Drug Development & Delivery

May 2011 Vol 11 No 4 www.drug-dev.com

Vaccines: Sustainable Blockbusters

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

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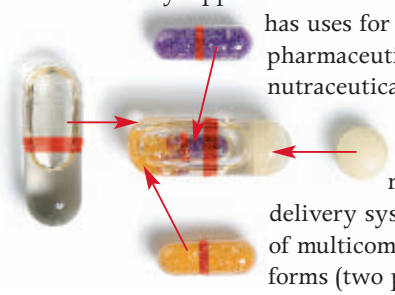
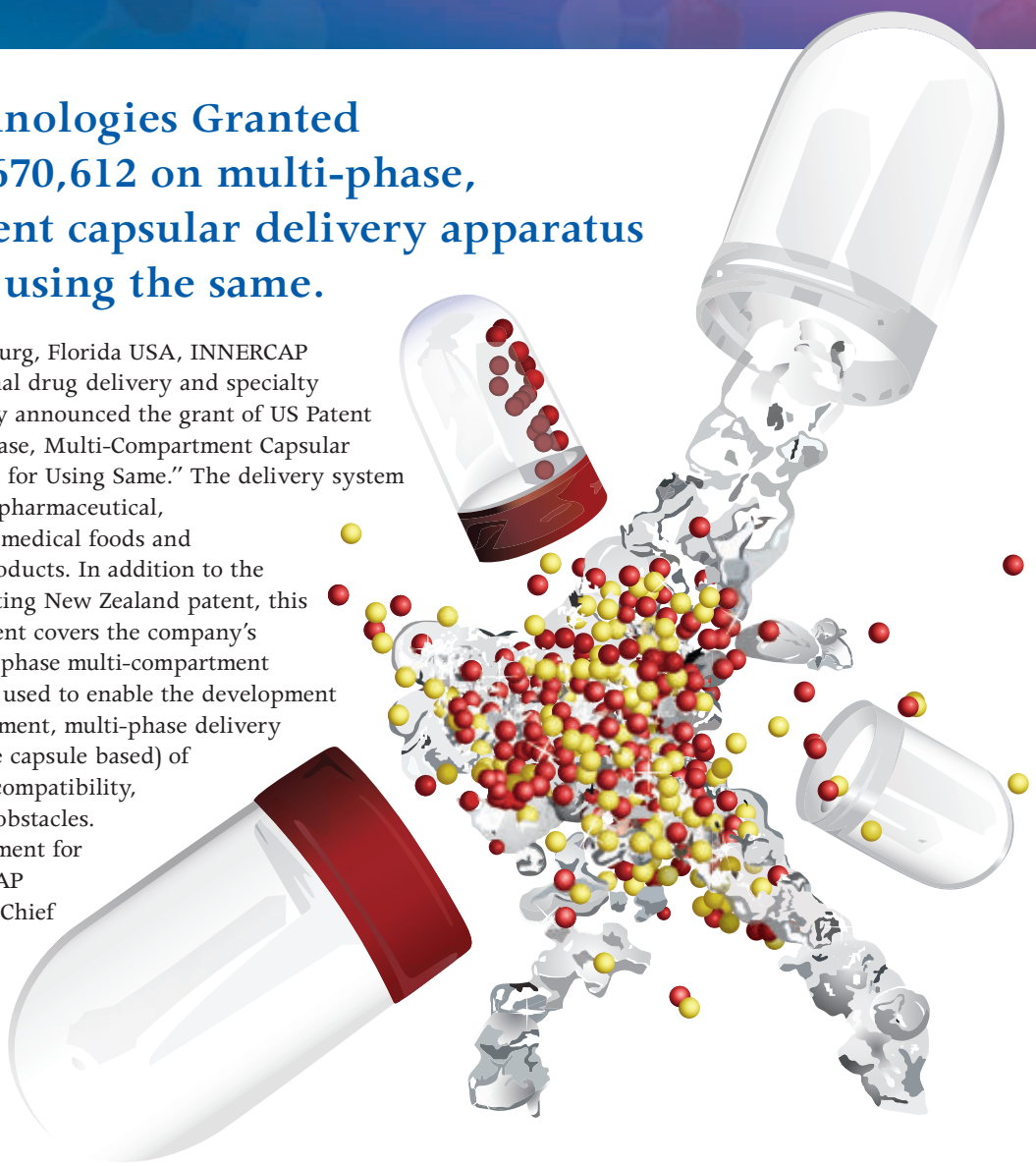
THE ADVANTAGES

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
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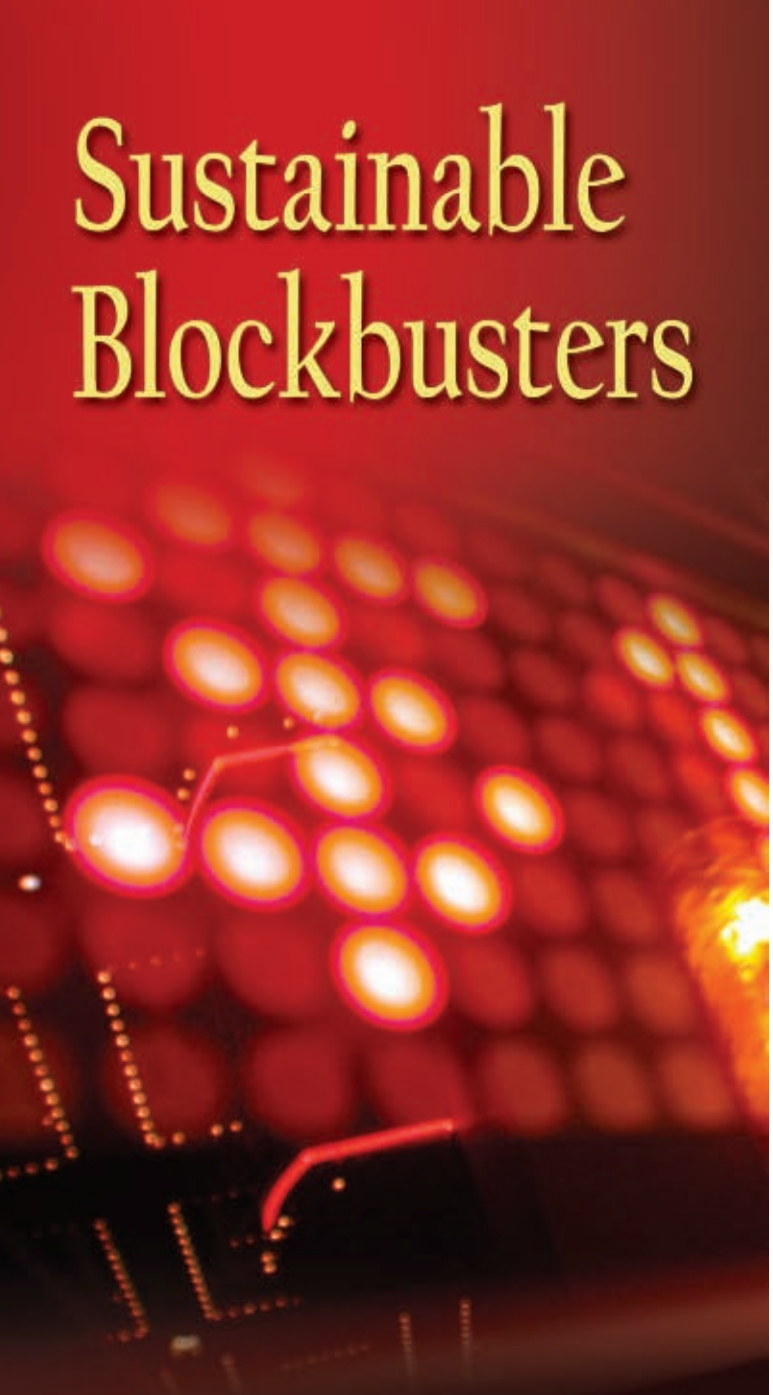

"One of the key factors of continued strength of the vaccines market has been the strength of the vaccines pipeline. The late-stage pipeline has more than 80 candidates, and almost 40% of those are for diseases that currently do not have vaccines in the market. The rest are expected to be more effective than the current vaccines in the market. This is expected to have a major positive impact on the health and economics of both developing and developed economies."

