolio establishes INNERCAP as one of the leading companies in this space."

The delivery system and combinations covered by the patent have the ability to deliver therapeutic entities that have never been combined previously and now can be administered together, via an oral, implanted, or suppository capsule, in the most advantageous pharmacokinetic profile, utilizing different physical phases. This technology can therefore be used to enable capsule administration of compounds that are not normally administered as a combination product. The efficacy, safety, and side-effect profiles of drugs can be substantially improved using this delivery technology. It will also provide very significant quality-of-life improvements for patients and substantial economic savings for hard-pressed healthcare systems.

"INNERCAP's multi-phase, multi-compartment technology has been commercially manufactured and validated in several products, demonstrating that INNERCAP's delivery system creates real value to consumers and branded manufacturers," added Mr. Miller.

INNERCAP was represented by Cliff Davidson, Esq. of the patent firm Davidson, Davidson & Kappel, LLC (www.ddkpatent.com) based in New York City.

For more information contact us at the telephone number and email address below:

INNERCAP® TECHNOLOGIES, INC

United States Patent No. 7,670,612
US and International Patents Pending

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MARKET BRIEF

Injectable Drug Delivery - Easing the Pain With Technology

By: Debbie Toscano, Senior Industry Analyst, Frost & Sullivan

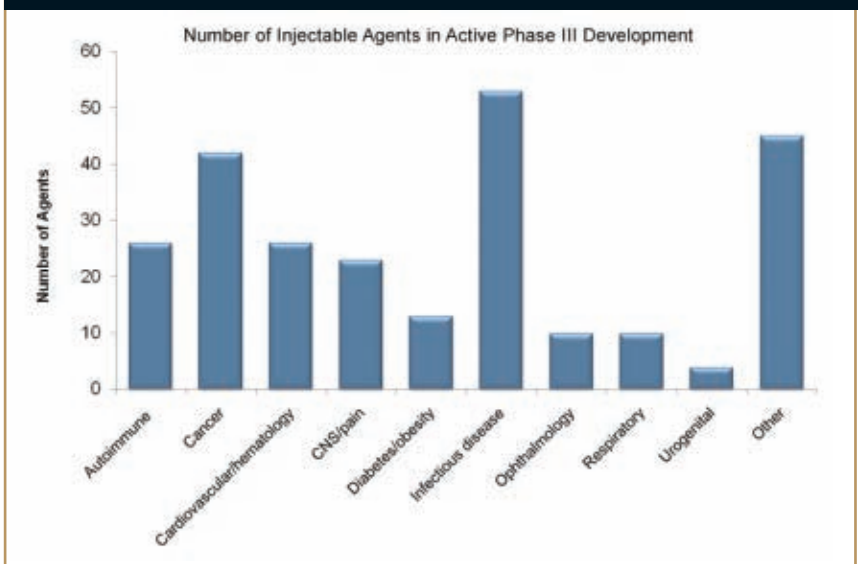
INTRODUCTION

Injectable drugs are used for the treatment and prevention of a wide variety of diseases, such as diabetes, cancer, autoimmune disorders, and infectious diseases. Of the 111 routes of administration for drugs recognized and approved by the US Food and Drug Administration, the injection route is probably the least desirable among the majority of patients and healthcare providers, particularly for chronic therapy. From a patient perspective, it can be painful, inconvenient, complicated, and expensive. Physicians are mainly concerned for their patients' lack of compliance and the side effects sometimes associated with injections, such as immune reactions. It is estimated that 50% of all long-term medications are discontinued in the first year. However, injection is often the only option for introducing certain types of drugs to the body due to their vulnerability of degradation by digestive enzymes, poor solubility, or poor absorption. Targeted delivery of the drug to the intended site is another factor that may necessitate injectable delivery in order to reduce the systemic exposure of certain drugs and therefore reduce side effects. Injectable drugs are available in several forms, most commonly prefilled syringes, autoinjectors, vials, and ampules.

The current drug development pipeline is filled with numerous injectable candidates across a wide spectrum of disease areas. Therapies targeted for infectious diseases and cancers top the list, followed closely by autoimmune diseases, such as rheumatoid arthritis and multiple sclerosis, and cardiovascular/hematology indications, such as heart failure, thrombosis, and anemia. Figure 1 depicts the number of drugs or biologics in late-stage development by disease area.

One of the most important advances in pharmacotherapy is biopharmaceuticals, which are therapies derived from biological sources, such as living cells or animal tissues and may be composed of sugars, proteins, or nucleic acids. As these large and complex molecules are easily denatured or altered with harsh handling or processing, in most cases, oral drug delivery is not an option. Due in part to their complexity, many biopharmaceuticals, such as monoclonal antibodies and insulin, are effective in ways not duplicated by synthetic small molecules, providing desperately needed therapeutic options to millions of patients. In such cases, the clinical benefits offered by the therapy far outweigh the disadvantages of injectable delivery. The physical properties of many biologics,

FIGURE 1



Number of Injectable Agents in Phase III Development

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such as high viscosity and the necessity of injection of volumes up to 1 ml, are driving the market for improved drug delivery devices. Injectable delivery also presents a challenge when formulating biologics. Ultra-fine gauge needles can make for virtually pain-free injection, but they often cannot handle delivery of large molecules or highly viscous formulas. Innovation in injectable drug delivery system design is in a constant state of evolution as manufacturers strive to meet the ever-changing demand for safe, functional, and patient-friendly devices.

VIALS

One of the oldest primary containers for injectable drugs is vials. These containers are usually made from glass and have a stopper over the neck from which the medication can be drawn with the use of a hypodermic needle. To help ensure sterility and safety from contamination or tampering, injectable drug vials have secondary seals made from aluminum shells and an attached plastic button. The dosage preparation from vials and ampules can be daunting and complicated. It requires multiple steps, including reconstitution or dilution if needed, placing the needle on the syringe, drawing up the correct amount of medication into the syringe, and performing the injection. In addition, because the glass vials that injectable drugs are packaged in are typically overfilled by 25% to 30% to ensure the end-user can withdraw the required dose, more drug is often drawn than required. When the excess drug is purged out in efforts to reach the correct dosage, many times the final volume of drug in the syringe does not match the dosage requirement.

PREFILLED SYRINGES

Prefilled syringes help to overcome several barriers to injectable delivery, such as safety and ease of use. A prefilled syringe contains a single-dose of medication and a fixed needle. They can be made from glass or plastic and are typically reserved for medications that are administered either by subcutaneous or intramuscular injection. Compared to using the traditional vials as a primary container, prefilled syringes are easier and more convenient for patients, caregivers, and medical staff to use. For instance, they eliminate several steps in the injection process, such as the need to remove the drug from the vial and the reconstitution of lyophilized medications. In addition, use of prefilled syringes helps ensure safety by eliminating dosing errors and minimize the risk of needlesticks. They also help eliminate waste by decreasing the number of containers and packaging required to perform an injection. In addition, use of prefilled syringes reduces medication waste because vials are intentionally overfilled by 20% to 30% to account for potential drawing errors.

SELF-INJECTION SYSTEMS

Self-injection systems contain multiple doses of medication in a cartridge and are used several times. These devices are typically reserved for medications that are taken daily or multiple times per day such as insulin, human growth hormone, and fertility treatments. Self-injection systems can be either reusable or disposable. The first and most commonly used self-injection system is the pen injector. Another self-injection system is the automatic injector, which automatically inserts the needle into the injection site and performs the injection. Historically, automatic injectors were reserved for emergency situations like the administration of epinephrine. Examples of automatic injectors include Rebiject and SureClick.

AMPULES

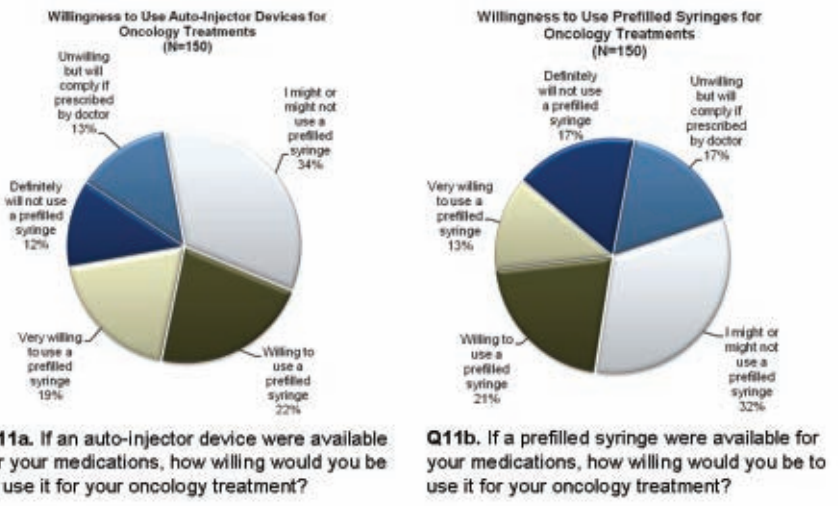
Ampules were the first containers just for injectable medications. They are essentially glass vials that are hermetically sealed to protect the medication from the air. The ampule is opened by breaking open the top and removing the medication with a hypodermic needle. Only a few medications, like local anesthetics, still come in ampules.

SELF-INJECTION ON THE RISE

With increases in the number of Americans suffering from diseases like

FIGURE 2

Respondents indicated various degrees of willingness to use auto-injectors and prefilled syringes. Roughly 4 out of 10 (41%) were willing or very willing to use auto-injectors, while 31% were willing/very willing to use a prefilled syringe. About one-third of each group in each category indicated uncertainty ("might or might not use"), which could represent an education opportunity.



Q11a. If an auto-injector device were available for your medications, how willing would you be to use it for your oncology treatment?

Q11b. If a prefilled syringe were available for your medications, how willing would you be to use it for your oncology treatment?

Willingness to Use Auto-Injector & Prefilled Syringe (US), 2009

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diabetes and cancer that require the use of injectable medications, the number of patients who self-administer their medication via this route is escalating. Further propelling this trend is the increasing number of medications that are available in easier-to-use platforms, such as self-injection systems and prefilled syringes. Other trends that are contributing to the growth of self-injection are the development of novel injectables and biopharmaceuticals for chronic diseases that were previously untreatable, such as genetic disorders like hemophilia and Gaucher's disease. Another important factor is increased use of home healthcare. Historically, home healthcare was reserved for the elderly or terminally ill. As insurance companies and agencies are increasingly trying to find ways to cut healthcare costs, the range of treatments done on an outpatient basis has expanded. Also, home treatment, particularly for injectable drugs, is seen as an area of opportunity for many pharmaceutical and biotechnology companies. Figure 2 presents the willingness of cancer patients to use prefilled syringes and autoinjectors in the US in 2009.

As an example of patient feedback in the injectable drug area in a 2009 Frost & Sullivan research piece, cancer patients (n = 150) with breast, colorectal, prostate, and lung cancer were asked about willingness to use autoinjectors and prefilled syringes as delivery mechanisms for their oncology treatment. This research found that 41% of patients were willing or very willing to use an autoinjector, while 31% were willing or very willing to use a prefilled syringe. Approximately one-third of patients were neutral for both delivery types, which could yield an education opportunity to developers if product benefits can be translated to the patient. Furthermore, a segment of patients were unwilling but would comply if prescribed by their physician (13% for autoinjector, 17% for prefilled syringes). Overall, platforms that allow patients to self-inject at home and simplify their injection experience are beneficial and often sought after for treatment.

LATEST ADVANCES

Areas still open to technological advancement are improvements in ease of use for patients and innovative safety features that help avoid needlestick injuries. Some of the more recent advances in injection device technology include development of multi-chamber prefilled syringes that have the capability to reconstitute lyophilized drugs with the push of a button. Unilife has combined functionality and safety with the development of the EZMix, a multi-chamber prefilled syringe that also incorporates an integrated safety mechanism designed to avoid needlestick injuries. Needle-free injection jet devices are another alternative to parenteral administration, which can ease patient anxiety and offer increased safety. EMD Serono's cool.click™2 provides pediatric patients with a needle-free way to deliver their weekly dose of growth hormone.

Although there are a few industry players taking a shot at converting injectable-only drugs into oral forms, this still remains a challenging field of experimentation, which has not yet produced any winners. Development of biologics continues to produce promising treatments that are fulfilling important unmet medical needs. Many biosimilars, or "generic biologics," of expensive biologic therapies are also in development and promise to deliver more affordable treatment options here in the US in the near future (several are already approved in Europe and other parts of the world). Injectable medications will continue to occupy an integral portion of the pharmaceutical market. However, the continual advancement of injection device technology promises to help ease the pain for patients and their caregivers. ◆

For more information on this and other relevant topics, please visit Frost & Sullivan at www.frost.com.

BIOGRAPHY

Debbie Toscano is a Senior Industry Analyst with the Frost & Sullivan North American Healthcare practice. Utilizing more than 20 years of life sciences industry experience, she maintains particular expertise in analysis and interpretation of scientific data as well as preparation of deliverables with attention to technical detail. Mrs. Toscano has an experience base covering a broad range of sectors, including focus on diabetes and metabolic diseases, cardiovascular diseases, and preclinical animal modeling and pharmacology. Prior to joining Frost & Sullivan, she conducted preclinical research with Novartis Pharmaceuticals. Mrs. Toscano earned her BS from Delaware Valley College in Biology and her Master's Certificate from Thomas Edison State College in Clinical Trials Management.

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Recent Trends in Drug Discovery & Drug Solubility: A Novel Hybrid Particle-Engineering Approach to Solving the Insoluble

By: Gary G. Liversidge, PhD

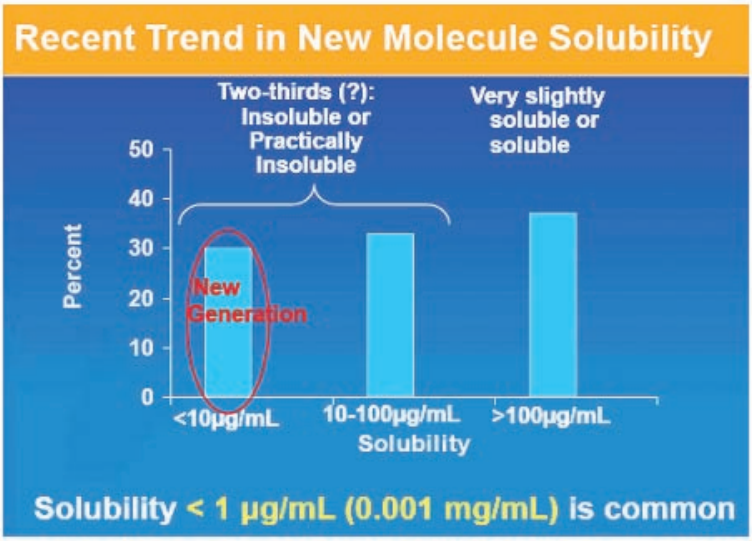
TRENDS IN DRUG DISCOVERY

Increasingly, combinatorial chemistry and high-throughput screening approaches have resulted in a significant shift in the drug discovery landscape. Widespread use of sophisticated automation and miniaturization technologies have enabled large libraries of compounds to be synthesized and screened for biologic activity and are, as a result, leading to molecules exhibiting greater lipophilicity, higher molecular weight, and a weakly basic chemistry. Modern approaches to lead identification and optimization focus increasingly on the broader spectrum of drug-like properties, including aqueous solubility, intestinal permeability, metabolic stability, and susceptibility to transporter effects that are likely to impact drug absorption, disposition, and toxicity.[1]

RECENT TRENDS IN DRUG SOLUBILITY

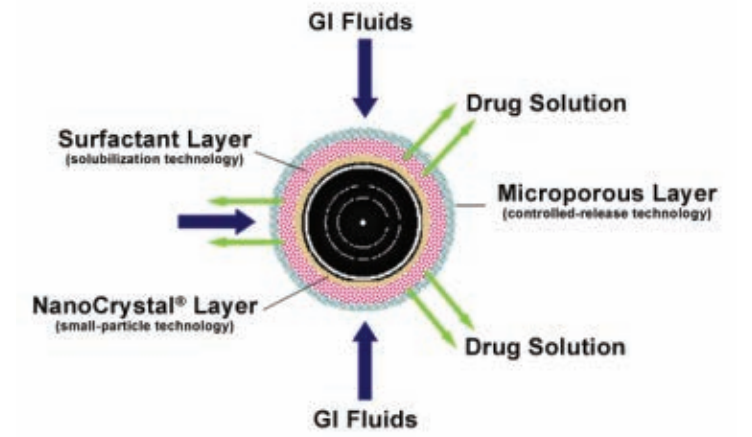
Owing to the biologic complexity associated with new disease targets and their location behind increasingly hydrophobic barriers, today's drug discovery pipelines continue to exert significant formulation pressure on newly emerging drug candidates. Trends in drug design increasingly favor greater degrees of lipophilicity, higher molecular weight, greater physical form complexity, and significantly lower aqueous solubility.[2]

FIGURE 1



Recent trend in new molecule solubility. Adapted from reference 4.

FIGURE 2



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Accordingly, it is estimated that up to 90% of new molecular entities now suffer from poor aqueous solubility.[3] More specifically, it is estimated that about two-thirds of new molecules exhibit aqueous solubility < 100 µg/mL (ie, insoluble or practically insoluble), with at least one-third exhibiting aqueous solubility < 10 µg/mL (Figure 1). Increasingly, the pharmaceutical industry is looking to supersaturating drug delivery systems (SDDS) to address the biopharmaceutical limitations associated with solubility-limited oral bioavailability.

POTENTIAL SOLUTIONS

As a consequence of the clear trends emerging from the drug discovery process, it is expected that solubility-limited oral absorption will continue to pose a significant challenge in small-molecule drug development. Accordingly, formulation scientists are increasingly in need of reliable and robust technology solutions capable of surmounting this important drug delivery issue. Several technology approaches, each capable of enhancing drug solubility in-vivo are available, with varying degrees of success. These include solid amorphous dispersions, pharmaceutical co-crystals, self-emulsifying and self-microemulsifying drug delivery systems, and a relatively new hybrid particle engineering approach.

HYBRID PARTICLE ENGINEERING APPROACH – THE NANOSMOTIC® TECHNOLOGY APPROACH

A new approach to the challenge of solubility-limited oral absorption utilizes Alkermes Contract Pharma Services' NanOsmotic® technology, which combines particle engineering, solubilization, and osmotic controlled-release technologies in unique spatial arrangements within a single drug delivery system.

NanOsmotic® technology is a family of novel, closely related formulation and process approaches for the efficient and effective delivery of poorly water-soluble drugs by the oral route. The technology is a synergy of proprietary particle engineering technologies with widely available solubilization and osmotic controlled-release technologies that afford potential for significant improvement in drug product performance relative to more conventional formulations approaches or utilization of particle engineering technologies alone.

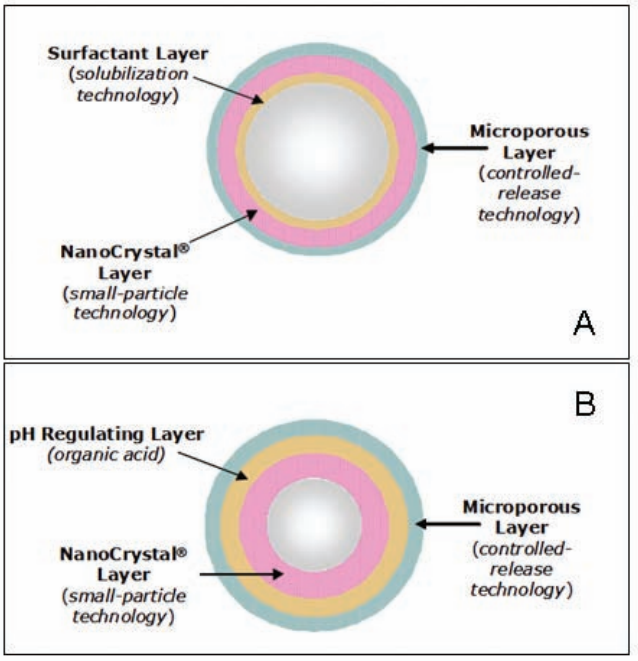
NanOsmotic® technology has the ability to maintain a drug in its original crystalline form until biologically activated. Following activation, a thermodynamically enhanced form of the drug is delivered from the system and maintained for a period of time sufficient to achieve absorption.