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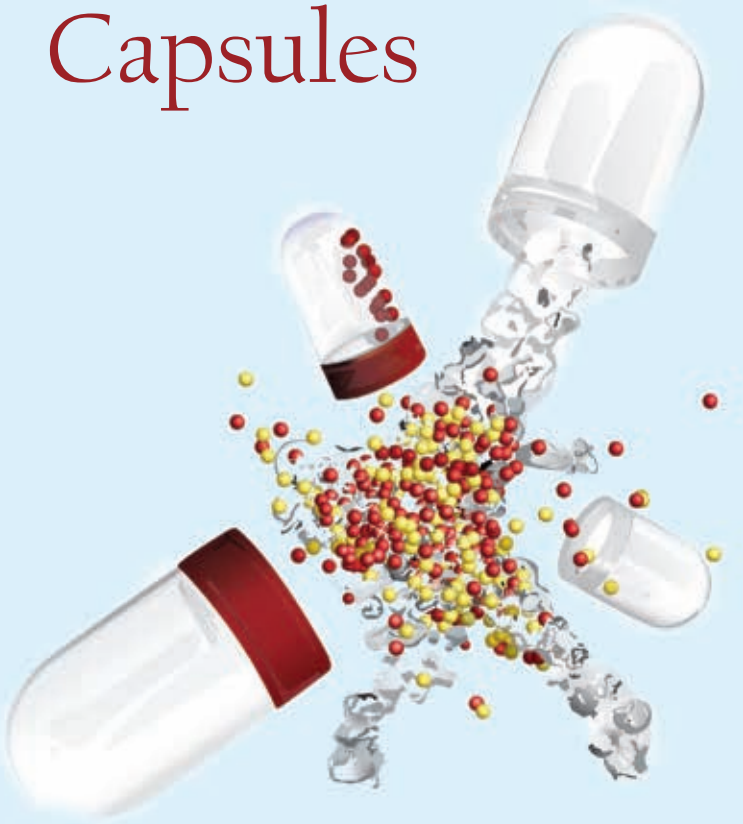

"Compartmentalized or multi-phase capsules are also being developed to deliver a cocktail of drugs simultaneously in one vessel. The idea is to develop a drug delivery system in which a single oral dosage unit comprises a capsule-in-a-capsule; two independent compartments form one dosage unit that can target incompatible drugs to different regions of the body. The outer capsule normally contains a liquid or semi-solid formulation with the inner capsule housing the more delicate powder formulation. The multi-layer aspect of the structure fosters sustained-, pulsed-, or delayed-release delivery."

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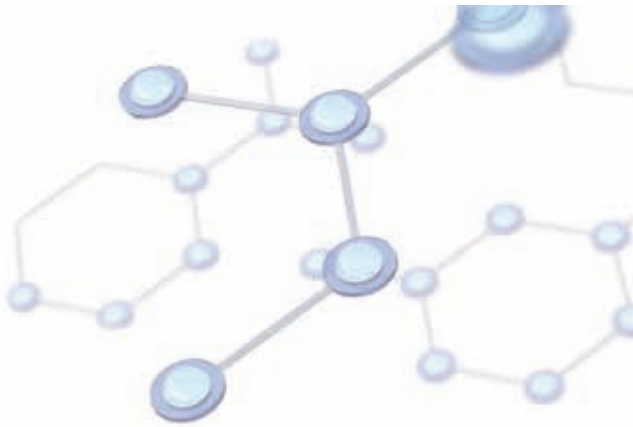

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Market News and Trends

Brainlab & SurgiVision Announce Strategic Alliance

Brainlab AG and SurgiVision, Inc. recently announced a collaboration aimed at integrating SurgiVision's ClearPoint product line with Brainlab's iMRI product line, with particular focus on local delivery of drugs and other therapeutic agents to precision targets in the brain under magnetic resonance imaging (MRI) guidance. Brainlab and SurgiVision believe the integration of their technologies will allow patient-specific treatment planning, simplified clinical workflows, and optimal delivery of drugs to the brain.

Under the terms of the agreement, Brainlab also received the right to sell SurgiVision's ClearPoint product line, including the right to exclusively sell ClearPoint products in the neurological drug delivery field, and Brainlab made an investment into SurgiVision. SurgiVision will continue to sell its ClearPoint product line directly for all applications outside the neurological drug delivery field.

SurgiVision's ClearPoint system provides guidance for the placement and operation of instruments during neurological procedures performed within the MRI environment. Using the ClearPoint system, a physician sees and selects a neurological target, aims SurgiVision's targeting device, and watches via MRI as the surgical instrument is advanced to the target and the therapy is delivered. SurgiVision's ClearPoint system has received both FDA clearance and CE Mark. SurgiVision also recently received FDA clearance for its SmartFlow injection cannula.

Brainlab's Brainsuite iMRI integrates intra-operative MRI with surgical planning and ceiling-mounted navigation, allowing full utilization of intra-operative data for making informed decisions during the procedure. iPlan Flow enables neurosurgeons to optimize local drug delivery to the CNS, based on patient-specific imaging.

"Direct, image-guided delivery of therapeutic agents into the brain provides the next-generation platform for delivering a wide range of promising therapies for patients suffering from CNS disorders, such as Parkinson's disease and malignant brain tumors," said Dr. Krystof Bankiewicz, Vice Chair and Professor, Department of Neurosurgery and Director of the NeuroTherapeutics Delivery Center at the University of California San Francisco. "This collaboration between two important players in the field is welcome news to pharmaceutical companies, biotech companies, and researchers with therapeutic agents that need to be delivered in a targeted, patient-specific, image-guided fashion."

"MRI-guided interventions is an important, emerging area of medicine. We are excited about the partnership with SurgiVision, the integration of our technologies in functional neurosurgery, and the opportunity to offer these innovative solutions to customers through our global sales network," added Stefan Vilsmeier, CEO of Brainlab.

"We are very pleased to announce this collaboration with Brainlab, a pioneer and leader in image-guided interventions," said Kimble Jenkins, CEO of SurgiVision. "Together with our new partner, we are excited about providing to clinicians powerful, new capabilities in targeted drug delivery and other MRI-guided therapies to benefit patients who suffer from CNS disorders."

Brainlab develops, manufactures, and markets software-driven medical technology that supports targeted, less-invasive treatment. Brainlab technology drives collaboration between hospitals and clinicians from a wide variety of subspecialties - from neurosurgery and oncology to orthopedics, ENT, CMF, and spine & trauma.

Founded in 1998, SurgiVision, Inc. is a leader in the emerging field of MRI-guided interventions, creating innovative platforms for performing the next generation of minimally invasive surgical procedures in the brain and heart. Utilizing a hospital's existing MRI suite, SurgiVision's FDA-cleared ClearPoint system is designed to enable a range of minimally invasive procedures in the brain.

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Comprehensive Clinical Development Finalizes Acquisition

Comprehensive Clinical Development, formerly operating as Comprehensive NeuroScience, Inc., a strategic clinical research organization delivering high-quality clinical development services from early proof-of-concept through commercialization, recently announced the acquisition of Charles River Clinical Services Northwest, Inc., including its 250-bed, 77,000-sq-ft, Phase I-IIa facility located in Tacoma, Washington.

The newly combined companies offer over 160 years of collective industry experience and provide an end-to-end turn-key clinical development solution, from inception of clinical testing through proof-of-concept trials. The increased capacity and capabilities deliver numerous benefits to support clients' complete drug development programs, including geographic diversification allowing clients a more proximal location to conduct studies and increase service offerings from coast to coast, established experience in conducting radiolabeled studies; streamlined optimization and extensive expertise in biologics studies; access to leading physicians in numerous specialties including oncology, expansive patient populations, and unique nuclear pharmacy capabilities, allowing for highly differentiated studies;s pecialized pharmacy services optimized for compounding, including radiolabeled compounds; and extensive access to populations for targeting treatments for patients with hepatitis C.

"We are thrilled to have the team from Charles River Clinical Services joining the Comprehensive network," said Comprehensive Clinical Development CEO Jack McGovern. "We are uniquely aligned with similar cultures, industry experience, and business philosophies. What is just as exciting is how complementary the businesses are in terms of customer mix, service offerings, geographic location, and subject populations."

"Joining Comprehensive Clinical Development is a very positive development for our future in the clinical trials industry," added Charles River Clinical Services General Manager Colleen Hoke. "Leveraging best practices and the expertise of each firm will provide clear benefits to our clients. The similar cultures and aligned goals of the organizations will facilitate a smooth integration of operations."

Precision NanoSystems & Alnylam Form New Delivery Collaboration

Precision NanoSystems, Inc. and Alnylam Pharmaceuticals, Inc., a leading RNAi therapeutics company, recently announced the two companies have formed an exclusive collaboration focused on the discovery and development of novel lipid nanoparticles, known as small lipid nanoparticles (sLNPs), using microfluidics technology. Based on their small particle size of approximately 20 nanometers, sLNPs have the potential for broadened biodistribution beyond liver delivery.

"We look forward to working with Precision NanoSystems to support research efforts around the discovery of novel sLNPs that we believe have the potential to significantly improve and broaden biodistribution," said Kenneth Koblan, PhD, Chief Scientific Officer at Alnylam. "sLNPs represent an exciting and innovative approach in Alnylam's advancement of proprietary LNPs for RNAi therapeutics."

"We are excited to have formed this exclusive collaboration with Alnylam focused on the discovery and development of novel sLNPs using microfluidics technology," added James Taylor, PhD, Chief Executive Officer of Precision NanoSystems. "Alnylam is leading the translation of RNAi technology into human therapeutics, and we look forward to working with them."

Alnylam is a biopharmaceutical company developing novel therapeutics based on RNA interference, or RNAi. The company is leading the translation of RNAi as a new class of innovative medicines with a core focus on RNAi therapeutics for the treatment of genetically defined diseases, including ALN-TTR for the treatment of transthyretin-mediated amyloidosis (ATTR), ALN-PCS for the treatment of severe hypercholesterolemia, and ALN-HPN for the treatment of refractory anemia. As part of its Alnylam 5x15 strategy, the company expects to have five RNAi therapeutic products for genetically defined diseases in advanced stages of clinical development by the end of 2015. Alnylam has additional partner-based programs in clinical or development stages, including ALN-RSV01 for the treatment of respiratory syncytial virus (RSV) infection, ALN-VSP for the treatment of liver cancers, and ALN-HTT for the treatment of Huntington's disease.

Avantor Certifies All Doe & Ingalls Sites Under Certified Excipient Distributor Program

Avantor Performance Materials (formerly Mallinckrodt Baker) recently announced that Doe & Ingalls, a national chemical services provider and Avantor distributor, is the first distributor to have all company sites certified under the Avantor Certified Excipient Distributor (CED) Program.

Avantor Performance Materials manufactures and markets high-performance chemistries and materials around the world under several respected brand names, including the J.T.Baker®, Macro™ (formerly Mallinckrodt®), Rankem, and Diagnova brands. Avantor products are used around the world in a wide range of industries, including biotechnology and pharmaceutical production; electronics and photovoltaic manufacturing; and in research, academic, and quality control laboratories.

Doe & Ingalls, based in Durham, NC, is an Avantor distributor specializing in providing chemical services expertise and high-quality chemicals to the life science and electronics industries. The company sources materials from suppliers who can meet the specific supply chain needs of life science and electronics manufacturers.

In October 2010, the last Doe & Ingalls facility, Riverside, CA, received certification. The 41,600-sq-ft facility includes a fixed modular cleanroom for pre-shipment sampling and dip tubing services. Last year, Avantor also re-certified Doe & Ingalls regional service centers in FL, MD, MA, and NC.

"Avantor has a long history of working with Doe & Ingalls to supply high-quality performance chemicals to the pharmaceutical, biotechnology, photovoltaic, laboratory, and electronics industries," said Avantor Executive Vice President, Pharmaceuticals and The Americas, Paul Smaltz. "Doe & Ingalls' business model aligns with our vision of service excellence. Doe & Ingalls has met our rigorous standards time and time again, making it the only distributor to receive this distinctive certification for all sites."

"Doe & Ingalls is pleased to have received Avantor's Certified Excipient Distributor distinction at each of its service centers," added Doe & Ingalls Chief Executive Officer John Hollenbach. "Doe & Ingalls is focused on building secure chemical supply chains for the life science and electronics industries. We do this by partnering with quality suppliers like Avantor and then offering supply chain services that create efficiencies and manage risk. This certification demonstrates to our customers our commitment to supply chain security."

Launched in August 2008, the Avantor CED program is designed to provide customers with the assurance that a certified channel partner utilizes fully documented chain of custody and change management procedures. An Avantor CED delivers its regulated products through an optimized supply chain that is compliant with the International Pharmaceutical Excipient Council's (IPEC) guidelines. In order to receive certified status, a potential channel partner must annually pass a strict quality audit conducted by the Avantor regulatory department. The audit process is designed to ensure that each distributor in the program is in compliance with all IPEC Good Distribution Practices for Pharmaceutical Excipient guidelines.

Gilead & MicroDose Therapeutx Announce License & Collaboration Agreement

Gilead Sciences, Inc. and MicroDose Therapeutx, Inc. recently announced they have entered into an exclusive worldwide license and collaboration agreement for the development and commercialization of MDT-637, MicroDose's inhalable small molecule antiviral fusion inhibitor for the treatment of respiratory syncytial virus (RSV).

Under the terms of the agreement, Gilead will pay MicroDose an upfront payment and provide research funding to support MicroDose's continued development of MDT-637 through Phase IIa clinical trials. Gilead can assume full responsibility for clinical development following Phase IIa. MicroDose also could receive additional payments based upon the achievement of certain development, regulatory, and commercial milestones, as well as development fees and royalties on future potential net sales.

MDT-637 is a fusion inhibitor that has been shown to block RSV infection in preclinical testing. The product is formulated for pulmonary delivery via MicroDose's proprietary dry powder inhaler, which allows for rapid delivery to the site of infection (in the respiratory tract). MicroDose plans to file the IND reactivation with the US FDA and to initiate a Phase I study this year with MDT-637.

"This strategic collaboration is a significant milestone in MicroDose's vision to develop first-in-class therapies for major unmet medical needs," said Anand Gumaste, President and CEO of MicroDose. "Given Gilead's scientific and clinical expertise in virology, this partnership provides a strong validation of the potential for MDT-637 to become an important therapeutic advance for those affected by RSV infection."

"There is an urgent need to improve upon RSV treatment and care," added Norbert W. Bischofberger, PhD, Gilead's Executive Vice President, Research and Development and Chief Scientific Officer. "We believe this program aligns well with our expertise in both antiviral and respiratory drug development, and we look forward to working with the MicroDose team to advance MDT-637 into clinical testing."

MicroDose Therapeutx is a private pharmaceutical company dedicated to improving the quality of life for people suffering from serious diseases. The company focuses on developing proprietary products that address large unmet market opportunities, and on pulmonary and oral drug delivery platforms. The company develops its products and technologies independently, as well as in partnership with leading pharmaceutical companies. MicroDose's current pipeline targets respiratory diseases, such as asthma, COPD, and RSV, as well as IBS-C and constipation.

Gilead Sciences is a biopharmaceutical company that discovers, develops, and commercializes innovative therapeutics in areas of unmet medical need. The company's mission is to advance the care of patients suffering from life-threatening diseases worldwide.

Gerresheimer Manufactures Insulin Pen for Big Pharma Company

Gerresheimer AG has commenced the commercial production of the ClikSTAR® insulin pens for sanofi-aventis. Medical plastic systems, such as insulin pens, will be increasingly important in the Gerresheimer product portfolio in the future because they incorporate a dosage and application function in addition to being a pure medication packaging.

The industrialization of the insulin pen was prepared in Wackersdorf, the Gerresheimer Plastics Division's technology center. Gerresheimer's Pfreimd plant (Germany) is the place where the individual components are manufactured and assembled under clean room conditions.

"We are delighted about this sanofi-aventis production project because it involves a complex product that demonstrates our leadership in the medical plastic systems market to the pharma industry," said Uwe Röhrhoff, Chief Executive Officer of Gerresheimer AG.

The re-usable ClikSTAR insulin pen has received the Good Design Award. Insulin pens are drug delivery systems in pen format that enable diabetes sufferers to reliably administer their regular insulin doses in a virtually pain-free procedure. Diabetes treatment is gaining in significance from year to year. According to World Health Organization (WHO) estimates, there will be around 350 million diabetes sufferers in the world by the year 2030. ClikSTAR is a registered trademark of sanofi-aventis.

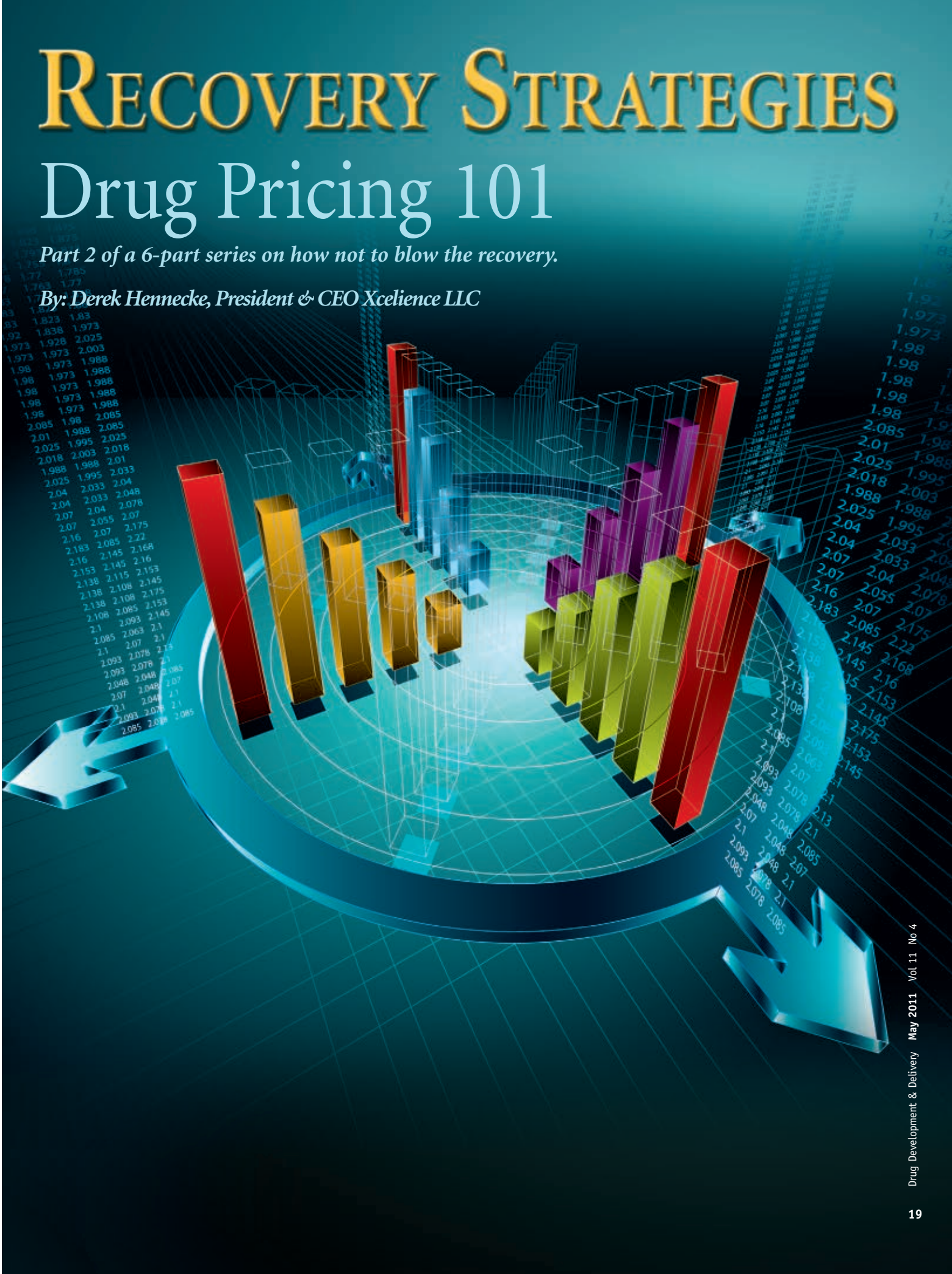
Gerresheimer is an internationally leading manufacturer of high-quality specialty products made of glass and plastic for the global pharma and healthcare industry. Its comprehensive portfolio of products extends from pharmaceutical vials to complex drug delivery systems, such as syringe systems, insulin pens, and inhalers for safe medication dosage and application.