WHAT IS NANOSMOTIC® TECHNOLOGY?

In its most simplistic form, the NanOsmotic® technology is composed of 1) an inert substrate, 2) a poorly water-soluble drug in the form of ultra-fine particles, 3) an inactive component capable of fully solubilizing the drug, and 4) a controlled-porosity, microporous membrane (typically the outermost layer) that serves to separate the internal composition from the external environment of use (Figure 2). The force that drives the NanOsmotic® technology is an osmotic pressure gradient that develops across the controlled-porosity membrane upon exposure of the device to gastrointestinal fluids. During normal operation of the system, aqueous fluids penetrate the inner core and completely dissolve the solubilizing component and, rapidly thereafter, the ultra-fine particles of drug (Table 1).

The technology can be designed for immediate and/or prolonged delivery of drug to the gastrointestinal tract, with initiation of drug release occurring either immediately upon contact with aqueous fluids or after a defined "lag time." Both the duration of the lag time and the rate of delivery of drug from the system represent programmable outputs that can be modulated by the porosity and thickness of the microporous membrane and the composition of the osmotically active core. NanOsmotic® formulations may also be combined with conventional, aqueous-based, enteric coatings in situations where pH-dependent release of drug is beneficial. Commercial NanOsmotic® presentations

FIGURE 3A&B



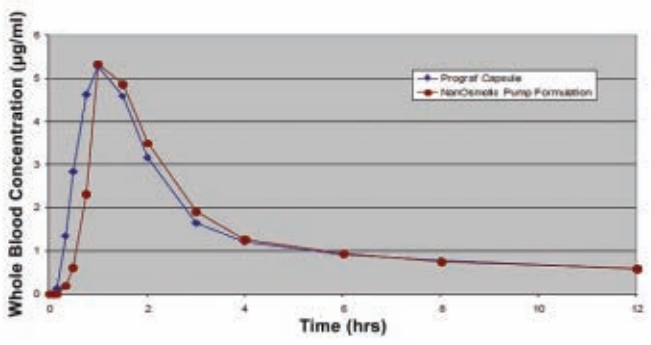
A- Schematic of Tacrolimus NanOsmotic® Formulation
B. Schematic of Clozapine MR NanOsmotic® Formulation

TABLE 1

Step 1	GI fluids dissolve water-soluble pore formers embedded within insoluble outer shell of ethylcellulose.
Step 2	GI fluids permeate newly formed controlled-porosity, micro-porous membrane and progress inward toward core.
Step 3	GI fluids dissolve solubilizing layer and other water-soluble components of the internal environment.
Step 4	Solubilizers attack NanoCrystal® layer and rapidly dissolve drug nanoparticles.
Step 5	Osmotically active drug solution draws increasingly more GI fluids into internal environment.
Step 6	Drug solution is progressively displaced from internal environment via convection (volume flow).
Step 7	Solubilized drug permeates outer shell, enters external environment, and is subsequently absorbed.

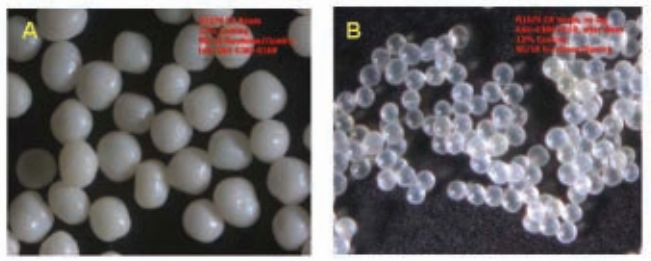
Sequence of events underpinning the operational principles of the NanOsmotic® technology.

FIGURE 4



Mean concentration-versus-time profiles following single, 1-mg, oral doses of tacrolimus in fasted beagle dogs.

FIGURE 5A&B



A. Micrograph of modified-release NanOsmotic® technology following curing of the controlled-porosity layer.

B. Micrograph of translucent modified-release NanOsmotic® technology "ghost" shells following in vitro testing in simulated GI fluids.

may take the form of monolithic tablets, hard gelatin capsules containing multiparticulates and/or mini-tablets, "sprinkle" dosage forms, sachets, etc, that can be manufactured using conventional pharmaceutical unit operations and processes.

ADVANTAGES OF NANOSMOTIC® TECHNOLOGY

The NanOsmotic® technology can offer a number of potential performance advantages over competing technologies in the poorly water-soluble drug delivery space. These include improved bioavailability, improved chemical and/or physical stability, higher drug loading, and the ability to achieve programmable drug release through minor changes in formulation composition.

SUCCESS TO DATE

To date, the NanOsmotic® technology has been applied successfully to the delivery of two poorly water-soluble drugs: tacrolimus (Figure 3A) and clozapine (Figure 3B). In the case of tacrolimus, the NanOsmotic® technology formulation was shown to provide equivalent Pharmacokinetic (PK) performance in fasted beagle dogs to that of an amorphous solid dispersion formulation (ie, Prograf®), as shown in Figure 4, despite presentation of the drug in a less energetically favorable but more thermodynamically stable (ie, crystalline) form. The NanOsmotic® technology has served as the core underpinning in the development of prototypes that are planned for dosing in a human pilot PK study (Figures 5A & 4B).

FUTURE POTENTIAL

It is envisioned that the NanOsmotic® technology may afford value-added performance advantages for a host of poorly water-soluble compounds, ranging from high-potency, low-dose steroids and immunosuppressants (eg, fluticasone, tacrolimus MR, sirolimus etc) to higher dose compounds that suffer from significant pH-dependent solubility. For NCEs, the NanOsmotic® technology may offer performance-enhancing capabilities, enabling "supercharged" NanoCrystal® formulations to compete more favorably with solid dispersion and melt technologies. Accordingly, the NanOsmotic® technology offers a number of potential performance advantages over alternative technologies in the poorly water-soluble drug delivery space, including enhanced bioavailability, improved chemical and physical stability, higher drug loading, and the ability to achieve programmable release of drug for extended periods of time.[5] ◆

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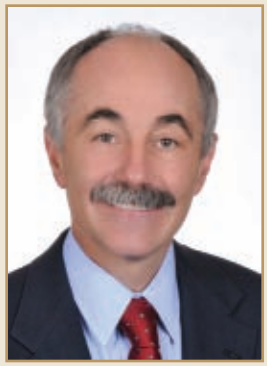


Dr. Gary G. Liversidge is Chief Technology Officer at Alkermes. For more than 20 years, he has been at the forefront of developing the NanoCrystal® technology and related technologies. Dr. Liversidge has served in a number of critical scientific and managerial positions related to the strategic advancement of Alkermes' technologies, products, and relationships.

INTRANASAL DELIVERY

Nose-to-Brain Drug Delivery: A Review

By: Hardik K. Patel, MPharm; Rajnikant M. Suthar, MPharm; Sandip R. Patel, MPharm; Meghana C. Patel, Mukesh B. Jadeja, MPharm; Rutvik M. Thumar, MPharm

ABSTRACT

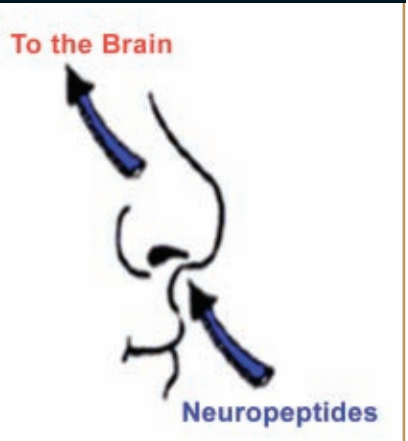
The central nervous system (CNS) is one of the most complex systems in the human body. Much of the clinical failure of potentially effective therapeutics for CNS disorders is often not due to a lack of drug potency but rather to shortcomings in the method by which the drug is delivered. The transport mechanisms through the blood-brain barrier (BBB) and physico-chemical properties of the drug molecules are major factors to be considered in designing a drug delivery system for brain targeting. A great deal of interest has recently been focused on the exploration of the intranasal route for the delivery of drugs to the brain due to the high permeability of the nasal epithelium, allowing a higher molecular mass cut-off at approximately 1000 Da, and the rapid drug absorption rate with plasma drug profiles sometimes almost identical to those from intravenous injections. Intranasal drug administration offers rapid absorption to the systemic blood, avoiding first-pass metabolism in the gut wall and the liver. Further, several studies have shown a direct route of transport from the olfactory region to CNS in animal models, without prior absorption to the circulating blood.

INTRODUCTION

Despite noteworthy progress in the neurosciences and a corresponding high interest in brain delivery technologies, very few drugs have been marketed for such indications to date. This is not due to a lack of new CNS drugs or ideas for improvement of drug transport to the brain, but to a negative interaction of sometimes much less sophisticated reasons. Qualified by its physical proximity, an interesting place for application of brain-active drugs is the nose.

The BBB and blood-cerebrospinal fluid barrier (BCF) are the major bottlenecks in drug delivery to the brain. Drugs used to treat CNS diseases should reach the brain via the BBB/BCF, which restricts the passage of hydrophilic and large lipophillic molecules to the brain.[1] An area of ongoing research is discovering methods of improving the delivery of drugs directly to the CNS through nasal administration - by manipulating tight junctions and by use of specific receptors present at the BBB. A great deal of interest has recently been focused on the exploration of the intranasal route for the delivery of drugs to the brain due to the high permeability of the nasal epithelium, allowing a higher molecular mass cut-off at approximately 1000 Da, and the rapid drug absorption rate with plasma drug profiles sometimes almost identical to those from intravenous injections. Even though a number of challenges are still to be overcome, especially with respect to toxicity, the potential of nasal drug delivery (NDD), including the ability to target drugs across the BBB, is very great.[2] In recent past, studies have shown the nasal route can also successfully be used for delivery to CNS. The direct anatomical connection between the nasal cavity and the CNS

FIGURE 1



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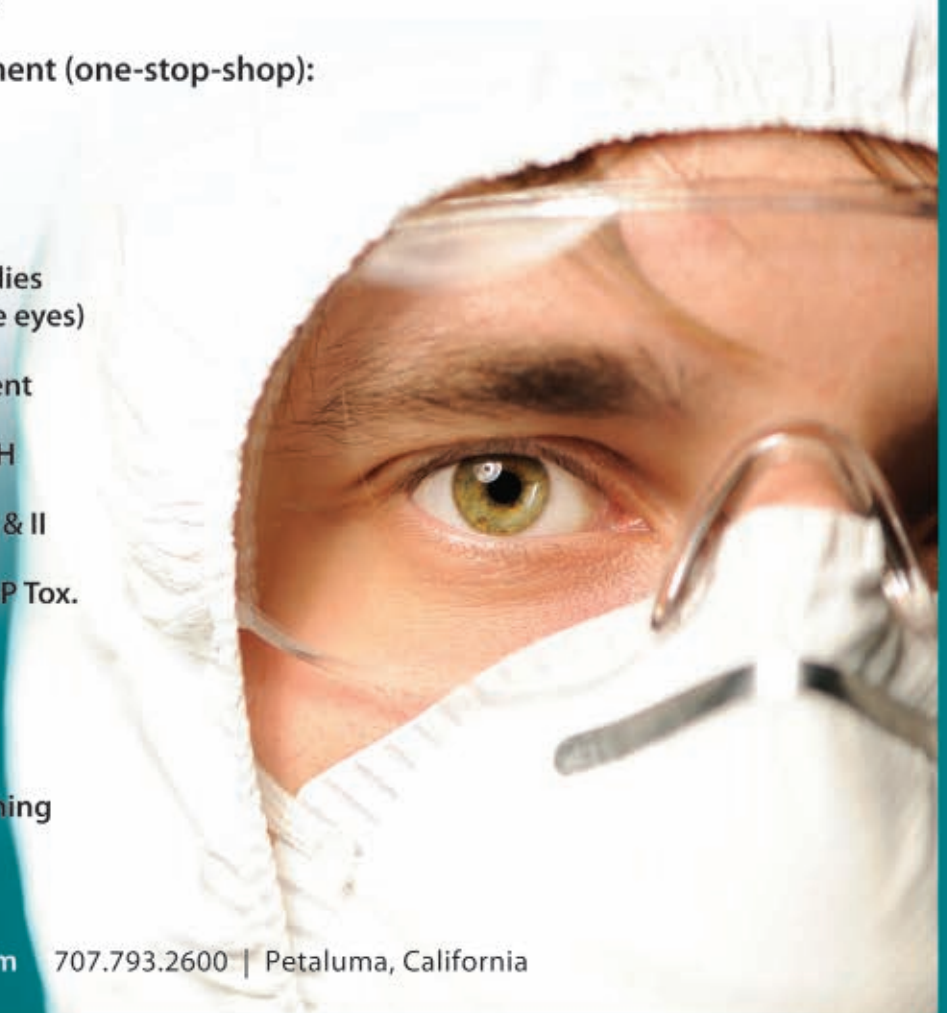

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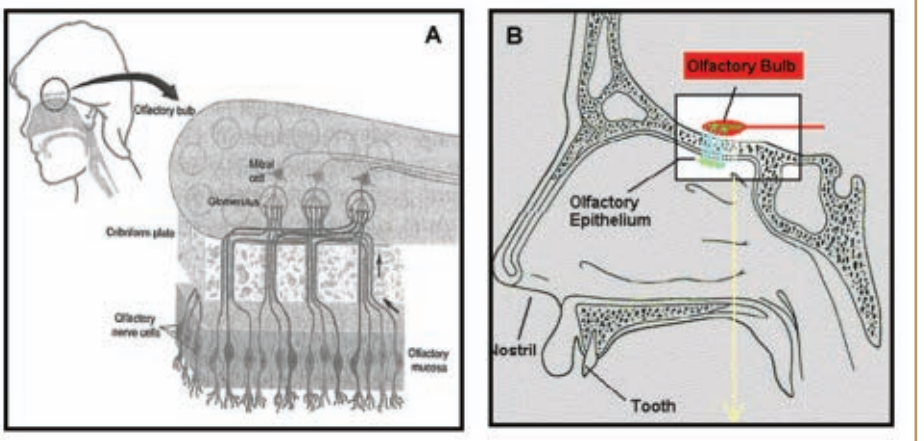
makes it possible to deliver many substances, including tracer materials, heavy metals, low molecular weight drugs, and peptides, directly into the CNS by circumventing the BBB, which provides the basis for the development of CNS therapeutic agents for intranasal administration.[3] It is the only site in the human body where the nervous system is in direct contact with the surrounding environment. Drugs have been shown to reach the CNS from the nasal cavity by a direct transport along the olfactory and trigeminal neural pathways.[4,5] Drugs administered to the CNS by the intranasal route circumvent the BBB as well as avoid the hepatic first-pass effect, systemic dilution effect, reduces drug delivery to non targeted sites, facilitates administration of lower doses, and in turn, reduces toxicity.[6,7] Intranasal drug administration offers rapid absorption to the systemic blood avoiding first-pass metabolism in the gut wall and the liver and has been shown to present a safe and acceptable alternative to parenteral administration of various drugs. Further, several studies have shown a direct route of transport from the olfactory region to the CNS in animal models, without prior absorption to the circulating blood.[8-11]

ADVANTAGES & LIMITATIONS

Nasal drug delivery is non-invasive, rapid, and comfortable. It bypasses the BBB and targets the CNS, thereby reducing systemic exposure and thus systemic side effects. Moreover, it does not require any modification of the therapeutic agent being delivered. It facilitates the treatment of many neurologic and psychiatric disorders. Rich vasculature and highly permeable structure of the nasal mucosa greatly enhance drug absorption. Nose-to-brain drug delivery minimizes to a certain extent the problem of degradation of peptide drugs. This type of drug delivery avoids destruction in the gastrointestinal tract, hepatic first-pass elimination, and gut wall metabolism, allowing increased, reliable bioavailability.

Nasal delivery is expected to decrease with an increase in the molecular weight of the drug. Some therapeutic agents may be susceptible to partial degradation in the nasal mucosa or may cause irritation to the mucosa. Nasal congestion due to cold or allergies may interfere with this method of delivery. Frequent use of this route results in mucosal damage (eg, infection, anosmia).

FIGURE 2A&B



The olfactory bulb, olfactory mucosa, and olfactory nerve cells in humans.

ANATOMY & PHYSIOLOGY OF NASAL CAVITY

Anatomical Features

The human nasal cavity has a total volume of about 16 to 19 ml, a total surface area of about 180 cm^2, and is divided into two nasal cavities via the septum. The volume of each cavity is approximately 7.5 ml, having a surface area around 75 cm^2.[12,13] Post drug administration into the nasal cavity, a solute can be deposited at one or more of three anatomically distinct regions: the vestibular, respiratory, and olfactory. The vestibular region (covered by a 2- to 4-mm thick nasal mucosa) is present at the opening of nasal passages and is responsible for filtering out the airborne particles.[14] The nasal cavity consists of both respiratory and olfactory mucosa. PH of the mucosal secretions is 5.5 to 6.5 in adults and 5.0 to 6.7 in children.[15] The enzymes present in the nasal cavity include Cytochrome P450, CYP1A, CYP2A, CYP2E carboxylesterases, and glutathione S-transferases.[24,25] Human nasal cavities are lined with three types of epithelia: squamous, respiratory, and olfactory.[16]

Functions of the Olfactory Region

The sense of smell is called olfaction and involves detection and perception of chemicals that enter the nasal cavity. The precise mechanism of olfaction is unknown. The electrical activity produced in the hair-like cells is transmitted to mitral cells in the olfactory bulb.

Nasal Transport Routes to Brain

Following nasal delivery, drugs first reach the respiratory epithelium, where compounds can be absorbed into the systemic circulation utilizing the same pathways as any other epithelia in the body: transcellular and paracellular passive absorption, carrier-mediated transport, and absorption through trancytosis. Although absorption across the respiratory epithelium is the major transport pathway for nasally administered drugs and may represent a potentially time-saving route for the administration of certain systemic drugs delivered in cryonics medication protocols (eg, epinephrine or vasopressin), the author considers the problem of BBB-mediated

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exclusion of brain-therapeutic agents to be of greater immediate concern. Accordingly, the remainder of this discussion will focus primarily on the transport of drugs to the CNS by way of the olfactory epithelium. When a nasal drug formulation is delivered deep and high enough into the nasal cavity, the olfactory mucosa may be reached, and drug transport into the brain and/or CSF via the olfactory receptor neurons may occur. The olfactory pathways may be broadly classified into two possible routes: the olfactory nerve pathway (axonal transport) and the olfactory epithelial pathway.

Axonal transport is considered a slow route whereby an agent enters the olfactory neuron via endocytotic or pinocytotic mechanisms and travels to the olfactory bulb by utilizing the same anterograde axonal transport mechanisms the cell uses to transport endogenous substances to the brain. Depending on the substance administered, axonal transport rates range from 20 to 400 mm/day to a slower 0.1 to 4 mm/day. The epithelial pathway is a significantly faster route for direct nose-to-brain transfer, whereby compounds pass paracellularly across the olfactory epithelium into the perineural space, which is continuous with the subarachnoid space and in direct contact with the CSF. Then the molecules can diffuse into the brain tissue or will be cleared by the CSF flow into the lymphatic vessels and susequently into the systemic circulation.[17]

PROPOSED MECHANISMS OF NOSE TO BRAIN

There are three likely mechanisms underlying the direct nose-to-brain drug delivery; there could be at least one intracellular transport-mediated route and two extra cellular transport-mediated routes (extraneural, intraneural, and trigeminal).18

The intracellular transport-mediated route is a relatively slow process, taking hours for intranasal-administered substances to reach the olfactory bulb. The olfactory neurons in the olfactory epithelium could uptake the molecules by such process as endocytosis, which could reach the olfactory bulb by axonal transport. The two likely extracellular transport-based routes could underlie the rapid entrance of drug into the brain, which can occur within minutes of intranasal administration. In the first extra cellular transport-based route, intranasal-administered substances could first cross the gaps between the olfactory neurons in the olfactory epithelium, which are subsequently transported into the olfactory bulb.