RECOVERY STRATEGIES

Drug Pricing 101

Part 2 of a 6-part series on how not to blow the recovery.

By: Derek Hennecke, President & CEO Xcelience LLC



The biggest threat to our industry's recovery may not be an economic double dip. It may, in fact, be my neighbor's opinion on the cost of drug development. My neighbor will tell you, if you'll just listen, that the rich drug companies gouge the common folk for ridiculous profits. He will complain about his diabetes treatment, which costs over $250/month, or his mother's cancer treatment, which costs $17,000 for a 12-week course.

It's hard not to sympathize, frankly. The nosebleed cost of those treatments is a cold hard fact. Congress and the President are listening. The drug industry's defense of these costs, by comparison, is supported by wildly divergent estimates of the average cost of drug development, all of which rest on uncharacteristically questionable scientific methodology. If you're looking for high-quality rigorous methodology, shouldn't our industry represent the pinnacle of achievement? Yet on this crucial issue, even when the financial lifeblood of the industry is threatened, we can't seem to come up with a handful of facts that stand up to examination.

The most-sited defense of high drug costs is the Tufts Center for the Study of Drug Development's study from 2003 estimating costs upward of $800 million to bring a new drug to market, based on a sample of 68 drugs from 10 pharmaceutical companies. While the best known of the cost estimate studies, by no means does it define the high end. Figures from PhRMA in 2006 calculate the cost of each new drug at a whopping $1.32 billion.

For even higher numbers, you can choose the Pfizer evidence. Pfizer claims to have spent $8 to $9 billion a year on R&D for each of the past 3 years. If you go to the FDA website and look up drugs@fda.gov, you'll see that Pfizer has been showing one first-time drug approval per year. That's $8 to $9 billion/drug. Looking back throughout the past decade, Pfizer spent $60 billion to get 12 drugs approved, averaging $5 billion per drug. Heady numbers, but hardly a representative sample of all the drugs out there.

On the other end of the spectrum, we have a new study that came out in March that pegs the "true" cost of developing a new drug at $55 to $59 million. The study, published in *Biosciences* by sociologist Donald Light of the University of New Jersey and economist Rebecca Warburton of the University of Victoria, attacks the Tufts study on almost every assumption.

Some parts of the Light and Warburton study are simply absurd. For example, they don't accept the cost of a drug includes the cost of capital. How it is that in every other industry the cost of capital is part of how costs are calculated, but in our industry it's somehow misleading, is beyond my understanding. The cost of capital needs to be included because when you commit to locking your capital up in the development of a drug, you're giving up what you could have earned by putting it to some other use. Giving up the profits you would've made somewhere else is a cost.

The Tufts study, however, errs just as egregiously in the opposite direction. It inflates the cost of capital by assuming you would've earned 11% returns if your money was elsewhere. They must have a better financial advisor than I do.

But I have other problems with the Light and Warburton study as well. Their calculation of how much time it takes to conduct clinical trials and have them reviewed by the FDA is only 4 years. That would be amazing if it were true, but I would be greatly surprised if studies bore that out. Granted, it's possible that the average length of time has been somewhat reduced because of an industry-wide shift toward therapeutic areas like anti-cancer drugs. Anti-cancer drugs require shorter times because of the nature of the disease - they need only demonstrate the ability to extend time to live by a matter of months. Clinical trials for a drug like Alzheimers could, by contrast, span years, much as the condition itself can.

But 4 years? Any drug that can get from trial to approval in 4 years is, in my experience, a wonderful anomaly. Phase III itself generally takes 3 years. My company enters the picture right before in-human testing, and I rarely see a drug that isn't already a few years into development.

But I'm presenting you with personal experience, not scientific fact. How can we possibly come up with a true average development time? Maybe it's impossible. I mean, what is an average development time? Do we measure every drug that has

SIDEBAR

Industry Update: The Python is Hungry

While we have by no means returned to the heady demand of 2007 and 2008, the Society of Toxicologists (SOT) reported in their late February meeting that both demand and pricing were stable and improving after bottoming last year, and that there is a mood of cautious optimism. Unit demand is stable to improving and cancellations in recent months are down. Demand is strongest from midsize clients, though they do report optimism that improved capital flows to small biotech companies could help drive growth later this year. Major labs don't reveal their utilization levels, but the SOT estimates toxicology CROs are operating at 60% of capacity compared to an ideal of 85%, but significantly better than the 50% of 2009. As capacity approaches 70%, the SOT expects wait times to increase and pricing to improve. The SOT issued a statement predicting that 2012 would bring a moderate recovery in IND-enabling study activity. The industry is showing "demonstrable improvement" in sentiment, as a result of improving RFP activity and conversion to sales.

The demand scenario these past few years represents a classic "pig in the python" scenario. The urgency of the recession led pharma companies to de-empasize early drug development, and shift funds to late-stage development, trying to get products to market faster to increase revenue in the shorter term. Early-stage development experienced a sharp decline in work, and late-stage development felt a boom. A colleague of someone we just hired jumped ship a couple of years ago and moved downstream to where the pig was. Now the boom is abating, and he's looking at a drier pipeline at his new company. Time to move back upstream? Hopefully soon things will normalize throughout the pipeline. But after the past 2 years, it's nice to feel the python is hungry again.

ever been developed? Do we measure just the recent ones? Even if we constrict ourselves to the recent only, it's complicated. Thalidomide was first developed in the 60s and is now being used as an anti-cancer drug. Any average that pulls in Thalidomide or a similar compound is going to be skewed. An Alzheimer's drug would do the same simply because the nature of the illness is long-lasting. Yet this question of average time is absolutely central to calculating cost because every additional year of study adds tremendously to the total cost.

This is just the beginning of the problems with the Light and Warburton study. I was surprised to see Light himself in his article "The Make-Believe Billion" published in *Slate* saying that the "estimate of pharmaceutical R&D costs consists of the unknown and highly variable costs of R (research) plus the net, median cost of D (development) of $59 million." He has completely discounted the cost of discovery.

Even if we overlook this magically appearing molecular phenomenon, the math still doesn't work. If discovery to approval costs $55 to $59 million, how do we account for the fact that Pharma companies typically pay $100 million for a Phase I and $500 million for a Phase II drug from a biotech company, with Phase III trials and all their inherent risks still looming ahead? The market has already determined what the expected cost of drug at each stage of development should be.

Here's another way of looking at the Light and Warburton study against the cold hard light of day. If it really did cost only about $50 million to develop a drug, then pharmaceuticals would be the all-time best investment out there over any period of time. Think about it. Just $50 million to develop a product with sales between $20 million and $1 billion per year and a 10% cost of goods? Count me in!

I'm not going to defend the Tufts study either. Its methodology is far from air-tight. The study surveyed 24 large drug companies, and 10 agreed to participate; hardly a representative or random sample. They don't reveal which drugs they are reporting, so we can't check any data. They may have selected only their most expensive drugs because it would be in their interest to inflate numbers to justify pricing. We can't even peek into the R&D data to see what they chose to consider as R&D costs.

Going beyond methodology, the Tufts averages - or the Pfizer ones for that matter - don't mesh with what I see coming through my plant either. If an average drug cost $1.3 billion for our sponsors to develop, I think few of them would ever get out of our sponsors' labs. Just to recoup those kinds of costs, much less to make a profit, every single drug would have to have blockbuster status with deep market penetration and high costs per unit. One-third of my business is large Pharma, and I see those largely pursuing niche markets in which the costs have to be lower to pay off.

There are other ways of calculating average costs. Using PhRMA numbers, some people calculate how much money the Pharma and biotech industries claim to have spent on R&D throughout the past 10 years, and divide by the number of drugs approved. The results come to about $1.2 billion/drug, in line with the Tufts number. This method, however, also relies on accepting whatever the drug companies choose to label as R&D. In those instances in which it has been possible to examine the raw data, the results have included things that might be interpreted as marketing, such as conferences on a single drug where all attendees are doctors who have come at the manufacturer's request with all expenses paid.

The true cost of development is probably somewhere in between. If you want a model you can believe in, go to *Life Sci VC* and search Bruce Booth's "Choose Your Own Drug Model". Here you can input your own assumptions, such as length of time per phase, size of market indications, cost per phase, choose whether or not to include the cost of failed molecules, and so forth, and come to your own average cost. Unfortunately, while you may arrive at a number you can believe in, it may not be a number that others will accept. Hence, our problem.