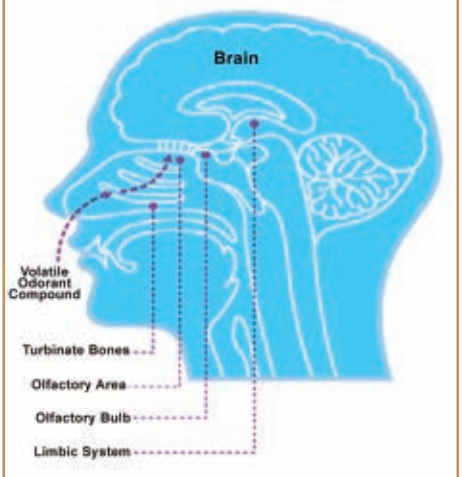
In the second extracellular transport-based route, intranasally administered substances may be transported along the trigeminal nerve to bypass the BBB. After reaching the olfactory bulb or trigeminal region, the substances may enter into the other brain regions by diffusion, which may also be facilitated by a perivascular pump that is driven by arterial pulsation.[19]

FACTORS AFFECTING NOSE-TO-BRAIN DELIVERY

The size of the molecule is the major determinant in whether a substance will be absorbed across the nasal respiratory epithelium and/or transported along the olfactory pathway. In general, molecules weighing more than 1000 Da are absorbed far less efficiently than smaller molecules.[20] However, the bioavailability of larger molecules may be increased with the use of permeation enhancers. Other factors affecting delivery to the brain include the degree of dissociation (determined by the pKa of a substance and the pH in the surrounding area) and lipophilicity (higher lipophilicity results in better transport). Once a drug is in the brain, it can be further influenced by BBB efflux transporter systems like P-glycoprotein (P-gp).

In addition to therapeutic agent efficacy, dosage form design also plays a key role in altering pharmacokinetics and bioavailability

FIGURE 3



Olfactory Regions in the Brain

following intranasal administration. After intranasal administration, drug can reach the brain directly bypassing the BBB through nasal olfactory and trigeminal pathways or by crossing the BBB after systemic absorption of the drug through the nasal respiratory epithelium.

Various factors affect nose-to-brain drug delivery, such as physico-chemical properties of drugs, eg, chemical form, polymorphism, molecular weight particle size solubility, and dissolution rate. Formulation factors include pH of the formulation, buffer capacity, osmolarity, gelling agents or gel-forming carriers, solubilizers, preservatives, antioxidants, humectants, drug concentration, dose, volume of dose, and role of absorption enhancers. Physiological factors include effect of deposition on absorption, nasal blood flow effect of mucociliary clearance, effect of enzymatic activity, and effect of pathological condition.

Due to the typical anatomy and physiology of the nasal cavity, distribution and deposition are mainly a function of the delivery system and delivery device. Many factors, such as mode of administration, particle size of the formulation, velocity of the delivered particles, spray angle, plume design, and spray cone, influence the uptake across the olfactory epithelium.

However, influence of these factors in nose-to-brain drug delivery is less critical.

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Drug retention at the absorption site and intimacy of the contact are two very important formulation factors in deciding the extent of CNS drug delivery following intranasal administration.

SUMMARY

Nasal drug delivery provides an exciting, novel, non-invasive, and convenient technique of delivering a variety of drugs directly to the brain. Many drug formulations for intranasal administration have been designed and marketed, and few are under active clinical investigations. Although limitations still remain, nose-to-brain drug delivery has great potential and an exciting future. It may not completely replace conventional solid dosage form therapy but could act in a synergistic way to offer a variety of options and strategies for better treating brain disorders and emergency situations. ◆

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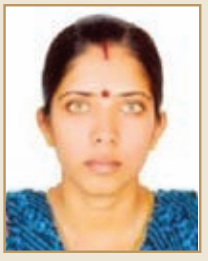

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Solid Dosage Forms for Biopharmaceutical Classification System Class II APIs

By: Garry Gwozdz, Robert Gwozdz, and Robert W. Lee, PhD

INTRODUCTION

It is well known and documented that a large number of new Active Pharmaceutical Ingredients (APIs) are poorly water soluble and are classified as Biopharmaceutical Classification System (BCS) Class II compounds (Figure 1).[1-4] This fact is one of the greatest challenges faced in current formulation development, and it is the formulator's job to ensure that the many promising APIs under development do not fail from poor bioavailability due to their low aqueous solubility. However, it should also be remembered that bioavailability is a function of more than just physical solubility. Many APIs administered as aqueous solutions still failed to provide good bioavailability due to poor membrane solubility (BCS Class IV). In contrast, biology can enhance bioavailability through interactions of the API with entities, such as bile salts and proteins, if properly presented - nature's surfactants. Also, intestinal efflux transporters can significantly impact oral bioavailability.[5]

The prevalence of low-solubility compounds has led to intensive research and generated many technologies to address it; although one size doesn't fit all, some may fit more than others. These technologies include chemical means, such as salt or pro-drug formation (not always an option) and physiochemical modification of the crystal structure, including amorphous forms, co-crystals, formulation with lipidic solubilizers, encapsulation by cyclodextrins, and particle size reduction techniques (eg, conversion into nanoparticulates/nanocapsules or into solid solutions/dispersions).[6-11] This article will focus on formulation of nanoparticulates via milling as well as solid solutions, as these are two of the most widely applicable of the available technologies. These techniques may be used for many routes of administration, such as intravenous, intramuscular, intranasal, intravaginal, and topical/transdermal. However, as oral administration of solid oral dosage forms is the most prevalent and preferred route of administration, conversion of the nanoparticulates into solid oral dosage forms will also be discussed.

PARTICLE SIZE REDUCTION

The surface area of a particulate is inversely proportional to the square of its effective diameter (Figure 2). As Ostwald and Freundlich taught us, increased surface area results in an increase in solubility (Figure 3), and Noyes and Whitney showed that increased surface area translates into an increased rate of dissolution (Figure 4). These properties are leveraged by formulators who employ particle size reduction as a technique to increase bioavailability. Particle size reduction can be accomplished by several top-down techniques, such as simple grinding, jet-milling, or wet-milling in

TABLE 1

SOLUMER FINGERPRINTS

Formulating lipophilic crystalline drugs results in a self-assembled drug-polymer complex. This provides two features that are required for improved bioavailability:

- Depression of melting temperature and energy
- Formation of colloidal dispersions upon contact with aqueous media

	API		Formulation		
	T_{melt} (°C)	ΔH_{melt} (J/g)	T_{melt} (°C)	ΔH_{melt} (J/g_{drug})	Particle size nm
Reservatrol	267.4	253.6	199.1	14.0	1224
Hesperetin	231.0	166.2	No peak of melting		1310
Nifedipine	172.4	113.4	140.9	8.4	749
Fenofibrate	81.5	74.3	64.4	9.3	669
Tacrolimus	135.0	60.5	118.0	52.0	836
Clarithromycin	227.6	70.2	207.9	40.1	1190
Albendazole	215.2	209.7	161.4	31.2	555
Fenbendazole	239.2	166.3	203.7	8.9	892
Itraconazole	169.7	84.4	155.6	21.9	910

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Solumer Fingerprints

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which existing larger particles are reduced in size. Simple grinding and jet-milling can reduce particle size, though normally these techniques are limited when attempting to achieve sub-micron size. However, for an API whose synthetic process provides poor control over particle size, these techniques may be useful as a first step to provide a starting material with reduced size and a narrower particle size distribution (PSD), prior to additional milling.

Historically, media milling in the wet state is the most common approach to achieve nanoparticulates. Media milling entails imparting movement to a coarse suspension of API in a vehicle with milling media. Energy is imparted to the API particulates through the impact of media-on-media. Aqueous-based vehicles are normally preferred, and may include milling aids, such as poloxamers or carboxymethyl cellulose, which may both wet the API, enhancing particle size reduction, as well as stabilize the resulting nanoparticulates. Milling media is available in a variety of materials, sizes, and shapes, though those made from very high purity, dense, non-porous ceramic as well as certain polymeric materials are intended for the strict requirements of pharmaceutical usage. As a general rule, smaller sized media normally results in smaller particulates due to increased points of contact with decreasing media size.

The simplest method of media milling is roller milling. Dense media and fluid are loaded into a jar or vessel, which is then rotated on a shaft or by rollers, and the "impacts" are driven by gravity. The speed of rotation, the amount and size of the grinding media, and the amount of fluid loading are all critical parameters that control the efficiency of the milling process. The impact depends on attaining a cascading motion and hence the media must be dense. However, even a very dense medium reaches a limitation for effective milling as its size decreases and/or as the milling fluid viscosity increases. This method is ideal for screening experiments to determine the proper conditions and formulation composition due to the small volumes that can be used.

Stirred media mills can use smaller grinding media, resulting in a finer grind. In a stirred media mill, the grinding media is moved by the rotation of some type of impellor, rather than relying on the force of gravity. This also enables the use of low-density polymeric media. In addition to impact, this motion generates shear fields leading to more efficient power consumption and shorter grinding times.

Stirred media mills may be as simple as a pegged impellor immersed into a slurry of fluid and media, or may be as complicated as a high-speed/high-energy, continuous flow media mill with cooling and recirculation capabilities. These are available in several designs and configurations.

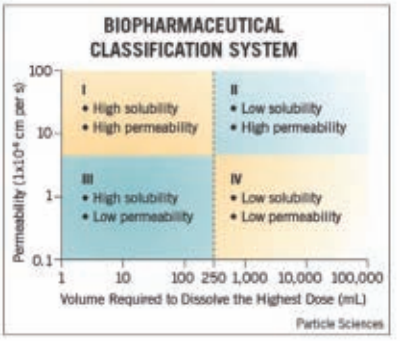
Microfluidizer® high-shear homogenizers are another widely used system to generate nanoparticulate suspensions. These pump the API fluid suspension under very high pressure and velocity through precisely defined microchannels within a proprietary interaction chamber. Various configurations of interaction chambers are available specifically designed for different applications and desired outcomes and are available constructed of ceramic or diamond. Fine particles with a narrow particle size distribution are produced by a combination of shear, turbulence, impact, and cavitation forces.

As the resulting PSD can have a significant effect on bioavailability, the milling technique used must be reproducible, in addition to be well characterized for regulatory considerations; the process must perform the same every time. A process that provides poorly controlled PSD (or one for which PSD is not adequately characterized) can negatively impact the ultimate product performance.

For crystalline materials, milling can induce changes in crystalline form (polymorphs) or may even introduce some degree of amorphousness to the particulates. Again, both of these events may have practical as well as regulatory implications for both stability and performance of the dispersion.

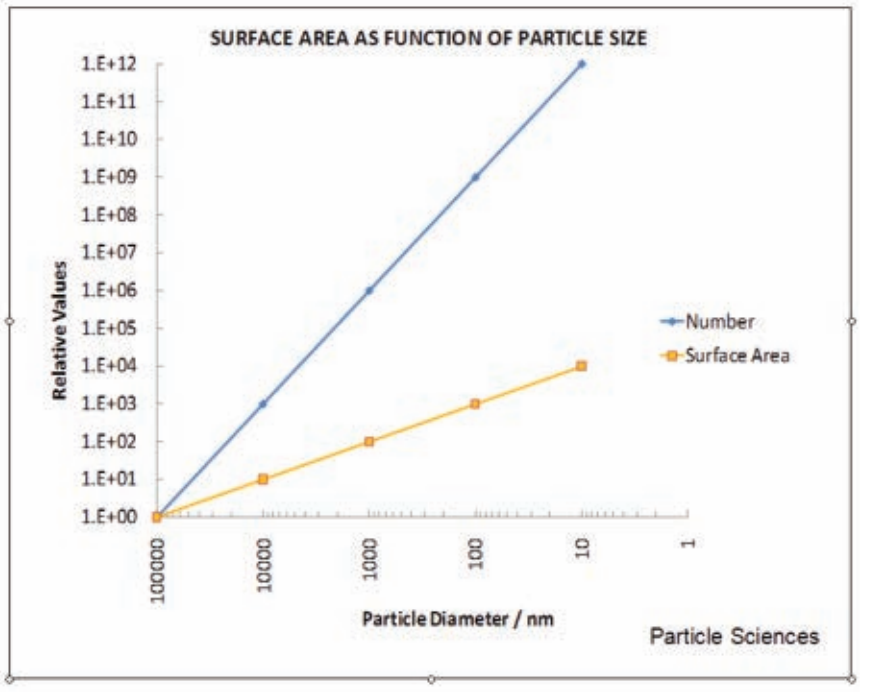
Alternately, when top-down techniques do

FIGURE 1



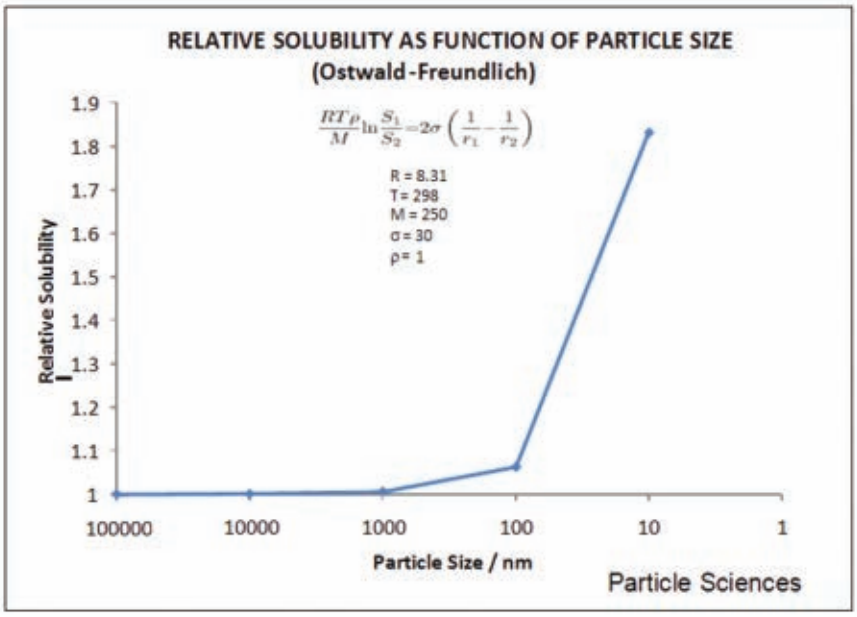
Biopharmaceutical Classification System

FIGURE 2



Surface Area as Function of Particle Size

FIGURE 3

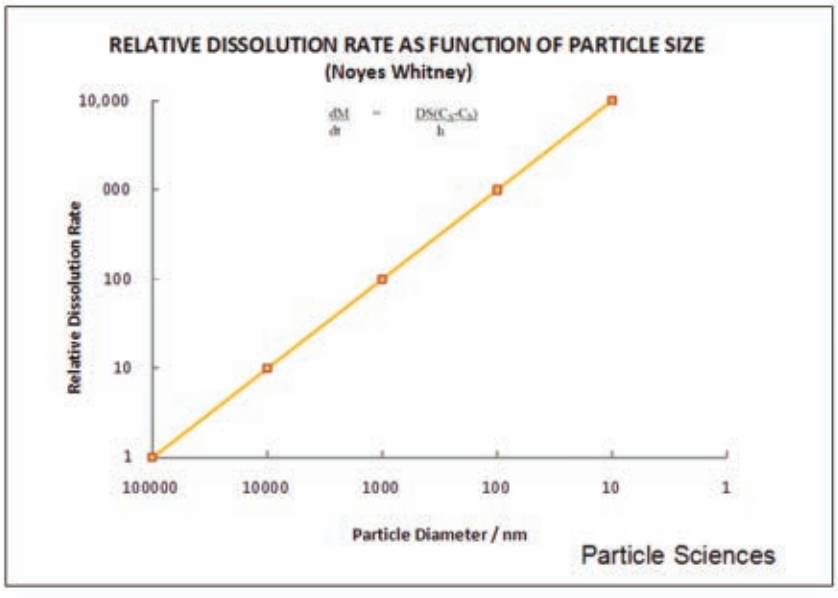


Relative Solubility as a Function of Particle Size

not provide the desired size, a bottom-up procedure, such as controlled precipitation, may be used in which the desired size particles are grown from the solution state. There is equipment available utilizing several different techniques to control the resulting particle size during the recrystallization, including high-shear homogenization, such as Microfluidics PureNano Continuous Crystallizer.

The common potential pitfalls of particle size reduction include generation of polymorphs and Ostwald ripening. Ostwald ripening is the phenomenon wherein larger particulates will grow over time, either by direct contact or by drawing material from the smaller particulates through limited solubility in the medium (Figure 5). This is a thermodynamically driven process and is of special concern with sparingly soluble materials as well as amorphous materials. By its nature, milling may convert an API into an amorphous form, or induce amorphous regions, thereby increasing the potential for Ostwald ripening. However, if the process is sufficiently slow, the nanoparticulate suspension can be lyophilized to lock in the PSD.

FIGURE 4



Relative Dissolution Rate as a Function of Particle Size

CONVERSION OF NANOPARTICULATE SUSPENSION INTO SOLID DOSAGE FORM

In order to convert the nanoparticulate suspension into a standard oral solid dosage form, such as a tablet or hard gelatin capsule, steps must be taken to convert it to a dry form, and to impart flow characteristics to the resulting material. In addition, if tablets are the end product, the material may need to be modified to exhibit compactibility. Liquid fill of the suspension into hard or soft gelatin capsules can be done for nanosuspensions in non-aqueous vehicles, though are not an option for aqueous-based suspensions.

Lyophilization is one method to accomplish drying, but usually results in powder with undesirably low bulk density and flowability. These characteristics can be overcome by dry compaction processes, such as slugging or roller compaction, or by high-shear or fluid bed wet-granulation. Flow and compactibility can be additionally enhanced using excipients especially designed for these properties, such as spray-dried lactose, microcrystalline cellulose, and directly compressible grades of starch.

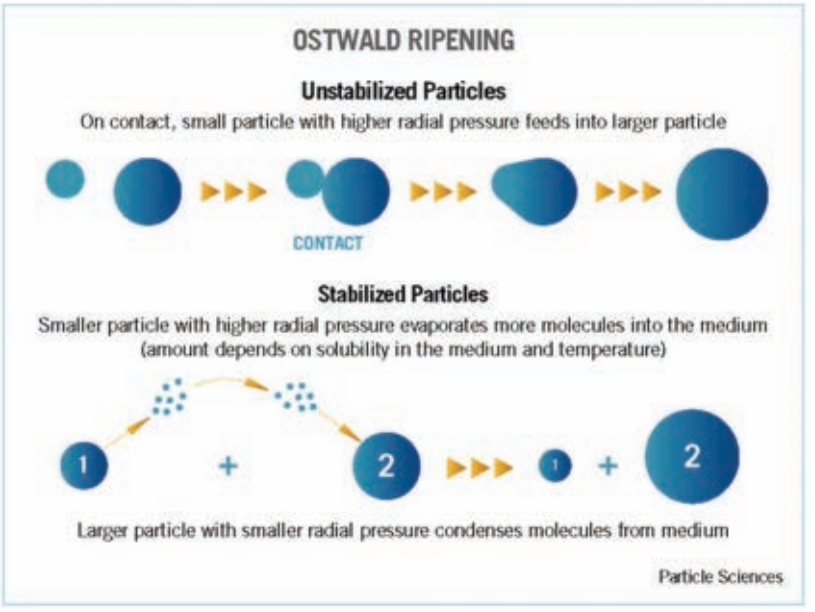
Spray drying of the nanoparticulate suspension typically results in much better bulk density and flowability, and should be used when possible. The use of excipients to impart favorable characteristics to the final blend must be balanced with the need to maintain an appropriate size of the final dosage form when the percent of drug loading is low and/or when the dosage strength is high. Additional excipients, such as lubricants and disintegration aids, can enhance the processability of the material on encapsulating and tableting equipment, and can ensure that the final product returns to a dispersion of fine particles upon presentation to gastrointestinal fluids after ingestion.