None of these methodologies stands up to the cold hard facts and personal tragedy of my neighbor's drug cost woes. None will keep Congress from reviewing the length of patents and assessing opportunities to reduce the cost of drugs. Until we can come up with a sound scientific argument to justify drug prices, our industry will remain under attack. ◆

BIOGRAPHY

Derek G. Hennecke, MBA
President & CEO
Xcelience

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 strong growth. This growth was recognized in May 2008, when Mr. Hennecke was selected as a finalist for the coveted 2008 Ernst & Young Florida Entrepreneur of the Year award, a nomination based on the demonstration of extraordinary success in the areas of innovation, financial performance, personal commitment to community, and perpetual growth. Mr. Hennecke was also recognized as a finalist for the Ultimate CEO awards by the Tampa Business Journal and Small Business of the Year by the Greater Tampa Bay Chamber of Commerce, in 2008. 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 radical 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.

DELIVERY DISCUSSION

Two Questions for Drug Delivery

By: Josef Bossart, PhD

INTRODUCTION

Two questions with no simple answers. What is Drug Delivery? Who speaks for Drug Delivery? First things first - what is drug delivery? We can define drug delivery as a growing collection of sophisticated formulation technologies that can enable, enhance, and expand the use and performance of pharmaceutical actives. This definition positions drug delivery as a set of toolbox assets that supports the development of therapeutically valuable products for the pharmaceutical and biotechnology industries. It also suggests that drug delivery is desirable but not really necessary; sort of like the air conditioning in your car.

We can also define Drug Delivery as a business sector focused on creating high-value next-generation therapeutic products through the application of technologies that alter the absorption, distribution, and excretion of pharmaceuticals. Taken in this light, Drug Delivery is seen as an engine of the next generation of therapeutic products; something like an alternate fuel technology driving the next generation of automobiles.

One term; two definitions. Depending on which definition of drug delivery you agree with, the original question of who speaks for Drug Delivery becomes critically important, or it remains a distraction.

If Drug Delivery is simply a set of formulation technologies, a complement to the pharmaceutical industry toolbox, it follows the lead of the biopharmaceutical business. It reacts. But if Drug Delivery is a business sector that develops technologies and products that provide for better therapeutic outcomes, it leads and rises to the level of an industry sector like Pharmaceuticals and Biotechnology. Arguably a smaller sector, but a sector nonetheless, and that can make all the difference.

Considering Drug Delivery as a sector rather than a collection of technologies not only raises the value of the business, its products, and its technologies, it also impacts how Drug Delivery is perceived and supported.

A ROLE & POSITION FOR DRUG DELIVERY

To capture public and investor support, Drug Delivery needs to define itself as a business sector that creates high-value therapeutic products. More than an accessory to pharmaceutical products, Drug Delivery needs to be seen as a unique high-value sector, much as Biotechnology is considered distinct from Pharma.

We all know how Biotechnology has developed. As a business sector, Biotechnology has attracted billions of dollars in investment from private, institutional, and government sources. Not only is Biotechnology considered a discipline separate from Pharma in the minds of the public, industry, and government, it receives separate and often preferential treatment from these groups. Even now there is discussion between the Biotechnology sector and Congress to extend market exclusivity for biologicals. Has Biotechnology really been commercially and therapeutically more successful than Drug Delivery? Perhaps, but Biotechnology has done a great job of getting their message out and securing widespread public, political, and investor support.

The irony is that Drug Delivery enjoyed significant support 2 decades ago as Alza, Elan, and others were delivering unique and exciting therapeutic innovations based on their drug delivery technologies.

The decline in public and private investor support started not because Drug Delivery was failing to deliver innovative products, but because drug delivery companies started focusing on the seemingly lucrative prospect of becoming specialty pharmaceutical companies. Not

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only did their attention to drug delivery wane, so did their investment in technology and product innovation.

And about then we saw the first-generation drug delivery technologies become commoditized toolbox assets for Pharmaceutical, Biotechnology, and Generic companies. Before anyone realized it, Drug Delivery was no longer a business sector, it was the term increasingly applied to a commodity technology.

THE DRUG DELIVERY PROBLEM

Demanding respect doesn't mean you will receive it. Right now, Drug Delivery demands little respect, and it receives even less. The result is limited influence and limited profitability.

Why the lack of respect? Is it a question of poor industry promotion? Definitely! Doesn't drug delivery create value by delivering important therapeutic products? Well yes, but the value is not nearly as great as it should be. The issue as we'll see is the limited exclusivity provided to drug delivery products.

The value of Drug Delivery is unreasonably undermined by generics; the directly substitutable AB-type generics. While generics are a necessary and valuable part of the pharmaceutical ecosystem, their reach and impact can lead them to destroy the very industry they depend on. It's much like living systems that depend on a balanced relationship between cell death and cell division to remain healthy. An excess of either, for too long, leads to death.

The problem is that generics are chewing away at drug delivery products too early in their lifecycles. While patents can offer extended market exclusivity for a new invention, in practice, this exclusivity is relatively limited as applied to drug delivery products. Because many of the actives incorporated into a drug delivery product have been subject to earlier issued patents, there is generally little or no exclusivity offered by the active. And while it is possible to secure patent protection for drug delivery technologies, it is difficult to secure exclusivity. This is not because the technology isn't novel or enabled but rather because technologies are subject to the development of functional equivalents. These are products, technologies, and processes that provide a similar benefit but do not infringe the originator patent.

Depending on patents to secure exclusivity for a drug delivery product is a risky bet. Not because a patent will not be issued, but because once you demonstrate and validate the use and potential of a drug delivery product, others will replicate it using non-infringing functionally equivalent technologies. There is nothing wrong with competition if the competition is subject to the same rules. This is not the case with generics.

The FDA approves non-biological pharmaceuticals through one of three regulatory pathways, 505(b)(1), 505(b)(2), and 505(j). New chemical entities are approved as 505(b)(1) products and receive 5 years of regulatory exclusivity. New formulations of previously approved actives are generally approved as 505(b)(2) products and receive 3 years of regulatory exclusivity. After the 5- or 3-year exclusivity periods, these products are subject to generic competitors, ANDA, or 505(j) products, unless there are issued and enforceable patents.

Because most drug delivery products are approved via the 505(b)(2) route, and there are often functionally equivalent technologies, these products generally enjoy no more than 3 years market exclusivity before a substitutable generic is introduced. And here is the rub. If a company is going to invest in developing and bringing a novel drug delivery product through to approval, it needs to have more than a 3-year period of market exclusivity to capture the investment costs. With a risk-adjusted cost in excess of $150 million to bring a drug delivery product to approval, and a 20% profit margin, it takes more than $750 million in sales for a product to break even. That is an average of $250 million per year if exclusivity is limited to 3 years. These numbers may work for billion-dollar products like Wellbutrin XL, but it doesn't work for most novel or therapeutically improved drug delivery products.

Three years of market exclusivity really doesn't pay for most products. Remember, it's only after $750 million in sales that a drug delivery product becomes truly profitable. This means the companies most able to develop and market drug delivery products have little financial incentive to do so. If a product addresses a small market and generates limited revenue, it is unlikely to attract generic competition, but it is also unlikely to be profitable. And if the drug delivery product is a big seller, there will most likely be a substitutable generic in exactly 3 years; note how quickly Wellbutrin XL generics hit the market. Where is the upside to developing and marketing drug delivery products?

Limited profitability translates into limited industry and investor interest in making the necessary investments to support the companies who will deliver the next generation of drug delivery technologies and products.

SIDEBAR

A Proposal for Extended Regulatory Exclusivity

It is proposed that the FDA granted period of regulatory exclusivity for new drug approvals based on previously approved actives be increased to 7 years from the date of first approval of a new formulation. This exclusivity would apply only to the approval of abbreviated new drug (ANDA) approvals. There is no exclusivity with respect to the approval of products using the same pharmaceutical active by any route so long as these products are approved without reference to a drug delivery product that has remaining regulatory exclusivity. The effective period of market exclusivity could be extended further if the product has issued patents listed in the FDA Orange Book that extend beyond the 7-year exclusivity period.

THE OPPORTUNITY TO DELIVER THE GOODS

Life is tough, but life is what you make it. If Drug Delivery finds it tough, it's because it hasn't invested much time or effort to improve its lot. And that is a real shame.

It is a shame because Drug Delivery has the potential to deliver remarkable therapeutics at lower cost and lower risk. Drug delivery products based on previously approved actives not only have twice the clinical development and approval success rate of new chemical entity pharmaceuticals, but they are much less likely to suffer from the post- approval safety issues of recently approved new chemical entity products.

Improving the prospects for Drug Delivery means extending the exclusivity period for drug delivery products. Congress is debating the pros and cons of granting biological products, those approved through the Biological License Approval (BLA) process, extended exclusivity as part of developing a pathway for biosimilar products. The period of exclusivity being discussed is 12 years. This would then be the minimum period of exclusivity for any product approved under the BLA pathway. That means at least 12 years of market exclusivity to recover development costs and generate profits.

Orphan drugs currently receive a 7-year exclusivity period regardless of patent protection. In the case of Orphan drugs and biologicals, the extended exclusivity periods are considered necessary to incent companies to develop new products. What incentive is there for drug delivery products?

For a pharmaceutical that is not a biological product or deemed an Orphan drug, the period of regulatory exclusivity is 3 and 5 years. Why the difference? Why do biologicals deserve more protection than non-biological pharmaceutical products?

The simple answer is that they are asking and lobbying for the increased regulatory exclusivity. And they get respect. How about an extended exclusivity period for drug delivery products? A modest proposal is presented in the sidebar.

WHO WILL CHAMPION DRUG DELIVERY?

There is much more that can be said in support of a longer period of exclusivity for drug delivery products; but who will speak up? Where is the organization or company who will champion this proposal? If no one steps up and makes a good case for change, it won't happen. Who will speak for Drug Delivery?

Well you could look to the big money players, PhRMA and BIO, but I'm not sure they really understand the potential of, or care about, drug delivery. Both organizations are most interested in what their members care about. PhRMA and its members, mostly large pharmaceutical companies, are focused on the impending patent cliff and price controls. The generic battle for small molecules is largely over and finished for this group. In the case of BIO, the big issue is biosimilars. With no existing pathway for the approval of generic biologicals, this group would be happiest if a regulatory pathway was never approved. And if a pathway is approved, they want to extract as much regulatory exclusivity for their members' products.

The last of the big three pharmaceutical industry organizations, the Generic Pharmaceutical Association, is unlikely to take up any initiative that will delay generic product introductions.

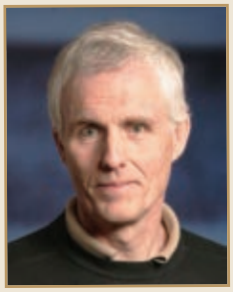
There are science- and technology-focused organizations that could take the lead in demanding more respect for Drug Delivery and securing a longer exclusivity period for drug delivery products, but these organizations seem more focused on science and technology than business issues.

Drug Delivery, Specialty Pharma, Big Bio, and Big Pharma will all benefit from an extended exclusivity period for drug delivery products. Sales and profits would improve, and this would support investment in new technologies and products leading to better products and better therapeutic outcomes. It's a virtuous circle.

REVOLUTIONS DEMAND COURAGE & LEADERSHIP

Let's repeat the original question: Who will speak for Drug Delivery? Until there is a public voice for Drug Delivery the term drug delivery will be associated with a set of formulation technologies and not a vibrant productive business sector that deserves investor, political, and public support. Are there companies willing to make the necessary investments in Drug Delivery as a sector or are these companies hoping that drug delivery is simply a stage they need to endure, sort of like adolescence and acne, before they "grow up" and become a Specialty Pharma company?

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 under its Bionumbers label, Pharmanumbers provides 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.

MARKET BRIEF

Vaccines – The Sustainable Blockbuster Business

By: Barath Shankar Subramanian, Senior Industry Analyst - Frost & Sullivan

INTRODUCTION

While the small molecule business continues to struggle to keep up to pace with the growth of the global healthcare market, there is a segment of the market that continues to remain one of the most stable and reliable sources of growth for biopharmaceutical companies - Vaccines. Vaccines have been a mainstay of several major pharmaceutical companies, including sanofi-aventis, Merck, GlaxoSmithKline, and Novartis.

Vaccines have been instrumental in the elimination of some major diseases, such as smallpox and polio, while reducing the incidence of measles, tetanus, diphtheria, rubella, meningitis, and Hib. The economic impact of vaccines on both developing and developed economies has been significant. These include a reduction in infant and child mortality, an increase in life-expectancy, and a reduction in direct and in-direct medical costs.

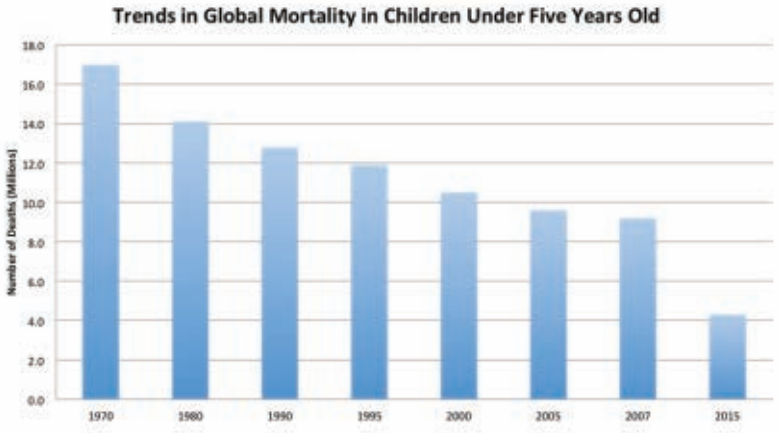
GLOBAL VACCINES MARKET

The global vaccines market has been witnessing strong above average growth throughout the past several years and is expected to continue its growth moving forward. Within the vaccines market, pediatric vaccines lead the market in growth, outpacing the adult vaccines market.

Europe is currently leading the global market in vaccine production, accounting for over 90% percent of total production. With the leading vaccine manufacturers headquartered in Europe, the strength of European vaccine manufacturing continues to become stronger. However, R&D spending is dominated by North America, which accounts for more than half of the total spend. The globalization of the vaccines industry is evident from this dichotomy.

However, the long-term trend for this industry suggests a shift in manufacturing from Western countries to emerging markets. Public funding from governments, which has been relatively small compared to private R&D spending, has continued to increase. In countries where public vaccination programs are gaining importance, especially underdeveloped and developing markets, these increases play a vital role in the

FIGURE 1



Trends in Global Mortality in Children Under 5 Years Old (Source: UNICEF)

future growth of the industry. Vaccine clinical trials have also gone global with a large number of trials being conducted in Asia (approximately 20%), North America (approximately 30%) and Europe (approximately 35%). Asia's share of clinical trials has continued to increase throughout the years and signals the increasing importance of emerging markets to the vaccines business.

The top five vaccine manufacturers, which are also Big Pharma companies, account for more than four-fifths of the global vaccine revenues, while the rest of the manufacturers (approximately 40) account for only one-fifth of the revenues. In terms of volume, North America and Europe account for only 14% of the supply to meet the global demands, while the rest is met from suppliers in developing markets. This signifies the importance of low-cost manufacturing and its impact on the vaccine market.

STRENGTH OF THE VACCINES PIPELINE

One of the key factors of continued strength of the vaccines market has been the strength of the vaccines pipeline. The late-stage pipeline has more than 80 candidates, and almost 40% of those are for diseases that currently do not have vaccines in the market. The rest are expected to be more effective than the current vaccines in the market. This is expected to have a major positive impact on the health and economics of both developing and developed economies.

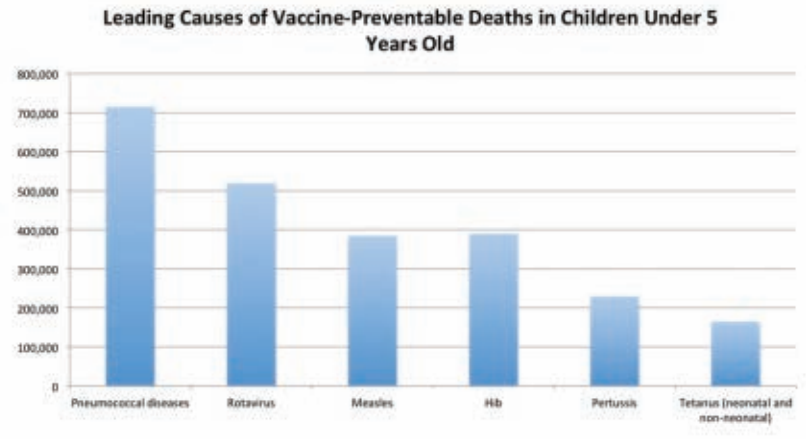
In the pediatric segment, the leading causes of vaccine-preventable deaths in children under 5 years of age are pneumococcal diseases, rotavirus, measles, Hib, pertussis, and tetanus. These diseases account for more than 2 million deaths, and pneumonia is the leading cause, accounting for more than 25% of the deaths.

Improvements in vaccine delivery will eliminate needles and enable better compliance. Some of the newer delivery platforms include aerosols, skin patches, oral drops, and pills. These new delivery methods combined with the development of heat-stable vaccines should improve the supply chain efficiency by reducing the dependence on cold chain and relieve the pressure on logistics.

SUMMARY

Partnerships have been the key to the implementation of vaccination programs. Governments, industry alliances/partnerships, and not-for-profit organizations have been critical to the success of immunization programs. In developing countries, the new vaccines expected to enter the market are likely to be added to the immunization program with the financial backing from various funds that continue to increase their support.

FIGURE 2



Leading Causes of Vaccine-Preventable Deaths in Children Under 5 Years Old (Source: WHO & GAVI)

BIOGRAPHY

Barath Shankar Subramanian is a Senior Industry Analyst, Pharmaceuticals & Biotechnology, with the Frost & Sullivan North American Healthcare Practice. He focuses on monitoring and analyzing emerging trends, technologies, and market dynamics for the Pharmaceutical and Biotechnology industries in North America. Since joining Frost & Sullivan in October 2004, Mr. Subramanian has completed several research studies and consulting projects on Specialty Pharma, Contract Research, and Contract Manufacturing. Prior to this, Mr. Subramanian was a Research & Development intern at IPCA Laboratories Ltd., Mumbai, India. He brings with him considerable analytical and quantitative experience, giving him a keen perception into the functioning of technology in the healthcare industry. He earned his BS in Pharmacy from the Birla Institute of Technology & Sciences (BITS), in Pilani-Rajasthan, India. He has received acclaim for his research through articles and quotes published in Drug Delivery Technology and Specialty Pharma magazines.