SOLID DISPERSIONS/SOLUTIONS

Hot Melt Extrusion (HME) has been used for decades to compound different materials into thermoplastic polymer melts, and is now finding interest and use in the pharmaceutical industry as a method to increase bioavailability of poorly water-soluble compounds. The process of compounding allows both particle-size reduction and mixing so that APIs can be incorporated into the polymer in dispersed form or, if the API solubility in the molten polymer is high enough, as a molecular solution. Because the extrudate cools rapidly upon exiting the extruder, any API that is dissolved in the polymer at the mixing temperature may quickly recrystallize into nanoparticulates or may be unable to recrystallize upon cooling, leading to supersaturated solid solutions. In the latter cases, stability of the product must be closely followed as recrystallization of the API over long time-scales is possible, especially at elevated storage temperatures and high API loadings, and may adversely impact the bioavailability due to formation of larger crystalline particulates of the API, and thus the shelf-life of the final product.

As with any dosage form, material selection is critical in the development of a successful product. For most applications, the polymer should be thermoplastic, stable at the temperatures used in the processing, and chemically compatible with the API during extrusion. For solid oral dosage forms, water-soluble polymers are usually chosen from among polymers already used in pharmaceutical products, such as polyethylene glycol and poly(vinylpyrrolidinone). With the increased interest in using HME for pharmaceutical products, major polymer suppliers are also beginning to offer polymers specifically designed for pharmaceutical applications. HME allows the API to be mixed with the polymer under the minimum of shear and thermal stresses and hence with the formation of minimal process-related API degradants. Antioxidants are often included within the formulation, and the short residence time in the barrel (typically on the order of minutes) also helps to minimize thermal degradation especially compared to batch mixing and other compounding processes.

FIGURE 5



Ostwald Ripening

For standard solid oral dosage forms, the compounded polymer and API may be extruded and cut directly into a slug, which can be encapsulated into a hard or soft gelatin capsule, or can be extruded into spaghetti-like rods, cut into small cylinders, and spheronized while still warm and pliable using suitable equipment, such as a spheronizer.

Another technique involves cryo-grinding the mixture to a powder followed by processing into a more conventional solid dosage form. In this case, the same techniques as described in the section on nanoparticulate suspensions can be useful to enhance flow, compactibility, processability, and disintegration properties.

SPRAY DRYING

Another technique to produce nanoparticulates of API dispersed in polymeric matrices is by spray-drying a solution of the API and polymer. Though this may appear to be straightforward, to achieve the optimum dispersion and smallest particle size, careful consideration must be given to the composition of the polymeric matrix and feed solution. Key parameters include the API's solubility in various organic solvents, the API's molecular weight, the solubilities of the polymeric excipients, and the compatibility of the API and polymeric excipients in the spray-drying solution. Combinations of different polymer types, if properly formulated, can provide improved performance as compared to a single polymer type.

A recent example of spray-drying technology is the Solumer technology, which employs a combination of a hydrophilic and amphiphilic polymer.[12,13] The drug product exhibits modified thermal behavior, including depressed melting temperature and enthalpy of melting of the drug (Table 1), spontaneous formation of nanocolloidal dispersions upon contact with aqueous media, and enhanced dissolution rate/solubility of the drug in aqueous media as well as prolonged supersaturation in relevant biological fluids, and GI site-targeted release of the drug.[13]

The resulting free flowing powder that typically results from spray-drying processes can contain high levels of API of 25% or more and are amenable to processing by various techniques, as described earlier in this article, into solid oral dosage forms.

CONCLUSIONS

This article briefly discussed formulation approaches that may be considered for BCS

Class II APIs and new chemical entities (NCEs). These approaches may also have utility in life-cycle management of pharmaceutical products in which drug delivery technologies that offer positive differentiation over first-generation products provide an important means for staying competitive in today's business environment. There is no doubt that new technologies will be discovered to formulate APIs and NCEs with the intention of enhancing oral bioavailability. It will be of interest to see if there is a *significant* leap from the current repertoire of solid solutions, particle size reduction, amorphous materials, and permeation enhancers. ◆

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BIOGRAPHIES

Garry Gwozdz is Director of Formulation Services at Particle Sciences, Inc., with responsibility for the development of products in a range of formats including semi-solids, suspensions/ nanosuspensions, and solutions covering most routes of administration, such as topical, mucosal, transdermal, oral, intravenous, intramuscular, nasal, and buccal. Mr. Gwozdz earned his BS in Chemistry from the University of Pittsburgh and holds 8 issued or pending patents. Before joining Particle Sciences, Mr. Gwozdz worked for 13 years at Koh-I-Noor Inc., beginning on the bench level though eventually leading a research group to exploit novel and propriety encapsulation technologies. He has been employed at Particle Sciences for the past 16 years working in both pharmaceutical and personnel care research and development. During the course of his career, Mr. Gwozdz has successfully scaled up several products to commercial levels. He also has extensive experience in the areas of particle size reduction, surface modification of particulates, and is versed in existing and novel encapsulation technologies

Robert Gwozdz is responsible for solid dosage form development at Particle Sciences Inc. Before joining Particle Sciences, he held formulation positions at Teva Pharmaceuticals and American Home Products, developing both NCEs and generic products. He earned his BS in Biology from Penn State University and a Masters in Pharmaceutics from Temple University. Mr. Gwozdz has more than 30 years of experience in Pharmaceutical Research and Development and Process Engineering, specializing in modified release and enhancement of bioavailability.

Dr. Robert W. Lee is Vice President of Pharmaceutical Development at Particle Sciences Inc. He is responsible for product development at Particle Sciences as well as providing support to clinical manufacturing operations and business development. His responsibilities include oversight of formulation development, drug delivery, analytical sciences, quality control, and quality assurance. Before joining Particle Sciences, Dr. Lee held senior management positions at Novavax, Inc., Lyotropic Therapeutics, Inc., and Imcor Pharmaceutical Co. He has also been in research positions at élan Drug Delivery, NanoSystems, and Sterling Winthrop. Dr. Lee earned his BS degrees in Biology as well as Chemistry from the University of Washington and his PhD in Physical Bioorganic Chemistry from the University of California-Santa Barbara. Dr. Lee has published articles in numerous peer-reviewed journals and three book chapters plus holds 11 issued patents and 14 provisional or PCT patent applications. He has more than 20 years of experience in pharmaceutical research and development of both therapeutic drugs and diagnostic imaging agents. He maintains strong academic ties, including an appointment as Adjunct Associate Professor of Pharmaceutical Chemistry at the University of Kansas in 1992, and serving as a reviewer for both the International Journal of Pharmaceutics and Journal of Pharmaceutical Sciences and Editorial Advisory Board Member of Drug Development & Delivery.

TIME TO MARKET
EARLY STAGE

Fast-Tracking Time to Market in the Early Stages of Drug Development

By: Thomas Pointeaux, MS, and Julien Meissonnier

INTRODUCTION

It is no mystery why time to market has become such a critical concern for pharmaceutical and biotech companies. In 2008, the top 200 drug products generated $133.2 billion in sales, which computes to an average annual turnover of approximately $666 million for each product.[1] Within 6 months of patent expiry, a brand may lose more than 80% of market share; just 4 years ago, that figure was only 55%.[2] Because patent life starts at filing, any reduction in the time-to-market will increase revenues over the lifetime of the drug product. An improvement of 6 months in getting a drug to market could equate to $200 million in additional revenues over the product's life. Consequently, as many drug makers strive to significantly shorten their traditional product development processes, concepts such as speed in feasibility (including quick to fail), speed to clinic, and speed to market have become the mantra of pharmaceutical development.

Amidst these market pressures, Catalent Pharma Solutions' formulation development experience can be a valuable tool for drug companies that are willing to be aggressive in expediting the early stages of drug development. Our experience can be particularly useful to companies seeking to verify a drug candidate's viability (a concept increasingly referred to as *drugability*), as well as to companies seeking early establishment of proof-of-concept (POC) for a drug delivery technology.

ADDRESSING SOLUBILITY ISSUES

For many years, expediting early stage development of poorly soluble drug substances (BCS Class II drugs) had been a key focus of product development teams, often resulting in poorly soluble new chemical entities (NCEs) entering into clinical development.[3,4] However, solubility may not necessarily be the only critical issue in the early stages; dissolution kinetics may be at least as important.[5]

True solubility limitations can often result in insufficient exposure in toxicological studies in animal species. As illustrated in Figure 1, this can manifest itself as an inability to achieve dose escalation, a limited ability to escalate the dose in the absence of toxicity, or inconsistent escalation from one animal species to the next (ie, effective dose escalation observed in one species but not in another). If not addressed correctly, insufficient exposure may produce an inadequate safety margin to proceed with human studies, and may result in the need to re-initiate preclinical studies so as to ensure application of a sound formulation principle.

TABLE 1

Criteria	Standard Approach (HPLC/UV)	Catalent Approach (UHPLC/MS)
Method Evaluation	2 weeks	1 week
Solubility Screening	2 weeks	1 week
Compatibility Study Launch	4 days	1.5 days
Compatibility Study Time Point (Analysis)	4 days	1.5 days
Method Validation	6 weeks	3 weeks

Typical timeframes for various components of analytical science.

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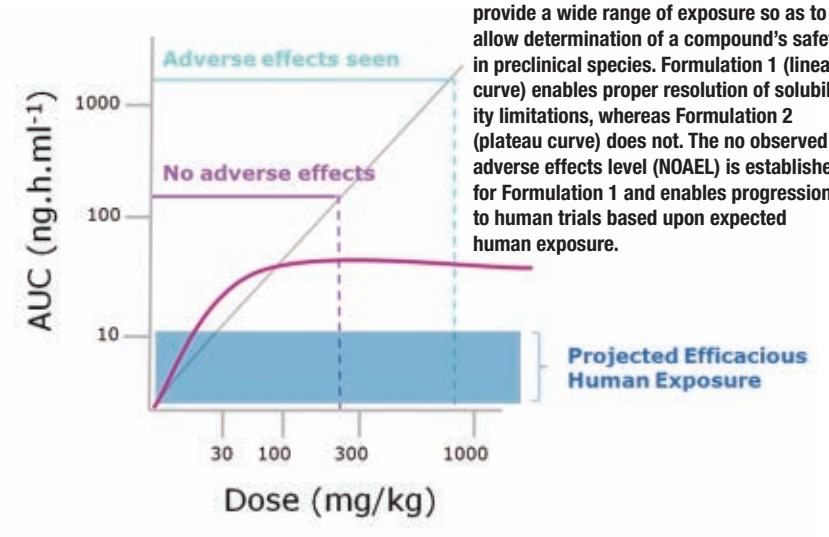
There are various approaches to solving formulation issues in order to conduct toxicology studies in animal species. However, when it comes to preparing a robust dosage form for Phase I dose-escalation studies in humans, additional solubility-related issues need to be considered, especially if a clinical developer seeks to accelerate progression to Phase I as a means to shorten the overall time to market.

One key consideration is adhering to the principle of "fit for purpose," under which every active pharmaceutical ingredient (API) is considered a specific and separate case. According to this principle, rigid application of the same drug delivery principles or an "ideal" drug delivery principle to every API would waste resources and time, potentially leading to the premature loss of a promising drug candidate.

The "fit for purpose" principle was illustrated in a recent case in which Catalent had been engaged to facilitate the oral delivery of a poorly soluble NCE. In this particular case, poor solubility was linked to excess lipophilicity (partition coefficient between octanol and water - log P ~ 8). The NCE had been previously formulated under a liquid-filled hard shell (LFHS) capsule format and delivered via a self-emulsifying drug delivery system (SEDDS). Since the successful market introduction of Neoral® soft gelatin capsules, SEDDS and self-micro-emulsifying drug delivery system (SMEDDS) lipid-based formulations have been perceived as the ideal system to efficiently deliver poorly soluble drugs while optimizing their bioavailability. However, several studies have indicated that SMEDDS systems do not consistently offer the most optimum performance among all lipid-based formulations. In some cases, simple solutions in lipids and/or dispersions in lipids perform better while requiring less intensive development efforts.[6]

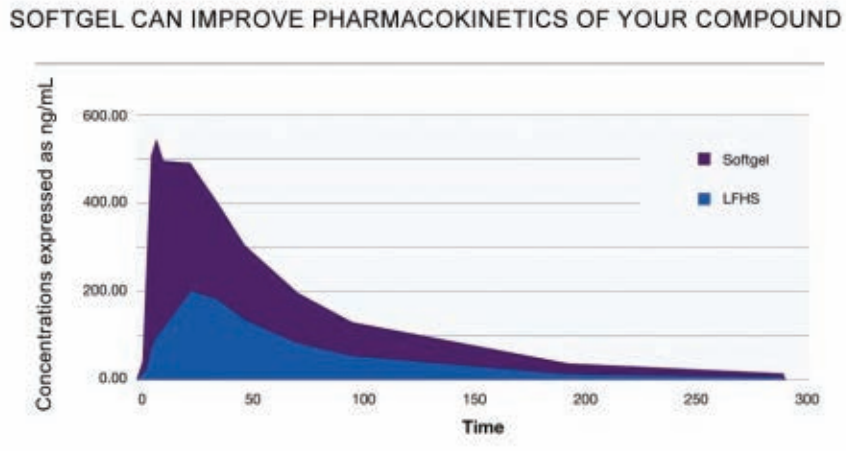
In the initial trials of the NCE, bioavailability was fairly limited, stability was not satisfactory, and the unit strength was low. Progressing this formulation through the clinics could have presented several constraints in terms of consistency of results and robustness of the formulation in the market. Our scientists addressed these issues by conducting accelerated and tailored preformulation studies to determine whether an alternate and potentially simpler drug delivery system would improve the performance of the NCE. These studies yielded a drug substance dispersion in lipids within a Softgel capsule format. This delivery system exhibited a positive solubility profile in lipid digestion products, satisfactory absorption in animal models, and positive chemical compatibility, which resulted in an improved stability. A small-scale clinical study in 24 human subjects demonstrated a 2.3-fold improvement in bioavailability compared to the LFHS SEDDS formulation (Figure 2). The study also demonstrated improved stability over the 36-month study period. This approach, which took 4 months from project initiation to clinic, enabled our partner to quickly progress to a combined Phase II/III clinical trial, ultimately increasing the product value and leading to an optimized drug product in the final commercial format.

FIGURE 1



Ideal scenario for exposure. The goal is to provide a wide range of exposure so as to allow determination of a compound's safety in preclinical species. Formulation 1 (linear curve) enables proper resolution of solubility limitations, whereas Formulation 2 (plateau curve) does not. The no observed adverse effects level (NOAEL) is established for Formulation 1 and enables progression to human trials based upon expected human exposure.

FIGURE 2



Improved bioavailability of a Softgel drug delivery system compared to a liquid-filled hard shell (LFHS) capsule self-emulsifying drug delivery system (SEDDS).

TABLE 2

Preclinical	Clinical Phase I	Clinical Phase II / III	Registration
None required	Assay	Identification	Identification
	Impurities	Assay	Assay
	Antioxidant	Impurities	Impurities
		Antioxidant	Antioxidant
		Content Uniformity	Content Uniformity
		Dissolution	Dissolution
			Microbiology

Drug product testing methods to validate at specific phases of the product development life cycle.

LEVERAGING ANALYTICAL SCIENCE

Analytical science is an essential tool for expediting the various processes leading from the first preformulation studies to first-in-human (FIH) clinical trials. The application of modern analytical science in each of the processes in early formulation development is highlighted in Figure 3. Applying the proper set of techniques, fully adapted and automated to the requisite preformulation and formulation development schemes, is essential to success and to expediting attainment of specific milestones.

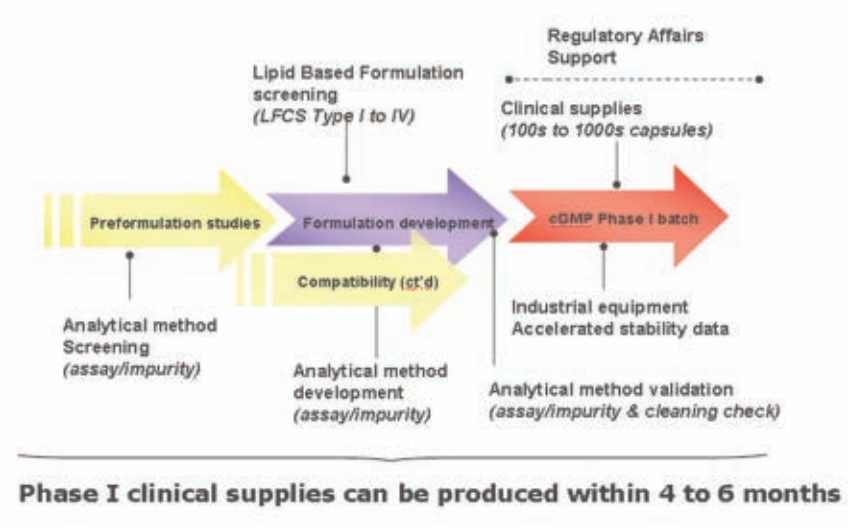
Throughout the past 5 years, Catalent has been progressively converting analytical methods from high performance liquid chromatography (HPLC) to ultra high performance liquid chromatography (UHPLC) to take advantage of sub-2-micron column particle sizes.

When compared to traditional HPLC systems, UHPLC systems are capable of driving eluent through the columns at subsequently higher pressure, with reduced system volume, a faster autosampler rate, and a faster data acquisition rate.[7] The technique enables significant gains in method selectivity, overall run time (typically yielding more than a 4-fold decrease), and solvent consumption (more than a 5-fold decrease). An example of HPLC-to-UHPLC method conversion is provided in Figure 4. This case study is related to the assay determination of a poorly soluble drug substance (BCS Class II) and its isomeric impurity dispersed into a lipid-based formulation (lipid formulation classification system [LFCS] Type II).[8] The comparison demonstrates a significant decrease in run time and an improvement in the resolution between the two peaks.

For BCS Class II drugs, preformulation studies invariably include solubility screening and compatibility screening of a large number of pharmaceutical excipients from various chemical classes. These screening processes can increase the probability of achieving the ideal target product formulation profile, though they may require the preparation and analysis of up to 80 samples per time point. The use of highly automated sample preparation techniques can allow the formulator to save up to 3 days' time in launching preformulation studies. Moreover, the use of UHPLC enables faster access to the development data to enable the orientation of prototype formulation selection based on solubility and chemical compatibility with selected ingredient classes.