EXCIPIENT UPDATE

Investigating the Influence of a Film-Forming Formulation on Oxygen & Moisture Vapor Transmission Rates

By: Maureen Mistry, Thorsten Cech

ABSTRACT

The aim of this study was to evaluate Kollicoat® Protect, to achieve both moisture and oxygen protection. Kollicoat Protect is a spray-dried instant-release polymer used for moisture protection formulations. Due to the fact that the rate of water vapor transmission across a polymer is directly related to the amount of insoluble pigments in the formulation, the elasticity and viscosity of Kollicoat® Protect is crucial in its effective barrier coating.[1] It is also essential that it be possible to incorporate large amounts of pigment into the coating polymer formulation without significantly reducing the film flexibility. A comparison of the flexibility of Kollicoat Protect, measured as elongation at break, was made and compared with those of HPMC 3 mPas, HPMC 6 mPas, HPC EF, PVA, and Kollicoat IR, all of which can be used in barrier coatings. The oxygen and moisture barrier properties of Kollicoat Protect film was achieved by incorporation of insoluble pigments into the polymer solution.

INTRODUCTION

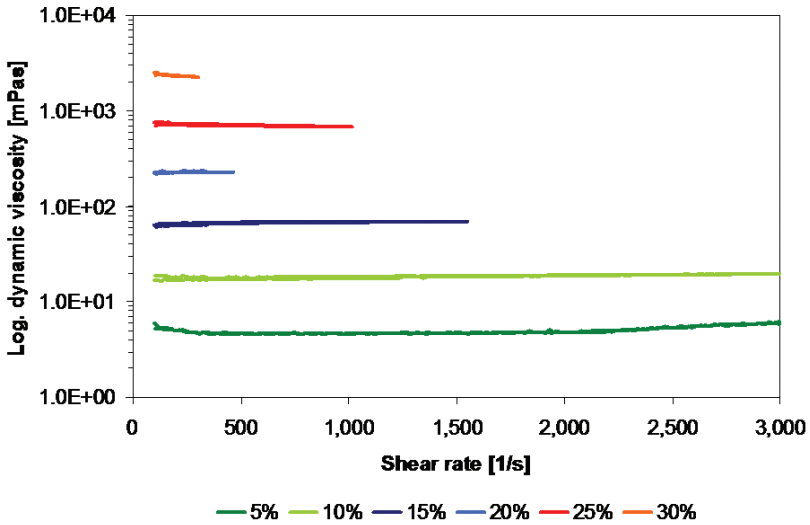
The use of polymeric film coatings to improve the stability of pharmaceutical formulations has gained increased importance in the pharmaceutical industry.[2]

The presence however, of intermolecular spaces in polymeric films means that polymeric materials alone do not provide complete barrier to the movement of air or vapor molecules.[1] Therefore, film compositions incorporating insoluble additives in the coating formulation is used as a means of blocking these intermolecular spaces. Thereby creating a hindrance to the free transmission of water and air molecules across the polymer membrane. It should also be noted that most barrier protection by polymer films reduces the rate of moisture or air transmission only.

In the data presented in this discussion, a formulation composed of 50% of the polymer PVA/PEG graft copolymer and polyvinyl alcohol in a 6:4 ratio, together with 50% of insoluble pigments, reduced water vapor transmission rate by > 50% for a 100-micron film thickness.[3]

The ability to successfully incorporate such large amounts of

FIGURE 1

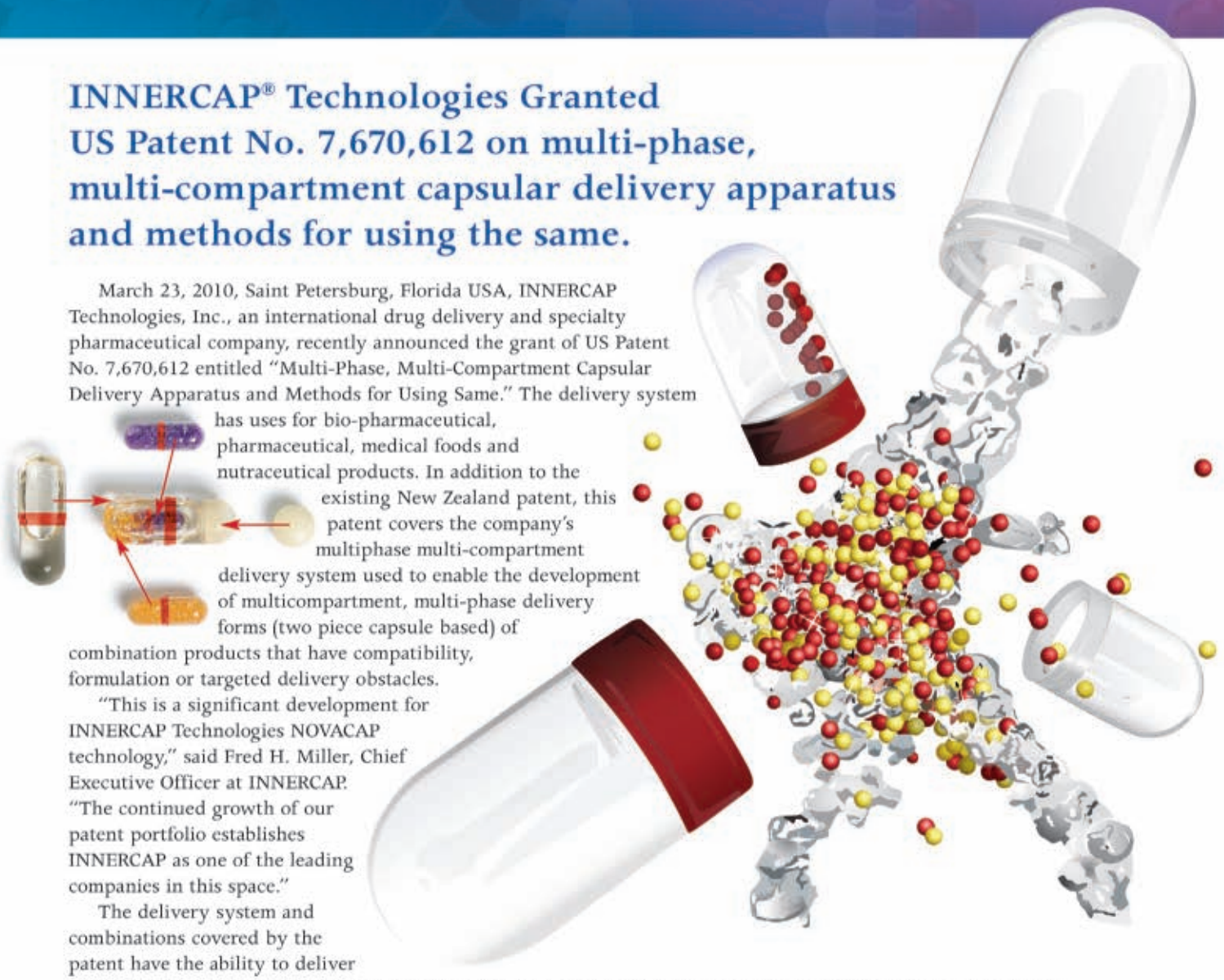


Viscosity of aqueous Kollicoat® Protect solutions as a function of shear rate.

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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TABLE 1

Excipient	Formulation			
	No. 1	No. 2	No. 3	No. 4
Kollicoat® Protect	50%	50%	50%	50%
Talc	15%	25%	35%	45%
Titanium dioxide	30%	20%	10%	0%
Sicovit® Red 30	5%	5%	5%	5%

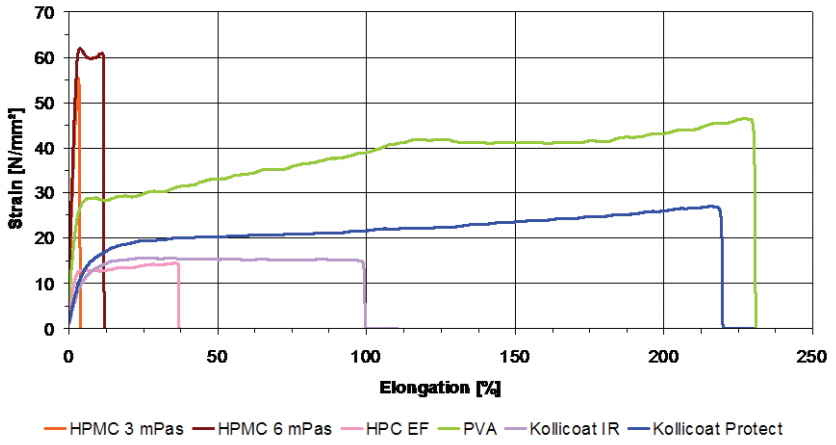
Film formulations tested to investigate the influence of the type of pigments.

insoluble pigments in the coating formulation, is due in part to the low viscosity of the polymer solution; a solution with 20% PVA/PEG graft copolymer (Kollicoat IR) and polyvinyl alcohol (6:4), has a viscosity that is much less than 100 mPas and a film with an elongation at break of > 200% . The PVA/PEG graft copolymer and polyvinyl alcohol (6:4) is commercially available as Kollicoat® Protect for moisture protection.