Solubility screening involves determination of the dissolved fraction of API from saturated dispersions of API at up to three time points, along with analysis (eg, differential scanning calorimetry combined with Raman spectroscopy) of the solid state, a parameter that is considered the "intimate partner" of the saturation concentration determination. In order to optimize preformulation studies, Catalent is leveraging the benefits of a type of spectroscopy that couples UHPLC with mass spectrometry (MS), which is derived from the molecular weight/charge ratio of the particular analyte. This technique is designed to be specific to the API (as opposed to pharmaceutical ingredients), provided that ionization conditions are not affected by other

FIGURE 3



Application of analytical science in the preclinical phases of drug development

ingredients. The UHPLC/MS approach enables faster access to key solubility data, potentially expediting formulation development. By contrast, conventional techniques combining liquid chromatography with ultraviolet technology (LC/UV) require a variety of adaptations (eg, mobile phases, gradient, flow rate, columns) to obtain an analyte-specific response that results in longer preformulation studies. Consequently, solubility screening can be conducted on an ever-increasing number of pharmaceutical ingredients of various chemical classes and of various lipophilicity/hydrophilicity profiles in order to maximize the probability of finding suitable excipients or ingredients that form the basis of a prototype formulation.

Compatibility screening involves determination of the API degradation pathway while the API is in contact with selected pharmaceutical ingredients of various functions and chemical classes. The API and other ingredients are combined in homogeneous binary mixtures that are subjected to the desired accelerated storage conditions and subsequently tested for their impurity profiles. In particular, drug formulators often find it challenging to conduct assay/impurity method evaluation, which is necessary to ensure proper specificity for selected ingredients and arising impurities. Catalent has thus favored the use of an automated method evaluation approach based upon known design spaces combined with UHPLC. Chromatographic systems are equipped with multiple mobile phases and columns so that mobile phase composition and column properties can be automatically screened during method development for a particular project.

Once the screening method is fixed, further optimization can yield improvements in the efficacy and quality of the data recorded. This is an important consideration when formulating lipid-based drug delivery systems, as the complexity of the ingredients (eg, transesterification products of polyethylene glycol with glycerides) can trigger a series of chemical interactions/reactions with the API. Consequently, the use of liquid chromatography combined with mass spectrometry (LC/MS) can help identify the potential API degradation pathways and address as early as possible the most appropriate mitigation strategy, providing a level of data that can facilitate ingredient selection or withdrawal.

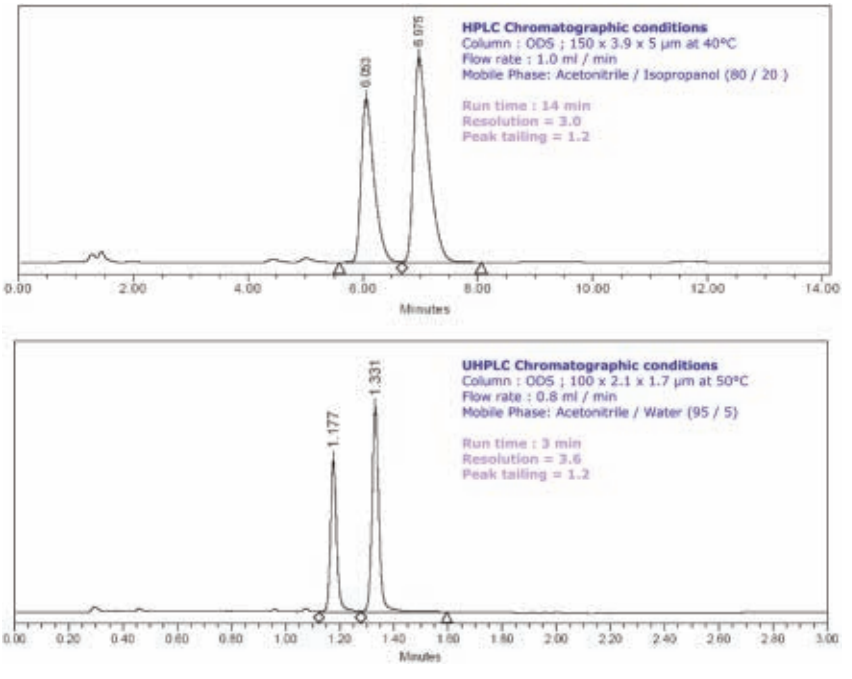
For example, Figure 5 illustrates a typical LC/UV chromatogram of a compatibility sample (first time point) subject to potential oxidative degradation, with impurities observed at retention times of 4.77, 6.01, and 7.31 minutes. In this example, the Orbitrap® mass spectrometer is combined with a UHPLC/UV system to determine the mass spectra of each individual impurity. The isotopic profile and the accurate mass determination of the impurities enables confirmation of

TABLE 3

Criteria	Clinical Phase I	Clinical Phase II/III Registration
Pre-validation	No	Yes
Calibration Standard	5 levels 2 replicates / series 2 series	5 levels 3 replicates / series 3 series
Calibration Standard With Matrix	5 levels 2 replicates / series 2 series	N/A
Validation Standards	N/A	5 levels 3 replicates / series 3 series
Intermediate Precision Variables	Day	Day, Operator, Equipment
Robustness	No	Yes
Typical Validation Time	3 weeks	6 weeks

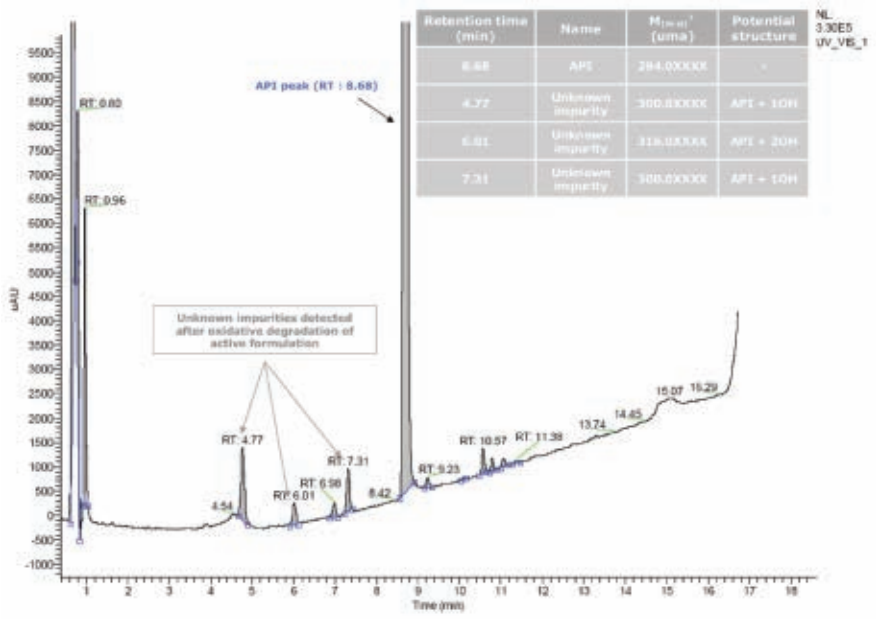
Proposals of design plans for progressive validation of analytical methods.

FIGURE 4



API isomeric impurity separation using HPLC and UHPLC systems.

FIGURE 5



UHPLC/UV profile with ESI+ FTMS data of a compatibility sample of API-related compounds.

hydroxylation of API as the root cause of API degradation. Therefore, the ingredient is re-introduced the same week in compatibility screening along with an anti-oxidant, a process that produces positive compatibility data. The ingredient was ultimately selected for formulation screening. The typical time savings derived from Catalent's use of analytical science are depicted in Table 1.

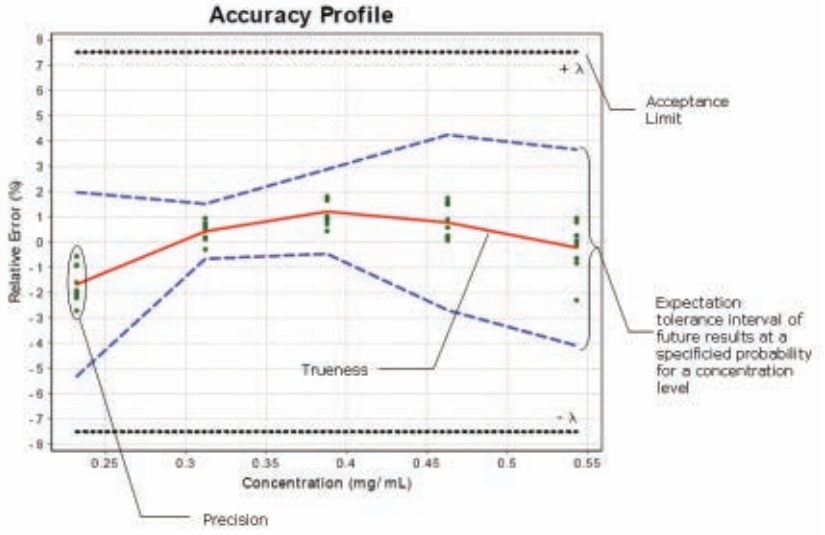
Upon completion of analytical method development, method validation must precede the manufacture of clinical trial material (CTM). A statistical evaluation of analytical method performance allows the developer to streamline method validation activities and maintain compliance with International Conference on Harmonization (ICH) Q2 (R1) requirements, which govern the validation of the most common types of analytical procedures (eg, identification tests, quantitative tests for impurities' content, limit tests for control of impurities, and quantitative tests of the active moiety in samples of drug substance/product or other selected component[s] of the drug product). Statistical evaluation also enhances our knowledge and confidence with regard to method performance. Statistical evaluation is based upon execution of specific design spaces, combined with determination of an accuracy profile relative to the acceptability limit (+ or -).

The analytical methods are characterized by both systematic error and random error to comprise total error. Extrapolation of total error as a B-expectation tolerance interval allows prediction, at a determined risk interval, of results likely to be obtained as a function of method performance (Figure 6).

Master plans for test method validation are based on a statistical evaluation, which can provide an important means to evaluate the performance of the particular method through each stage of product development by challenging the process parameters at each stage. Suggested approaches for methods to be validated throughout the product life cycle are listed in Table 2. These plans permit faster completion in early development phases with a sound scientific data package.

The validation package for a given method typically evolves throughout the product life cycle, potentially yielding significant time-savings. Table 3 provides a sample design plan for method validation for Phase I and Phase II/III studies.

FIGURE 6



Method Accuracy Profile - Method for the determination of glycerol fatty ester content in a soft gelatin capsule by HPLC/UV.

EFFECTIVE PROJECT MANAGEMENT

The success of fast-track development programs depends upon effective project management, which itself is a collaborative process with prospective customers. Programs work best when working in a close partnership with customers, and when partnerships are facilitated by easy and flexible contracting terms.

Effective project management frequently involves acceptance of a certain degree of risk in order to streamline the development process. Leveraging both parties' expertise in chemical and dosage form development can help partners identify and assess potential risks at each stage of product development, as part of a dynamic risk-management plan that incorporates risk-mitigation strategies to be deployed if and when required. Such an approach can thus enable acceleration of development timelines without sacrificing the principles of sound experimental design.

Technical expertise and project management experience make product encapsulation possible at a low batch size. For example, batches of hundreds of grams of fill can produce a relatively high yield (> 50% and up to 85%). This benefit is enhanced by an inherent ability to scale-up quickly to the larger batches required for clinical trials. By employing a liquid fill (which is considered easier than scaling up a dry blend), all small batches are manufactured on commercial equipment, applying similar quality process parameters, thereby enabling a true scalability to larger batch sizes if required for market launch and commercial supply.

Moreover, handling liquid systems enables easier containment of highly potent APIs (up to operator exposure band 5) and/or APIs without assigned toxicity and/or potency. This ease-up in handling conditions can therefore accelerate early development activities.

With its global internal network of support services, Catalent Pharma Solutions can provide an integrated project management offering that enables seamless coordination of dosage form development, analytical development/validation, clinical packaging, Investigational Medicinal Product Dossier (IMPD) documentation, and final quality product (QP) releases. Integration of these services can greatly simplify project management for our partners. ◆

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BIOGRAPHIES

Thomas Pointeaux is Analytical Development Manager in Catalent's European centre of excellence for the development of lipid-based drug delivery solutions. He has 7 years experience in analytical development of soft gelatin capsules from preformulation studies to commercial launch of the product. Mr. Pointeaux earned his Masters degree in Analytical Chemistry from Louis Pasteur University of Strasbourg.

Julien Meissonnier, with 13 years of experience in pharmaceutical development, leads Catalent's European centre of excellence for the development of lipid-based drug delivery solutions. He provides technical and scientific leadership for the development of poorly soluble drugs that lead to approvable regulatory dossiers. Mr. Meissonnier earned his Engineer degree in Physico-Chemistry from the ISMRa in Caen, France. He is an expert in his field and currently sits on the Board of Directors with the Alsace BioValley life sciences and healthcare cluster based in France. As a board member, he supports Alsace BioValley in its efforts to continue driving growth in the life sciences by identifying and coordinating ambitious projects that will create employment opportunities in the region.


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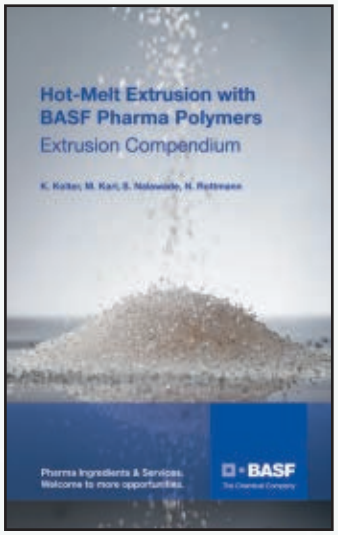
Aveva has a number of products for license from its development pipeline along with a full complement of R&D capabilities to produce transdermal drug delivery systems that fortify pipelines and maximize product life cycles. Aveva Drug Delivery Systems is one of the world's largest manufacturers of, and a pioneer in, transdermal drug delivery systems with a rich history of providing pharmaceutical partners with fully integrated, controlled-release transdermal products that fulfill unmet market needs. Products for licensing include Sufentanil, Fentanyl, Clonidine, and Nicotine. For more information, contact Robert Bloder, VP of Business Development, at (954) 624-1374 or visit **www.avevadds.com**.

Technology & Services Showcase

Hot-Melt Extrusion



The first edition of the Hot-Melt Extrusion (HME) Compendium is now available. In this compendium, scientists at BASF present a range of polymers with both low and high glass transition temperatures for pharmaceutical technology. HME is currently generating a significant interest in the pharmaceutical industry as the percentage of poorly soluble compounds continues to increase. HME thus enables such molecules to increase their solubility and bioavailability. The compendium covers the chemistry and applications of polymers in melt-extrusion to achieve the robust processing conditions and desired release profiles of poorly soluble drugs. Download and comment on the Compendium at **www.innovate-excipients.basf.com**.

Capsule Filling & Sealing

Designed to allow formulation scientists the ability to better exploit the potential of lipid-based formulations for poorly soluble compounds, the CFS 1200 helps accelerate the development timeframe and achieve Faster Time to First in Man. A fully automatic cGMP-compliant machine, it fills and seals up to 1,200 capsules per hour with liquid or semi-solid formulations without banding. It is designed for ease-of-use and high reliability, with the ability to quickly clean and change capsule sizes with available change parts. Product integrity is ensured with gentle handling of capsules before sealing and during the drying cycle. Other features include a robust filling pump with highly accurate temperature control, improved capsule manipulation before sealing and during drying using new "Cap-edge" handling system, and improved design of filling and sealing process that ensures better control and cleanability. Fore more information, contact Capsugel at (888) 783-6361 or visit **www.capsugel.com**.

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Catalent Pharma Solutions is a world leader in patented drug delivery technologies. For more than 70 years, we have developed and manufactured advanced drug delivery systems and partnered with nearly every major global pharmaceutical company. We continually work to advance the science of drug delivery and enhance the therapeutic and market performance of our customers' drugs. Our advanced drug delivery technologies bring new options to resolve the technical challenges development scientists face every day. These patented technologies can improve the odds of successful formulation by enhancing bioavailability, optimizing the rate of release, and targeting the site of absorption. Our technologies include softgel and Vegicaps® Soft capsules; Zydis® fast-dissolve dosage form; modified-release technologies; and a range of inhaled technologies, including MDIs, DPIs, nasal sprays, and solutions/suspensions for inhalation, nebulizers, and liquid inhalers. For more information, contact Catalent Pharma Solutions at (866) 720-3148 or visit **www.catalent.com**.

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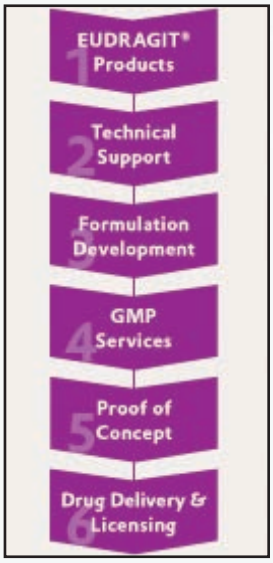
New Auto-Injector Line

Elcam Medical recently launched its Flexi-Q line of auto-injectors for self-medication - the only fully disposable auto-injectors designed for life-cycle management. Flexi-Q DV is designed for drugs in vials in liquid or lyophilized form, and the Flexi-Q PFS is for drugs in prefilled syringes. Both incorporate our unique platform with flexibility in customization: dosage between 0.3-1.0 ml, needle length & gauge, viscosity, injection force, and injection time. Elcam Medical is a leading worldwide OEM supplier of Fluid Management, Drug Delivery, and Vital Signs Monitoring systems and devices. As an OEM partner, we have significant experience in partnering with pharmaceutical companies in many disease states and therapeutic classes. Our dedicated team of auto-injector engineers and technical staff has worked with many leading companies in the field. For more information, contact Elcam Medical at (201) 457-1120 or visit **www.elcam-medical.com**.

Pharma Polymers



Evonik Industries is a global market leader in specialty chemicals, offering a broad portfolio of products and services to meet the drug delivery challenges of the pharmaceutical market. Evonik Pharma Polymers manufactures EUDRAGIT® acrylic polymers used for enteric, sustained-release, and protective formulations. The unique functionality of EUDRAGIT polymers can also meet high sophisticated drug delivery requirements (eg, pulsed drug release). We have adapted our services to meet the requirements of the pharmaceutical industry's value chain. As a result, we are able to support our customers in the development process to bring products safely and quickly to the market. From excipients supply to the development of custom tailored drug delivery solutions, our customers benefit from our knowledge and expertise. For more information, contact Evonik Degussa Corp., Pharma Polymers at (732) 981-5383 or visit **www.eudragit.com**.

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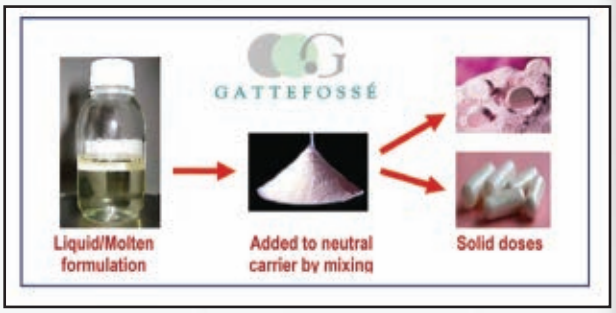
Solvent-Free Adsorption



Designed for enhancing the solubility of poorly soluble drugs in solid dosage forms, this technique allows the transformation of liquid or semi-solid lipid formulations into solid particles that can subsequently be filled into hard shell capsules or alternatively compressed into tablets. The active may be dissolved or dispersed in the formulation prior to adsorption onto a solid neutral carrier, such as calcium silicate, with the aid of conventional mixers. The success of the technique depends much upon the properties of the carrier, notably its flow characteristics and capacity to absorb the desired amount of formulation. Our laboratory has successfully loaded up to 68% liquid SELF onto solid support. For more information, contact Ron Permutt of Gattefosse at (201) 265-4800 or visit **www.gattefosse.com**.

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When it comes to drug delivery, NuSil provides numerous solutions that fit a variety of device needs. While most silicone products are customized for individual delivery systems, all are developed with FDA regulatory concerns in mind. In addition to its role as a supplier, NuSil offers research and development capabilities for those looking for proprietary, custom formulations. Regardless of batch size, NuSil delivers quality, high-performance silicone materials based on your unique property requirements, as well as provides precise, custom formulations. NuSil offers an even wider range of silicone material and compound options for transdermal, transmucosal, implanted intrathecal, and external delivery devices, as well as ingestible materials. For more information, contact NuSil Technology at (805) 684-8780 or visit **www.nusil.com**.

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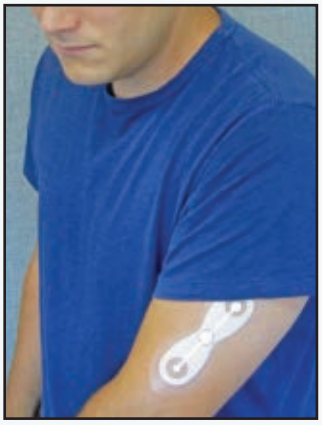

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Technology & Services Showcase

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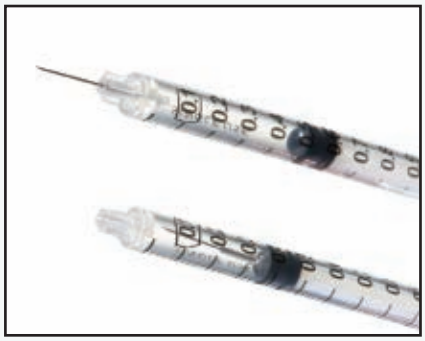

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DRUG DEVELOPMENT
CAPTISOL® Executive

LIGAND: PROVIDING SOLUTIONS TO THE SOLUBILITY, STABILITY & COMPATIBILITY ISSUES IN THE PHARMACEUTICAL INDUSTRY

Matt Foehr
Executive VP & COO

Ligand

"Much of Captisol's business comes from approved drugs and pending products. In many instances, we see the potential for pharmaceutical companies to accelerate the regulatory filing process as well as significantly cut down on development costs. Reformulation can truly bring meaningful innovation to established medicines."

Ligand has evolved into a unique biopharmaceutical company with a model of creating a myriad of revenue streams that arise from many segments within the pharma universe. In January 2011, Ligand recognized the increasingly important role of the drug reformulation segment in the pharmaceuticals industry and completed its acquisition of CyDex Pharmaceuticals and Captisol®. The Captisol technology platform was originally created and patented by scientists from the University of Kansas and subsequently exclusively licensed to CyDex. Captisol's powerful formulation potential has enabled five FDA approved products, including Pfizer's VFEND® IV and Baxter International's Nextertone®. There are currently more than 20 Captisol-enabled® products in development, including programs partnered with The Medicines Company, Merck, Bristol-Myers Squibb (BMS), and Lundbeck. Drug Development & Delivery recently interviewed Matt Foehr, Executive Vice President and Chief Operating Officer of Ligand, to discuss Ligand's Captisol-enabled® technology and its significant role in the pharmaceutical marketplace of today and tomorrow.

Q: For any of our readers who may be unaware, can you please tell them about Captisol?

A: Captisol is our patented, chemically modified cyclodextrin. Cyclodextrins are enzymatically modified starches with a wide range of applications in food, chemical, cosmetic, and pharmaceutical industries. Captisol is used to improve solubility, stability, and bioavailability of active pharmaceutical ingredients (APIs). It also has the potential to influence other properties of a product, such as reducing site reactions and eliminating the use of toxic excipients that are commonly included in a formulation to solubilize highly insoluble active agents. Captisol is versatile across multiple molecule families and sizes. It's a very safe material, which was a designed feature and is a key benefit of the Captisol-enabled

technology. And that claim is supported by extensive data in our Type IV and V Drug Master Files (DMFs).

Q: What role do you see Captisol playing in the pharmaceutical and healthcare industries?

A: Line extensions and reformulation have become increasingly valuable solutions to the issues related to market erosion due to generic competition and continued clinical and regulatory uncertainty. Captisol can enable new dosage forms of existing drugs.

There is also a lot of evidence to suggest that poor solubility in drug development is one of the leading challenges for pharmaceutical companies. Between 70% and 90% of drug candidates in pipelines are believed to have low solubility.

Captisol enables solubilization and is so important because it is not only a drug delivery platform, but one that also has the potential to impact health outcomes, dosage, administration, and possibly the cost of care.

Q: Do Captisol-enabled products face the same clinical and regulatory challenges?

A: Much of Captisol's business comes from approved drugs and pending products. In many instances, we see the potential for pharmaceutical companies to accelerate the regulatory filing process as well as significantly cut down on development costs. Reformulation can truly bring meaningful innovation to established medicines. I have seen this first-hand in my career - how slight changes to dosage form or optimization of how an active ingredient is delivered in a clinical setting can bring major innovation to a product and have a positive impact on patients' lives.

A good example is Ligand's Propylene Glycol-Free Melphalan product, which we plan to progress into its Pivotal Clinical Trial next year. Propylene-Glycol-Free Melphalan was granted Orphan Drug status by the FDA as a conditioning treatment for use in autologous transplant for patients with multiple myeloma. Our Captisol-enabled formulation would be a new IV formulation for Melphalan, which is currently formulated and sold as Alkeran® for Injection. Captisol-enabled Melphalan completely avoids the use of propylene glycol, which has been used as a co-solvent in other formulations and has been reported to cause renal and cardiac side-effects that limit the ability to deliver higher quantities of intended therapeutic compounds. The use of the Captisol technology to reformulate melphalan is anticipated to eventually allow for longer administration durations and slower infusion rates, potentially enabling clinicians to safely achieve a higher dose intensity of pre-transplant chemotherapy.

Q: Why should the pharmaceutical industry be interested in Captisol?

A: Captisol's success is primarily based on solving drug formulation problems, particularly in the area of parenteral delivery, oral, nasal, and inhalation formulations. Based on a number of high-profile partnerships - like Pfizer, BMS and Merck, we believe Captisol is a proven and powerful technology for our industry. Ligand acquired and is continually adding to our extensive DMFs to which our partners can refer to when

filing with regulatory agencies around the world. In addition, Captisol is covered by two Orange Book listable patents that offer some partners extended patent protection for their products. Ligand also has an exclusive and very productive partnership with Hovione FarmaCiencia SA to manufacture Captisol. We have a 50-metric ton capacity for Captisol now and the ability to significantly increase that capacity. Hovione's manufacturing operations allows us to have a steady stream of reliable cGMP supply.

Q: Is there existing clinical data relating to Captisol's safety?

A: Captisol has been tested in more than 100 clinical and safety studies reported in our Type V DMF. It appears safer than other cyclodextrins and is, we believe, of a higher quality than other cyclodextrins. Captisol was specifically designed to be safe and well tolerated. There are a number of studies that report, for example, that Captisol can control the physical stability of proteins, which is a growing concern in the pharmaceutical industry, especially with the growing number of protein-based biopharmaceuticals currently in development.

Q: How has Ligand's business model played in the marketing and licensing of Captisol?

A: The Captisol technology was really a great fit for Ligand. The business model at Ligand is all about partnering to create a large portfolio of potential revenue streams. Ligand now has over 50 fully funded partner-driven programs in various stages of development, and Captisol is obviously a technology built to be partnered. We have relationships with a large number of companies, and introducing the Captisol technology into these conversations has been very fruitful. Ligand plans to take the Captisol brand to a new level and really exploit the aspect that this is a validated, patented, enabling technology.

Q: What are some of the partnerships you have with Captisol-enabled products?

A: We have partnerships with more than 25 companies that span in all phases of development. Our collaboration with Onyx Pharmaceuticals began in 2005 to explore the use of Captisol technology as a method to create an IV formulation of Carfilzomib. Carfilzomib is a next-generation proteasome inhibitor for the potential treatment of patients with relapsed and refractory multiple myeloma. Multiple myeloma is the second most common hematologic cancer. In the US, more than 50,000 people are living with multiple myeloma, and approximately 20,000 new cases are diagnosed annually. Recently Onyx announced its plans for submission of an NDA for Carfilzomib.

A January 2006 article in this journal, titled Partnering with Big Pharma, reviewed our established long-time relationship with Pfizer in bringing forth this technology out of the University of Kansas, from which several products have been realized including VFEND® IV, Cerenia®, and Geodon® products. The active ingredient in VFEND, voriconazole, is known to be extremely insoluble. Captisol enabled an IV formulation to be developed for this product that treats invasive fungal infection. I believe VFEND IV would not be on the market if it weren't for Captisol. Cerenia is a veterinary health product

in which Captisol was able to increase the solubility to enable the product as well as provide an injection site tolerance, which was a major issue for Cerenia while it was in development. Geodon is a product used to treat symptoms for schizophrenia. It is also highly insoluble by itself. Captisol was able to increase the solubility of the active.

Baxter International recently launched Nexterone®, a product it acquired after its development through FDA approval by Prism Pharmaceuticals. Amiodarone, the active in Nexterone, is a commonly used anti-arrhythmic agent used for the treatment of ventricular tachyarrhythmias, or fast forms of irregular heartbeat. For Nexterone, we were able to design a formulation that eliminated the co-solvents and interest Prism in licensing and furthering the development of the product.

Lastly, Abilify® is a product marketed by Bristol-Myers Squibb in the manic bipolar arena. The solubility of the active was increased and at the same time, site reactions were reduced, solving major drug precipitation issues.

Q: What are your criteria for securing the right partner, and what types of partnerships or deals are you working on now?

A: We are looking at forming broader platform relationships with partners who can truly leverage Captisol in many therapeutic areas. We see forming these sorts of platform relationships with companies that have libraries of compounds as being a really important way to grow the business in the long-term.

Following our acquisition of CyDex in January 2011, we now really have our arms around the Captisol business and have welcomed some valuable new colleagues from CyDex onto the Ligand team. Together we have already begun to realize that there is an enormous amount of potential partnerships waiting for Captisol. The name of the game here is to get programs moving into development so that product development teams at companies large and small can see how enabling the Captisol technology is, for advancing their programs toward the marketplace. Ligand deal structures really help make that possible.

Q: Do you see other broader platform opportunities for Captisol?

A: We see a clear potential for forming broader platform relationships with pharmaceutical companies who can truly leverage Captisol. Captisol is a proven drug delivery system that has worked across several therapeutic categories involving small molecule and biotechnology drugs, including injectables, oral drugs, inhalations, nasal, and ophthalmic delivery. The possibilities are enormous.

Most of the drugs that get eliminated from a pipeline are often eliminated at the earliest stages when they are placed on the formulator's bench. Not only does Captisol have the ability to solve the solubility issues in many cases, but we have the ability to affect the entire formulation and therefore affect the outcomes that the products eventually see. ◆

Hot-Melt Extrusion Technology - A Versatile Tool for Drug Delivery

By: Pirthi Pal Singh, PhD; Paramjit Singh, PhD; and Sarabjit Singh, MPharm

INTRODUCTION

Hot-melt extrusion (HME) technology has been exploited by the polymer industry since the 1930s, and has been widely used in the polymer, food, chemical, rubber, and metal industries. Throughout the past 2 decades, HME has emerged as a potential drug delivery technology and has been used for the manufacturing of extrudates, powder, pellets, granules, immediate- and extended-release oral dosage forms, ophthalmic inserts, transmucosal and transdermal films, implants, etc.

As indicated in Figure 1, the number of patents issued on HME for pharmaceutical applications has significantly increased since 1970 (Data till August 2011). Melt extrusion is a technology wherein the drug and carrier blend is passed through a barrel with the help of rotating screw under controlled conditions of temperature, mixing, feed rate pressure, etc., and then passed through the shaping die to form a product of desired size and shape.

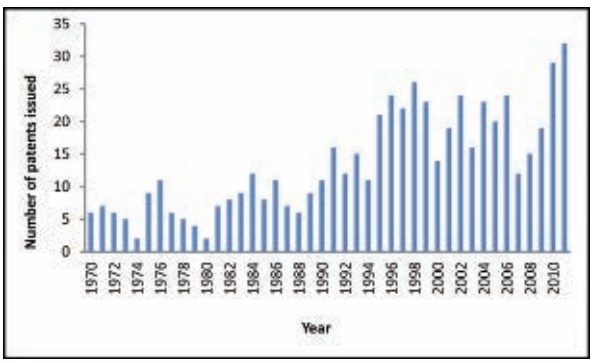
Recently, melt-extrusion technology has shown promising results in enhancing the bioavailability of poorly soluble drugs belonging to BCS class II.

Crowley et al have compiled and reported pharmaceutical applications of HME, including equipment, principles of operation, and process technology.[1] HME offers the following numerous advantages over existing drug delivery technologies:

- Solvent-free green technology that makes the process environmental friendly and cost effective;
- Thermodynamically stable composition compared to spray-drying, solvent-evaporation methods;
- Smaller batch size possible for initial development trials;
- Improved content uniformity due to high shear mixing;
- Continuous operation for large-scale production;
- Number of drug delivery systems (such as immediate release, modified release, and formulations with enhanced bioavailability) can be formulated using a single machine; and
- High machine output.

The major disadvantage of the hot-melt process is drug and carrier mixture is subjected to higher temperature, restricting its application to thermostable drugs. However, recent developments in screw design and use of plasticizers enable processing at relatively lower temperatures. Apart from the number of advantages offered by HME, development of patented, non-infringing delivery systems has caught the attention of major pharmaceutical industries. HME has been reported in the literature for the development of a number of drug delivery systems, such as pellets, solid dispersion, topical dosage forms, powder coating, gastroretentive dosage

FIGURE 1



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forms, tablets, sustained release oral dosage forms, implants, and ophthalmic inserts.[2,3] The following sections summarize the principles, operation, and potential applications of HME in the pharmaceutical industry.

HOT-MELT EXTRUDER

There are two types of extruders available for HME - ram and screw extruders. Ram extruders work on the principle of positive displacement of ram or a piston inside a heated barrel that pushes the softened mass through the die. Screw extruders work on the principle of positive displacement of the softened mass by the action of the rotating screw inside the heated barrel. Screw extruders can be made up of single or twin screw. Manufacturing of pharmaceutical-grade melt extruders is slightly different from the extruders used in the plastics and metals industries with respect to construction and screw design. Apart from being non-reactive and non-corrosive, the contact parts of the pharmaceutical-grade extruder should neither absorb nor leach any components. Screw designing in pharmaceutical extruders is most important as it ensures uniform mixing and content uniformity in the product. As depicted in Figure 2, every extruder has five basic components: extrusion drive system, extruder barrel, rotating screw, extrusion die, and supplementary equipment required for cooling, cutting, and collection of extrudates. Additionally, the extruder is composed of a feeding hopper, temperature controlling device, and a collector unit. Monitoring devices on the equipment consists of a screw-speed controller, an extrusion torque monitor, and temperature and pressure gauges. It is common for the extrusion screw to be characterized by the length/diameter (L/D) ratio, which typically ranges from 20 to 40:1.

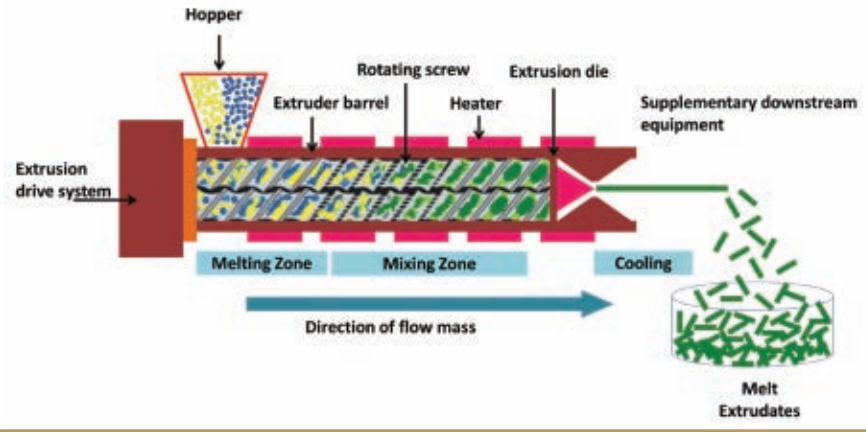
MELT-EXTRUDABLE POLYMERS

Apart from drug and plasticizer, thermoplastic polymers constitute the major components of melt extrudates. Optionally, other pharmaceutical excipients such as release modifier, solubilizers, filler, antioxidants, and lubricants can be used. Prior to planning the design of experiments for HME, it is essential to gather complete technical information, especially solubility of drug, polymer, and other excipients. Different types of polymers can be employed while designing the dosage form, for example, immediate-release and delayed-release formulations prepared using HME. The physical and chemical stability of melt extrudates is dependent upon the physico-chemical properties of polymer and excipients, the physical state and form of the drug in the final extrudate, ability of the extrudate to retain the polymorphic form of the drug, and storage and packaging conditions.[4] Leuner et al have published a comprehensive summary of all polymers used for improving drug solubility using solid dispersion, a majority of which can be melt extruded.[5]

Some of the polymers that have generally been used in HME include polyvinyl pyrrolidine (PVP), ethyl cellulose (EC), methacrylic acid copolymer, hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), polyethylene oxide (PEO), Eudragit® RSPO and Eudragit® S100, polyethylene glycol (PEG), chitosan, xanthan gum, polyvinyl acetate phthalate (PVAP), hydroxypropyl methylcellulose acetate succinate (HPMCAS), starch and microcrystalline wax mixtures, cellulose acetate butyrate (CAB), ethyl vinyl acetate (EVAC), and cellulose acetate phthalate (CAP). Some polymers like EC, acrylates, and waxes are used for sustained release only, and other polymers like PVAP, HPMCAS, and CAP are used for providing delayed release or as alternates to enteric coatings. Hydrophilic polymers like HPMC, PEO, HPC, and xanthan gum are used to modify release, depending on the desired purpose. Many polymer industries are now manufacturing copolymers, such as Soluplus® (a polyvinyl caprolactam-polyvinyl acetate - polyethylene glycol graft copolymer) and Kollidon® VA 64 (vinylpyrrolidone-vinyl acetate copolymer), having ideal properties for HME. Soluplus is reported to solubilize various lipophilic and hydrophilic chemical entities thus enhancing bioavailability of poorly soluble drugs.[6] PEO, HPC, and Eudragit RSPO can be used as thermal binders for modified-release dosage forms. PEO can be used to prepare melt-extruded transmucosal films with excellent film flexibility and bioadhesive properties.

Plasticizers such as PEGs, triacetin, citrate esters, and citric acid are the second most important components of the HME process as they enable the processing of HME at relatively lower temperatures.

FIGURE 2



Plasticizers, to a certain extent, help in extending the application of HME technology toward thermolabile drugs.

MELT-EXTRUDED DRUG DELIVERY SYSTEMS

Oral Drug Delivery Systems

Recently, HME has captured the attention of formulation development scientists due to its flexibility to manufacture a variety of solid oral dosage forms, such as immediate release and delayed release, as well as for bioavailability enhancement of poorly soluble drugs.

Immediate-Release Drug Delivery Systems: Orally fast-disintegrating tablets of non-steroidal anti-inflammatory drug (NSAID) and paracetamol were prepared using HME technology.[7] Sun et al have prepared solid dispersions of nimodipine using HME technology.[8] The HME process has also been exploited for the development of effervescent granules using twin screws.[9] Sodium bicarbonate and anhydrous citric acid were added from different hoppers into the extruder, and ethanol was added as a non-aqueous granulating solvent. The mixture was extruded to form effervescent granules. Carbamazepine, when melt extruded with PEG 400 and lactose, resulted in fast- disintegrating extrudates having improved dissolution rates.[10]

Modified-Release Drug Delivery Systems: Modified-release oral dosage forms have always been an evergreen area of research and development for the formulation scientist. Many sustained-release formulations have been developed using the HME process and reported in the literature. Calcium stearate is reported as a thermoplastic carrier for the development of sustained-release pellets of paracetamol.[11] The calcium stearate matrix was melt extruded, equipped with a hot strand cutter as a downstream system to form spherical pellets. Researchers have also successfully prepared sustained-release pellets of diltiazem hydrochloride using HME technology.[12] PEO has been exploited for the development of sustained-release matrix tablets of chlorpheniramine maleate using HME.[13] Eudragit® L100 is reported as a potential melt-extrudable polymeric carrier for the development of sustained-release tablets of ketoprofen.[14] HME was also used to prepare sustained-release matrix-in-cylinder systems of EC pipe surrounding a core of propranolol hydrochloride, HPMC, and Gelucire®.[15] A four-fold increase in propranolol bioavailability was observed when compared with a commercial sustained-release formulation (Inderal®). Hot-melt extruded matrix pellets of theophylline were prepared using Eudragit®, microcrystalline cellulose, and polyethylene glycol 8000.[16] The matrix pellets exhibited diffusion-controlled drug release. Literature reports the preparation of floating tablets by HME of a powder blend containing sodium bicarbonate and Eudragit RSPO and Eudragit® EPO.[17] The tablets exhibited buoyancy in the dissolution media and possessed sustained-release properties. Nakamichi et al have also reported the development of sustained-release floating tablets of nicaripine hydrochloride and HPMCAS using a twin screw melt extruder.[18] Delayed-release tablets of isosorbide nitrate were also developed using HME.[19]

Solid Dispersion/Bioavailability Enhancement: Solubility of drug is the most important parameter in determining its bioavailability. Most new drugs exhibit very poor solubility and belong to BCS class II or IV. Enhancement of oral bioavailability of such molecules remains the most challenging aspect in formulation development. Amongst various techniques reported in the literature, solid dispersion remains the most viable option for bioavailability enhancement. HME technology has been reported in the preparation of solid dispersions for the development of mini tablets that can minimize the risk of dose dumping and reduce inter- and intra-subject variability.[20] Solid dispersions of nifedipine with improved dissolution and absorption, prepared by HME technology using PEO as a carrier, has been reported in literature.[21] Nimodipine solid dispersions were prepared by HME using HPMC (Methocel® E5), PVP/VA (Plasdone S630®), and ethyl acrylate, methyl methacrylate polymer (Eudragit EPO) and was compared with the marketed formulation Nimotop®. The mean bioavailability of Nimotop was found to be comparable with melt-extruded solid dispersions prepared using Eudragit EPO, but the HPMC and PVP/VA dispersions exhibited much lower bioavailability. The $AUC^{0\text{-}12}$ h values of all three solid dispersions were significantly higher than physical mixtures with the same carriers and nimodipine powder.[22] HME technology is also reported to produce stable solid dispersion of itraconazole and HPMC (40:60), resulting in the formation of amorphous itraconazole.[23]

Transdermal & Transmucosal Systems

Transdermal and transmucosal are niche areas for formulation development. Problems associated with development of transdermal/mucosal via the conventional solvent-casting method has led formulation scientists to explore HME as a better option. Researchers have developed clotrimazole films by HME of HPC and PEO. The film exhibited ideal bioadhesive strength and release properties.[24] It is reported that HPMC imparts adhesive properties and strength to the hot-melt extruded films of lidocaine prepared using HPC.[25] Films manufactured using HME of PEO has been reported in the literature for topical delivery of ketoconzole.[26]

Impalnts

The release of the melanotropic

peptide, Melanotan-I (MT-I), from biodegradable implants of poly(d,l lactide-co-glycolide) (PLGA) copolymer was studied.[27] The implants were prepared by a melt-extrusion method. The in vitro release of MT-I showed drug release in three phases with an initial rapid release, followed by a slow release, and finally rapid release due to erosion of the polymer. Liang Cheng et al have demonstrated a series of praziquantel-loaded implants based on PEG/Poly(ε-caprolactone) (PCL), using a combination of twin-screw mixing and HME.[28] Compared to in vitro release, in vivo release showed to be more moderate, exhibiting zero-order kinetics after an initial burst release. The implant exhibited sufficiently high drug concentrations in plasma over a period of at least 6 weeks and was found to be compatible with tissues. Rothen-Weinhold et al have reported the formation of peptide impurity during the manufacturing of implants composed of vapreotide (somatostatin analogue) prepared using long-acting poly(lactic acid) via the HME process.[29]

A contraceptive vaginal ring of etonogestrel and ethinyl estradiol was prepared using polyethylene vinylacetate copolymers via a twin screw hot-melt extruder.[30] Implants composed of block copolymers via the HME process have been reported in literature, wherein the degradation of ABA triblock copolymers, consisting of poly(lactide-coglycolide) A-blocks and poly(oxyethylene) B-blocks, and PLG, poly(lactide-co-glycolide), with respect to swelling behavior, molecular weight loss, and polymer erosion, has been reported.[31]

Ophthalmic Inserts

Conventional ophthalmic formulations are associated with a number of drawbacks, such as rapid precorneal clearance kinetics resulting from reflex tearing and blinking and blurred vision due to ophthalmic ointments. Ophthalmic inserts are reported to overcome all these disadvantages of conventional therapy and exhibit better patient compliance. Jain et al have reported the development of extended-release ophthalmic inserts of acyclovir via HME technology using HPC as a thermoplastic polymer.[3] The drug release from the melt extrudates was found to exhibit first-order kinetics.

MARKETED FORMULATIONS

Meltrex® - Platform technology from SOLIQS

Kaletra® - Lopinavir/Ritonavir using polyvinylpyrroldione/vinylacetate matrix. The melt-extruded tablet offers numerous advantages over soft gelatin capsule formulations, such as reduced pill count from 6 soft gelatin capsules/day to 4 tablets/day. No refrigerated storage conditions required, more consistent plasma levels.

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Implanon® and NuvaRing® using polyethylene vinylacetate (EVA) copolymers. Implanon is a 4-cm x 2-mm rod containing 68 mg of etonogestrel (a progestin), which is released over a period of 3 years. NuvaRing is a contraceptive vaginal ring designed to release etonogestrel/ethinyl estradiol for a period of 21 days. It has an outer diameter of 54 mm and a cross-sectional diameter of 4 mm.

FUTURE ASPECTS

A combination of HME technology with supercritical fluid processing has recently been reported. Carbon dioxide is reported to act as a plasticizer, reducing the processing temperature during the hot-stage extrusion process, resulting in increased specific surface area and porosity of the extrudates.[32] Industries engaged in the manufacturing of biomedical devices, such as implants, medicated stents, and catheters, are growing at a faster rate, and HME technology is being explored for the manufacturing of such devices. Additionally, manufacturing of solid dispersions/solutions of poorly soluble drugs will always remain the green area for the formulation scientist to explore.

SUMMARY

Currently, HME technology has emerged as a most viable option for the development of a variety of drug delivery systems. Its versatile nature is evident from the fact that HME can be used for the manufacturing of almost all types of dosage forms ranging from oral, parenteral, topical, ophthalmic, and implants, as well as other medical devices. In addition, it can process even a wider range of drugs and excipients, with exception to thermolabile ingredients. Amongst the number of advantages associated with this technology, its ability to process the material without the use of any solvent has led to the acceptance of melt-extruded products in the regulated market. The unique property of this technology that makes it an economically viable option is that products with desired release characteristics (faster dissolution rate or sustained release) can be achieved in a single instrument through proper selection of thermoplastic polymers and other excipients. However, there are certain drawbacks such as limited use for thermolabile drugs and high energy consumption, but recent developments in process and screw design engineering may able to reduce these issues. ◆

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BIOGRAPHIES

Dr. Pirthi Pal Singh is an Assistant Manager in Pharma Research at Global Research and Development Centre of Panacea Biotec Limited, India. He has over six years of experience in pharmaceutical industries. He has earned his PhD in Bioprocess Technology from ICT, Mumbai, Diploma in Patent Law and Chemical Technology Management (Bronze Medalist) from University of Mumbai, India. His major research interests include Nanotechnology based Drug Delivery Systems, Melt Extrusion, Supercritical Fluid Processing, Taste-Masking, Mouth-Dissolving, Upstream and Downstream Processing of Biomolecules, Enzymatic Biotransformation and synthesis and formulation of inorganic compounds. He has also worked in the area of sales & marketing and Techno-marketing. He is currently Chairperson of Young Scientist Mentor-Protégé committee of Controlled Release Society, USA.

Dr. Paramjit Singh is currently working as a Senior Manager in Pharma Research at Global Research and Development Centre of Panacea Biotec Limited, India. He has more than 8 years of research experience in pharmaceutical industry at different levels. He is a university gold medalist at post-graduation level. He is honored with many state level and national level awards in academics and science. He has developed many products for Indian and export markets. He has 22 publications in peer reviewed journals to his credit. His area of research include nanoparticles for drug delivery, oral films/strips, orally disintegrating tablets, controlled release tablets, and modified release dosage forms.

Mr. Sarabjit Singh is vice president of Global Research and Development Centre of Panacea Biotec Limited, India and has contributed to company's product development initiatives since twelve years. He has obtained his M.Pharm degree from Jamia Hamdard University, India. He has more than 16 years of industrial experience. Prior to Panacea Biotec, he also held positions in Patent cell at Lupin Pharma Ltd. He is focused on developing and commercializing advanced technology based drug delivery systems. Sarabjit Singh is the lead contributor in various dosage forms which have led to filing of over 14 patent applications, two of which are platform technologies.

DRUG DEVELOPMENT Executive

Thomas Videbæk
Executive Vice President

Novozymes BioBusiness

"Built on Novozymes' original Albufuse® (albumin fusion) platform, the new Albufuse®Flex technology is an exciting step forward in drug delivery as it offers the potential to tailor half-life to specific medical needs. We expect the platform to have wide applications in drug delivery, where it may be used to enhance treatment efficacy and improve patient compliance."

Enhanced Albumin Fusion Technology: Tailoring & Controlling the Pharmacokinetics of Therapeutic Drugs

A leader in biomanufacturing and process development for more than 25 years, Novozymes develops and manufactures high-quality, animal-free, regulatory-compliant, biological ingredients and technologies to help pharmaceutical and medical device manufacturers deliver improved performance and get products to market faster. Biomedical products are an integral part of our modern society. As a result, considerable emphasis is placed on the development of safe and consistent sources of biologically derived solutions, focusing at the same time on ensuring economically viable and sustainable sourcing practices. Novozymes has dedicated a significant proportion of its recent R&D activity to developing solutions that will ultimately improve treatment regimes for patients with chronic or acute conditions receiving regular (often daily) injections. The company has recently unveiled enhanced next-generation albumin fusion technology, developed in association with the University of Oslo in Norway, one of Europe's leading institutions. This proprietary technology has been designed to offer flexibility and control over the pharmacokinetics (PK) of conjugated or genetically fused drugs at the same time as retaining drug efficacy. This could mean fewer injections for patients and less chance of toxic side effects, which may hamper compliance. Drug Development & Delivery recently interviewed Thomas Videbæk, Executive Vice President of Novozymes BioBusiness, to discuss the company's vision and how it is helping customers develop novel drugs with improved PK properties.

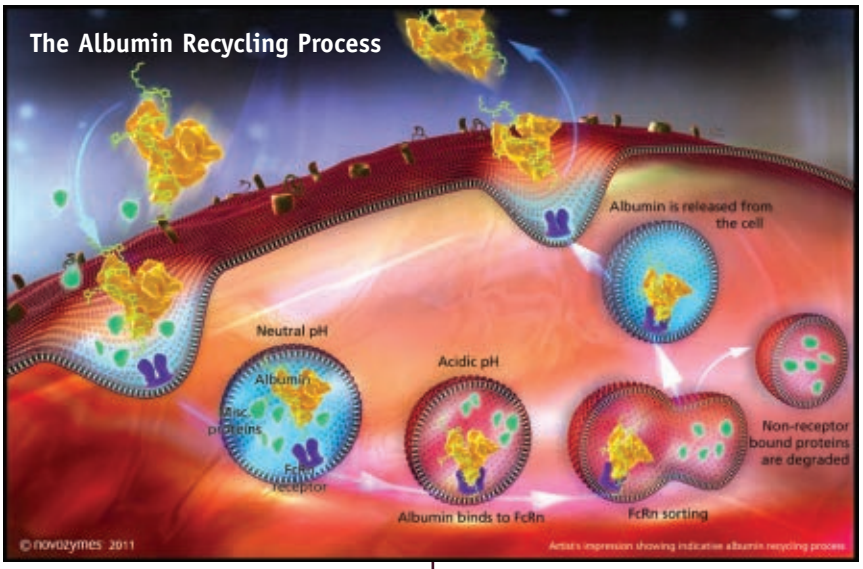
Q: Can you provide an overview of Novozymes Biopharma?

A: Novozymes develops and manufactures high-quality, animal-free, recombinant ingredients and technologies, providing pharmaceutical manufacturers with options based on our established technology platform developed over the past 50 years that will enable them to develop safer and more consistent products. Our worldwide manufacturing sites are run to cGMP/Q7 quality standards, ensuring that customers receive the essential product quality

and consistency, as well as the security of long-term supply. Currently, 14% of Novozymes' total revenue is spent on R&D projects, and more than 6,500 patent applications have been granted or are pending, demonstrating our commitment to scientific innovation.

Q: How is Novozymes working with its customers to develop improved drug products?

A: Novozymes' primary focus is on developing and producing recombinant products and technologies that offer superior safety and performance to our customers. We do this by providing access to high-quality ingredients, proprietary technologies, and unique know-how, contributing toward the development of improved therapeutic treatments providing real and sustainable benefits to patients. As a company, we are constantly reviewing industry trends and looking for new opportunities to improve our customers' processes by developing better and safer alternatives to the products they are currently using. However, we are more than a mere supplier of enabling technologies or products; we see our relationship with each customer as a partnership. By combining our scientists' unique knowledge of Novozymes' biological solutions with the customers' specific application knowledge, we work with our customers to deliver solutions that solve their most demanding challenges.



Q: What has driven the development of the Albufuse®Flex albumin fusion technology?

A: The efficacy of many drugs, especially those that are biologically based, is hampered by short serum half-life, which poses considerable challenges for pharmaceutical companies. Therefore, we have devoted a significant proportion of our research efforts to developing strategies that tailor serum persistence and biodistribution.

Built on Novozymes' original Albufuse® (albumin fusion) platform, the new AlbufuseFlex technology is an exciting step forward in drug delivery as it offers the potential to tailor half-life to specific medical needs. We expect the platform to have wide applications in drug delivery, where it may be used to enhance treatment efficacy and improve patient compliance. These innovations offer drug manufacturers greater flexibility as they seek to develop novel therapeutics.

Q: Can you tell us more about what albumin fusion technology is?

A: Albumin fusion technology enables the genetic fusion of a customer's target protein to albumin at the molecular level. The resultant moiety is secreted as a contiguous peptide linked via a peptide bond, enabling users to enhance the pharmacokinetics of their target protein with retained efficacy.

For the pharmaceutical industry, the technology provides the ability to manufacture completely new therapeutics that were previously out of reach. Many therapeutic drugs are rapidly cleared from the body. Albumin fusion offers a simple, flexible platform for the production of proteins with extended circulatory half-life, resulting in increased bioavailability. By fusing pharmaceutical proteins to

albumin via albumin fusion technology, a protein's half-life can increase from minutes to hours and from hours to days.

Q: How does the new platform offer improvements over the original Albufuse technology?

A: The key improvements center around flexibility, hence the name AlbufuseFlex. Flexible use translates as the ability to create either genetic fusions or chemical conjugates of a drug. In addition to protein- or peptide-based drugs, the enhanced technology also provides a delivery vehicle for small molecules or NCEs via conjugation, providing a broad scope of usability. Flexible half-life is achieved by modifying the receptor binding between albumin and the neonatal Fc receptor (FcRn) to offer increased residence time, or in other words half-life, in accordance with medical need.

Looking at the science behind the new technology, albumin is the most abundant plasma protein, making up approximately 60% of total protein, with a long serum half-life of about 19 days. This extended half-life is due, in part, to its large hydrodynamic radius, which protects the 67 kDa molecule from renal clearance, and also to its relationship with and affinity for the FcRn. FcRn is a dual binding receptor that binds both immunoglobulin_G (IgG) and albumin at distinct sites, while protecting them from intracellular degradation.

By exploiting the interaction between albumin and FcRn, it could be possible to tailor its half-life. Studies have demonstrated that altering the interaction between IgG and FcRn can alter the PK of the IgG. One such example is Avastin®, an antivascular endothelial growth factor. When engineered to have increased binding affinity for FcRn, a significant increase in half-life was observed (24 days instead of 11 days in macaques). Similarly, the AlbufuseFlex technology modulates half-life extension by constructing albumin variants with altered binding affinity to FcRn, providing drug developers with control and flexibility in their drug design.

Q: Why should drug developers be interested in AlbufuseFlex?

A: In addition to allowing manufacturers to design how long a drug is retained in the patient's system, albumin fusion-based molecules can lead to more favorable tissue distribution within the body, reducing the risk of localized retention at the site of administration. If designed as a genetic fusion, our proprietary yeast expression system provides a highly consistent and reliable supply of the therapeutic protein of interest, which is a major concern for companies as they develop their products through clinical trials and launch them to the market. Albumin fusions create new opportunities for the development of new drugs and treatments, creating value by providing solutions to the pharmaceutical industry.

Q: How does Novozymes' latest innovation support the company's goal of creating better lives for patients?

A: Our scientists work with the goal of the final product in mind, namely to deliver better quality of life to patients. A key clinical advantage of the AlbufuseFlex technology is an increase in the *in vivo* half-life of the therapeutic protein. For patients, this means reduced frequency of administration of a drug product and, as a result, a reduced overall dosage. For manufacturers, a less-frequent dosage rate also means the treatment is more cost effective, something that is becoming crucially important with the growing focus on healthcare costs and accessibility to medicine.

Furthermore, the technology produces more stable blood levels in patients and also confers a reduced risk of side effects because the lower dose rate means the toxicity level of the drug may not be reached. Instead, the drug dose remains within the therapeutic range, increasing the patient's tolerance to the drug. Since some biopharmaceuticals have to be administered by a nurse at home or at a clinic, the number of visits can also be reduced significantly, resulting in better compliance and ease of use. ◆

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The Best Chewing Out I Ever Received

By: John A. Bermingham

My second job after being discharged from the Army Signal Corps was Midwest Regional Sales Manager for Panasonic. I had the sales responsibility for the 13 Midwestern states. Part of my responsibility was to develop the sales budget twice per year for my region. It was a very complex time-consuming process as I had to develop that budget by month and by product model. It took days, not hours.

Rather than forecasting my sales for the 6-month period, I was given the 6-month sales budget by the Region General Manager (my boss' boss) and then had to work the budget numbers to agree with my assigned sales budget. I believed that this was not a good process as I had no say in what I thought I could sell, I was simply plugging in numbers.

During the Consumer Electronics Show in Chicago, one of the senior Japanese executives from Panasonic Japan who had flown in for the tradeshow asked me how I felt about meeting my sales budget for the coming 6-month period and what I had based the forecast on. I told him the sales budget number was assigned to me by the Midwest Region General Manager, so I had no say in the forecast. I just plugged the numbers in.

The next day, the Region General Manager asked me to meet him in his hospitality suite after the tradeshow closed for the day for a meeting with him. He did not say why. When I arrived at his suite the following day, he took me into one of the suite's bedrooms and asked me what I had said to this senior Japanese executive. I told him what I had said about the budgeting process. He proceeded to chew me out for about 15 minutes for putting him in a very bad position with this Japanese executive. Why didn't I just come to him and give my opinion to him directly rather than saying it behind his back to this Japanese executive. I was waiting for him to fire me right then and there.

He didn't. He instead did something that shocked me. He invited me to join him and two other Panasonic executives for dinner. Over dinner, the Region General Manager acted as if nothing had happened and was as cordial as always toward me. He also never mentioned the problem that I had caused him. I learned a great lesson that night on how to treat people. I was wrong for causing the Region General Manager a major problem with his management, and I am certain the chewing out he received was equal to or worse than mine. What I learned was that this man made the issue a business issue, explained to me in a very strong and concise manner the problem that I had caused him, and then moved passed it. Because of the treatment I received that night, I became his most loyal fan and employee.

Most times, when a person is called on the carpet and is chewed out, animosity with a negative relationship develops between the two people involved, and enemies are formed. Or the "chewee" decides to look for another job and has nothing but bad things to say about the other person. My reaction was quite the opposite due to the people skills this Region General Manager had. He took a very negative situation and turned it into a learning situation with a positive spin at the end. I have never forgotten this man and have always tried to emulate his management style. ◆

BIOGRAPHY

John A. Bermingham is currently the Co-President and COO of AgraTech, a biotech enterprise focused on chitosan, a biomaterial processed from crustacean shells (shrimp, crawfish, crab, etc). He was the President & CEO of Cord Crafts, LLC, a leading manufacturer and marketer of permanent botanicals. Prior to Cord Crafts, he was President & CEO of Alco Consumer Products, Inc., an importer of house ware, home goods, pet, and safety products under the Alco brand name and through licenses from the ASPCA and Red Cross. He successfully turned around the company in 60 days and sold Alco to a strategic buyer. Mr. Bermingham was previously the President & CEO of Lang Holdings, Inc. (an innovative leader in the social sentiment and home décor industries) and President, Chairman, and CEO of Ampad (a leading manufacturer and distributor of office products). With more than 20 years of turnaround experience, he 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 3 years 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.

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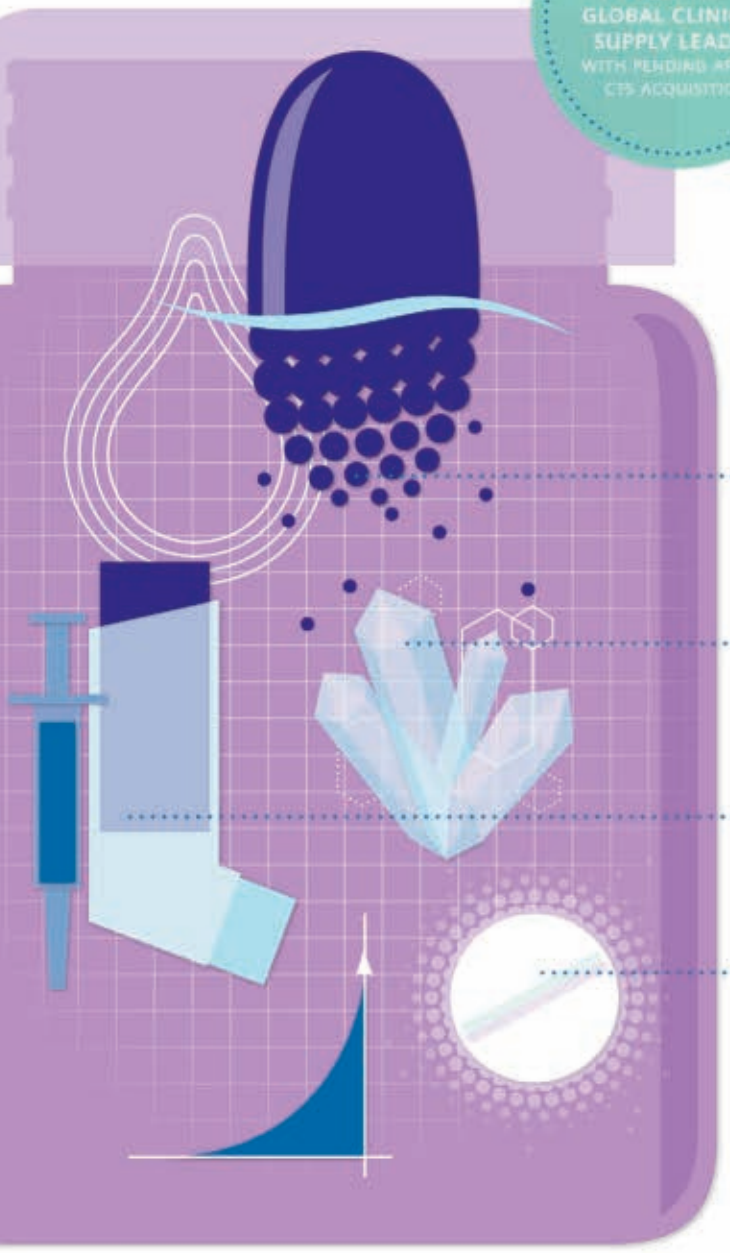

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Nanotechnology: New Name, Old Science

Introduction

Colloidal phenomena are encountered in everyday materials (polymers, plastics, and rubber, agrochemicals, pharmaceuticals and cosmeceuticals, paper, foodstuffs, fabrics, textiles, and detergents) and technologies (nucleation and precipitation, liquid crystals, chromatography and ion-exchange, flotation, and heterogeneous catalysis).

Historically, humans have observed and made use of colloidal phenomena for thousands of years. Stone Age paintings in the Lascaux caves of France were produced with stabilized colloidal pigments; the Bible and other early religious writings refer to strange clouds and fogs; ancient Babylonian tablets describe the preparation of inks and pigments; ancient Egyptian hieroglyphs show scenes of silting of the Nile delta, and Hebrew slaves made bricks of clay.

Nanotechnology

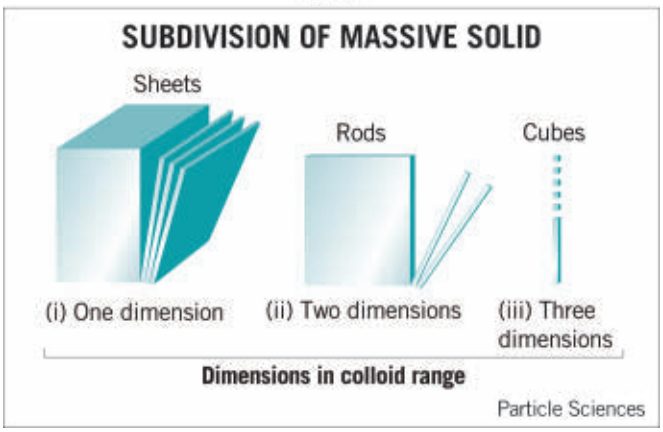
In 2007, the FDA issued its Nanotechnology Task Force Report[1] in which nanotechnology is defined as the ability to measure, see, manipulate and manufacture things usually between one and 100 nanometers. Nano-size particles are but a new term for colloids.

There is a continuing and increasing interest in "nanotechnology" applications for the pharmaceutical industries, due to improved drug delivery and targeting. One estimate suggests that about 80% of the 2015 market in those industries will relate to nanotechnology[2].

What's a Colloid?

The concept and the name of "colloid" are credited to Thomas Graham (1861). Using (a) restricted diffusivity (colloids are held back by a semi-permeable membrane) and (b) optical turbidity (colloids scatter light) he demonstrated (with gelatin solutions and gold sols respectively) that two distinct classes of material can be so qualified. The former is now referred to as "lyophilic" (liking and spontaneously dispersible in their liquid; they are thermodynamically stable) and the latter as "lyophobic" colloids (disliking their environment and potentially unstable).

Figure 1



Colloid science covers systems occupying an intermediate position (with respect to particle size) between true solutions of low MW substances and suspensions. As a rough guide, a colloid is any particle whose size includes a linear dimension (Figure 1) in the range from ~ 1 - 10 nm to ~ 500 - 1000 nm, (or alternately, between 10^3 and 10^9 atoms per particle).

Colloidal systems are termed dispersions (or sols for solid-liquid systems). For particulate systems in which the size exceeds 1 μ it is usual to refer to them as suspensions, though the two terms are often used interchangeably.

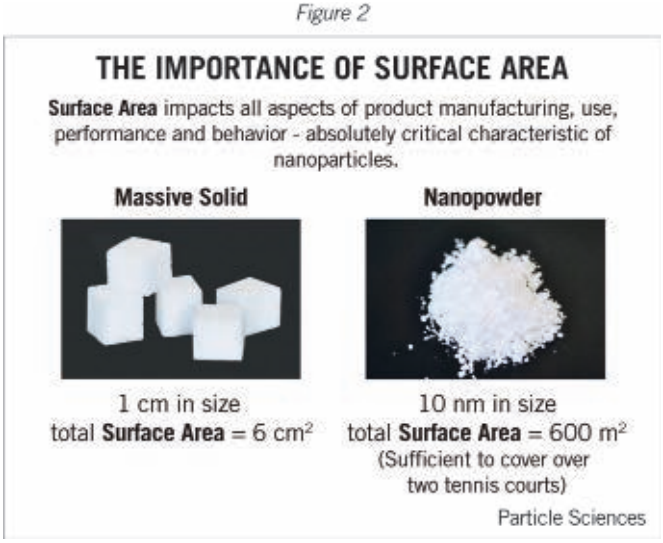
The Importance of the Colloidal State

The characteristic feature of colloid science lies in the importance of:

1. Particle size
2. Particle shape (and flexibility)
3. Surface chemical (and electrical) properties

The particles in a colloidal dispersion are sufficiently large for a well-defined surface of separation, an interface, to exist between the particles and the medium[3]. The presence of an interface also leads to effects such as capillarity (the "tears" in strong wine, the dew drops on spider webs, waterproofing and the breakup of liquid jets) and adsorption (carbon filters for clarification of water, beer, wine, bone-char to de-color sugar solutions, gas masks and the flocculation of muds at river deltas).

Figure 2



Particle Size

The particle size distribution (PSD) directly affects the bioavailability of active pharmaceutical ingredients (APIs) and the safety of intravenous lipid emulsions. As with suspensions, colloidal dispersions also contain a range of sizes and, hence PSD.

Two procedures are used for the preparation of colloidal dispersions[4,5]. In the dispersive (or "top-down") method one phase is "dispersed" in another by comminution and attrition using mills of various types; although the average particle size can be made small, the PSD is usually broad. In the condensation (or "bottom-up") method, conditions are created (starting from molecular solutions) in which individual molecules combine to form aggregates. Here the resulting PSD is much narrower; these dispersions are, however, subject to Ostwald ripening.

As the particle size is reduced, the surface area increases (as $1/d^2$), accompanied by a large surface area-to-volume ratio per given mass for the particles. This is illustrated (Figure 2) by taking a "particle" of side 1 cm and breaking it down into smaller cubes having a side of only 10^{-6} cm (or, 10 nm. The total surface area for the same amount of material then increases from 6 cm^2 (about the size of a sugar lump) to $6x10^6$ cm^2 (or, 600 m^2 – enough to cover the area of two tennis courts). The particle shape is immaterial - the surface area per mass of any colloid is orders of magnitude larger than it is for particles of even only a few μ in size. This huge increase in surface area effects not just adsorption of chemicals and other moieties onto the particle surface but also the interaction between particles and system properties, such as suspension rheology, coating and adhesion. It also allows for

much faster dissolution of API's leading to increased bioavailability in the case of sparingly water soluble but membrane permeable molecules. Low bioavailability can lead to inefficient treatment, higher cost and risk of toxic side effects; hence the drive to develop reformulations based on nanotechnology. There is also a growing body of evidence that, specifically with nanoparticulate materials, it is the surface area and not particle size that is the defining metric that controls toxicological interaction[6,7].

Additionally, as material is broken down, the hitherto internal surface becomes exposed and, with it, a change in the number or type of surface chemical sites and groups. Referring again to our particle (cube) of 1 cm, only two or three molecules in 10 million are "surface" molecules. However, when divided into 10 nm size particles, more molecules/atoms that comprise the molecular structure become "surface moieties" and the ratio rises to nearly 1:4; and at 1 nm particle size fully 80% of the atoms are on the surface. As a further example, a typical micellar solution containing 0.1 M amphiphile has ~$4x10^4$ m^2 of micellar-water interfacial area per liter of solution!

Thus, at the interfaces between the disperse phase and the dispersion medium, electrical (surface charge) effects that are normally negligible for massive solids become dominant in the description of colloidal behavior; they play an increasing part in determining the physico-chemical properties (such as surface chemistry/activity and catalysis) of the system as a whole[8].

Particle Shape

Particle asymmetry is a factor of considerable importance in determining the overall physico-mechanical properties of colloidal systems. Shape is a function of the history of the formation of the particles, i.e., crystallization[9]. Although the exact shape may be much more complex, colloidal size particles can be roughly classified as: corpuscular (spherical and ellipsoid), laminar (disc- or plate-like) or linear (rod- or needle-like).

"Globular" proteins (albumin, globulin, casein, hemoglobin) adopt a compact "random coil" configuration that approximates sphericity[10]. Many API's exist as rod- or needle-like particles. High MW macromolecular materials (proteins, polysaccharides and synthetic polymers) usually exist in the form of long thread-like or branched-chain molecules; these materials often exhibit a considerable mechanical strength and durability not possible with corpuscular or laminar particles[11]. Their shape is influenced by solution conditions (temperature, pH, salt/electrolyte concentration) and ranges in configuration from hugely elongated uni-dimensional strings to tightly compacted random coils[12]; their functional properties (i.e., to act as either a stabilizer or a de-stabilizer of a particulate dispersion or suspension) have been used since the days of antiquity (i.e., gum Arabic as a pigment dispersant).

Surface Charge

All dispersed particles spontaneously acquire a surface electrical charge when brought into contact with a polar medium (i.e., water); the various charging mechanisms are[13]:

1. Affinity differences of two phases for electrons
2. Ionization of surface groups
3. Differential ion adsorption from an electrolyte solution
4. Differential ion dissolution from a crystal lattice
5. Surface anisotropy
6. Isomorphous substitution

For all liquid-liquid interfaces and most normal colloidal dispersions Mechanism 1 is of little significance; an exception is metal sols (i.e., gold nanoparticles). Mechanism 2 is commonly observed with carboxylic acid- and amine-containing surfaces (i.e., proteins and ionic polymers) and all oxide surfaces. Lyophobic colloidal dispersions (i.e., polymer latices and API's) fall in the Mechanism 3 category. Ionic solids (i.e., silver halides, calcium carbonate) acquire a surface charge via Mechanism 4 by virtue of unequal dissolution of the oppositely charged ions of which they are composed. Mechanism 5 arises because most crystal lattices are anisotropic; it is the cause of amphoteric hydroxyl groups in oxides, including silicas[14]. Mechanism 6, isomorphous substitution, a more extreme case of Mechanism 5, occurs in alumino-silicate clay materials (i.e., montmorillonite and vermiculite)[15] where a large negative charge is initially developed on the clay crystallite because of the difference in valence between the Al^{3+} and the Si^{4+} ions.

Conclusion

Over 500 manufacture-identified, "nanotechnology-based" products have already been catalogued[16]. In consumer healthcare, sunscreen products use "microfine" zinc oxide and titanium dioxide to attenuate the UVA and UVB radiation that causes sunburn and skin cancer yet are non-whitening on the skin[17]; toothpastes contain nanoparticulate hydroxyapatite for filling minute cracks in tooth enamel and many anti-aging products use nanocapsule technology to deliver actives such as vitamins into the skin[18]. Nanosilver particles can be found in FDA-approved wound dressings. Bioactive ceramic material (based on mixtures of nanosize zirconia and hydoxyapatite) are in the development stage for orthopedic weight-bearing implants; one major advantage of nanoparticles is a vast improvement in sintering behavior. Thus, the new field of "nanomedicine" promises to impact all stages of healthcare[19]. Drug delivery is one of four main areas in nanomedicine (the others are molecular diagnostics, tissue engineering and cell/gene therapy). The challenge for traditional pharmaceutical companies is to deliver the right therapeutic to the right target with no, or minimal, side effects and ideally at reduced cost. Nanotechnology may provide improved, differentiated products for all common routes of administration - oral, injection, transdermal, transmucosal, ocular, pulmonary and implant. The global market for nanotechnology-enabled products in 2007 totaled $147 billion but is projected to grow to $3.1 trillion by 2015[20].

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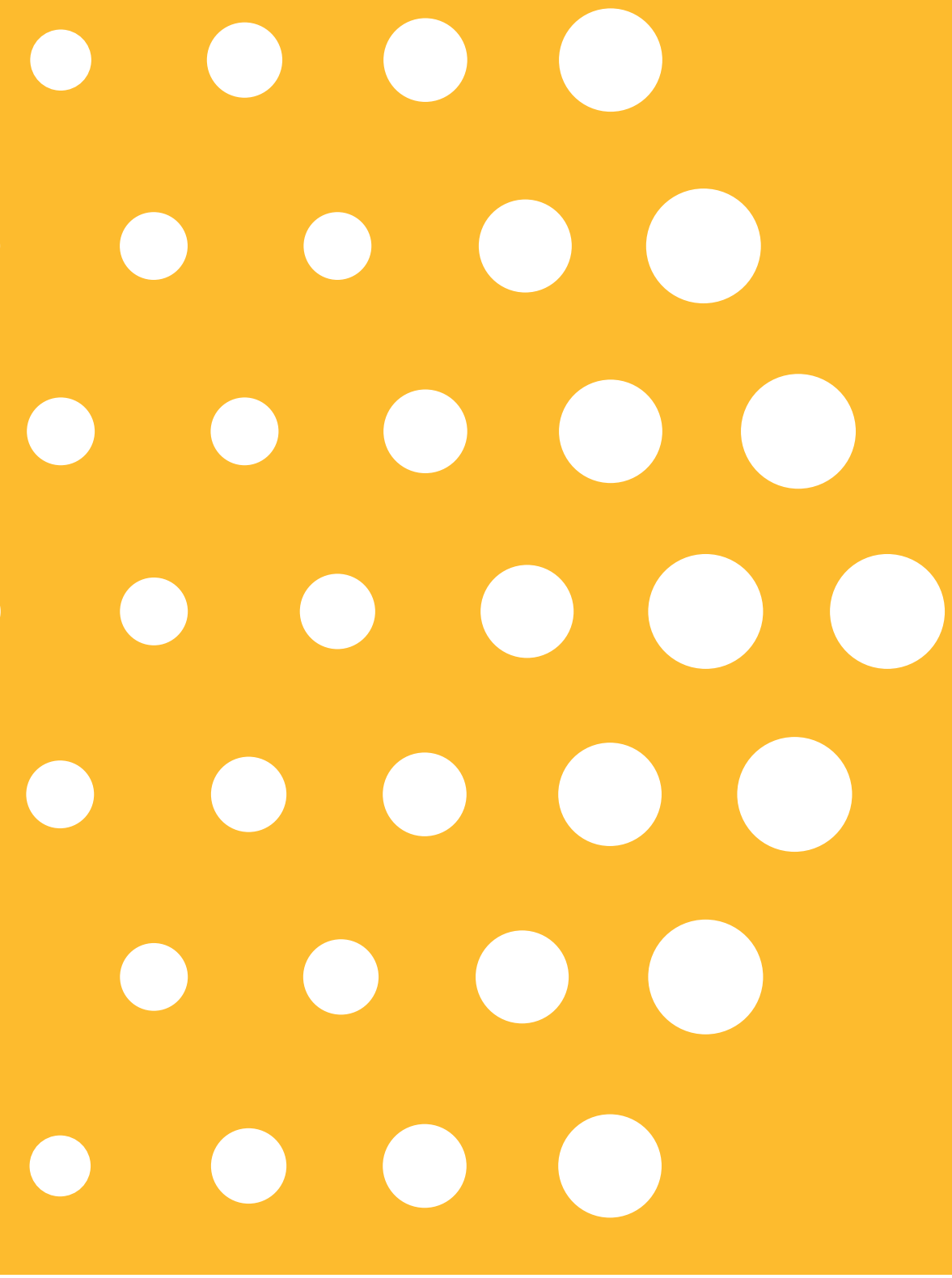

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