MATERIALS & METHOD

Free polymer films were produced by casting a 20% Kollicoat Protect coating solution using an Erichsen Coatmaster, equipped with a knife with die gaps of (150 to 500 microns). Films of about 100 microns in thickness were prepared by casting, and allowed to equilibrate for 48 hours in a controlled environment of 23°C/ 54% r.h. before testing. The viscosity of Kollicoat Protect polymer solution at different concentrations was measured at 25°C using a rotational rheometer (Thermo Scientific HAAKE RotoVisco 1, equipped with concentric cylinder measuring). A conditioning time of 180 seconds was applied to ensure the temperature of polymer solution remained constant. The

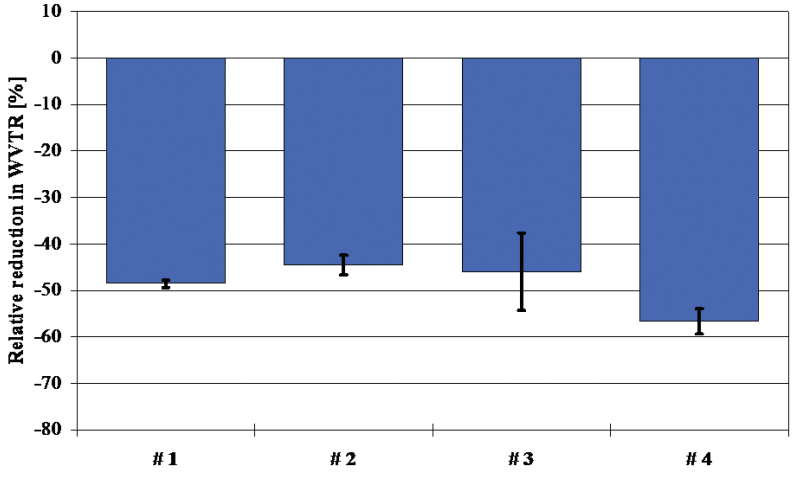
FIGURE 2



Elongation properties of various instant-release polymeric films.

shear rate was set at 100 seconds$_{-1}$ to prevent any sedimentation. To correlate the relationship between viscosity and shear stress, the shear rate was increased from 100 to 3000 seconds$_{-1}$. After applying the maximum shear rate for 30 seconds, the speed was further reduced to 100 seconds$_{-1}$. The entire process was completed in 180

FIGURE 3



Dependence of water vapor permeation rate on the type of pigment in the films.

TABLE 2

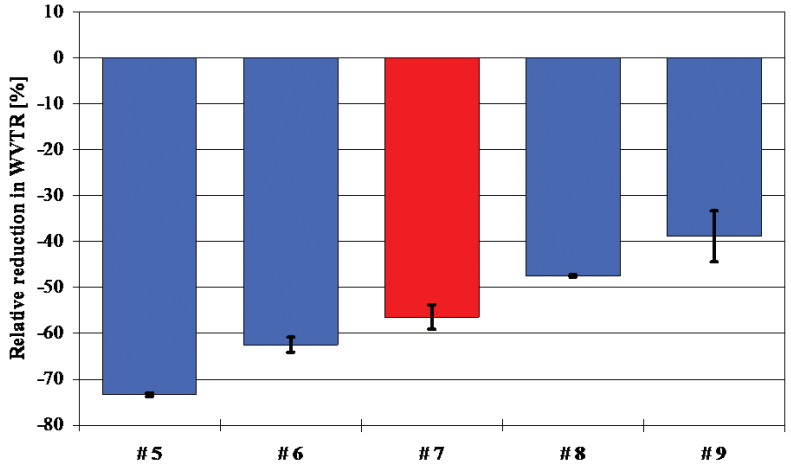
Excipient	Formulation				
	No. 5	No. 6	No. 7	No. 8	No. 9
Kollicoat® Protect	25%	40%	50%	60%	75%
Talc	67%	54%	45%	36%	23%
Iron oxide (red)	8%	6%	5%	4%	2%

Formulation No. 4 was further optimized by increasing the concentrations of talc in the formulation composition.

seconds. Figure 1 shows that shear viscosity did not change as a function of shear rate, and was dependent upon the concentrations of polymer in the solution. Interestingly, the shear viscosity was higher for higher concentrations and was lower for lower concentrations at the concentrations investigated between 5 wt% and 30 wt%. The shear stress did not adversely affect the viscosity of the polymer solution.

The elongation at break of pure Kollicoat® Protect was measured using a 100-micron film and a texture analyzer (TZ XT2i HR), and was compared with commonly used polymers for moisture barrier coatings. The film thickness was measured using a Mini test 600B Elektro Physik apparatus. The cross-section of the film was calculated to determine the strain. The data were recorded to indicate the flexibility of different pure polymer, as shown in Figure 2.

FIGURE 4



Dependence of water vapor permeation rate on the amount of pigment in the film.

Water vapor transmission rates were measured for both pure polymer film of Kollicoat Protect and the films containing insoluble additives using the cell method in accordance with ASTM F 1249.[4] The oxygen transmission rate was determined according to ASTM D 3985.[5]

The water vapor transmission rate was measured on a dynamic vapor tester Permatran C model 4/44 (Mocon) by determing the moisture using a photoelectric sensor. The oxygen transmission rate was measured on an Ox-tran (Mocon).

Both measurements use the principle of moisture and/or oxygen diffusing through an isolated film placed inside a cell, and the magnitude of signal is detected by the sensor within the instrument.

Based on the results from an earlier trial, 50% concentration of Kollicoat® Protect was used as a start concentration, for an optimal oxygen barrier.[6] The effect of increasing talc concentrations and the concentrations of other pigments in different ratios were investigated for oxygen transmission rate and water vapor transmission rate. The data is presented in Table 1.

The data suggests that the presence of different amounts of pigments lowered the water vapor transmission rate in all formulations evaluated. Formulation No. 4, however, showed a slightly higher reduction of water vapor transmission across the polymer film, as shown in Figure 3.

Formulation No. 4 was further optimized by increasing the concentrations of talc in the formulation composition shown in Table 2. Figure 4 shows that increasing amounts of talc to 67% (Formulation No. 5) resulted in a

significant reduction of water vapor transmission when compared to others with reduced amounts of talc.

Increasing the concentration of talc to > 50 wt% in the formulations, however, increased the brittleness of the polymeric film, but the films were less brittle with formulations containing < 50 wt% talc.

Formulations for barrier coatings sometimes also include lipophylic additives, such as stearic acid, carnauba wax, lecithin, xantham gum, etc.[6] These additives may affect the elasticity of the film. To avoid poor results caused by high brittleness of the film, Formulation No. 7 (50:50, polymer/pigment) - which still offers sufficient elasticity - was chosen as a basic formulation (Figure 4).

The effects of lipophlic compounds on the functional properties of Kollicoat® Protect formulated together with insoluble pigments in the formulation were investigated. The formulation compositions containing a range of lipophilic carriers are shown in Table 3.

Figure 5 shows the relative water vapor transmission rate for the formulation composition shown in Table 3. The optimum performance of the formulations was marked by the red line in Figure 5. Thus, Formulations Nos. 12, 13, 16, and 17 with polymer/pigment (50:50) outperformed others in terms of increased moisture protection. We observed however that Formulations Nos. 12, 13, 16, and 17 not only reduced the water vapor transmission, but also increased film brittleness, which made them unusable.

The same investigation was repeated using the formulations in Table 2, but this time with regard to the effect of talc concentration on oxygen transmission rate.

The results showed a clear dependence of reduction in oxygen transmission to talc concentration. As the concentration of talc increased, the rate of oxygen transmission was reduced (Figure 6).[6]

Formulation No. 4 gave the best combination for reduction in water vapor transmission and film flexibility. It also significantly reduced the oxygen

FIGURE 5

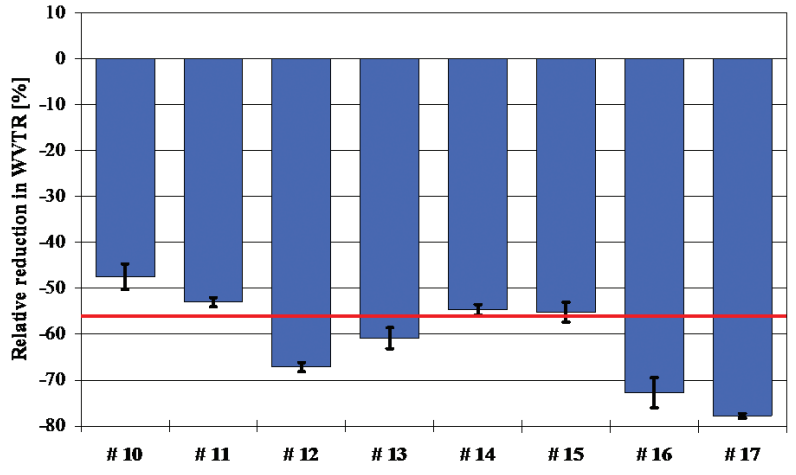
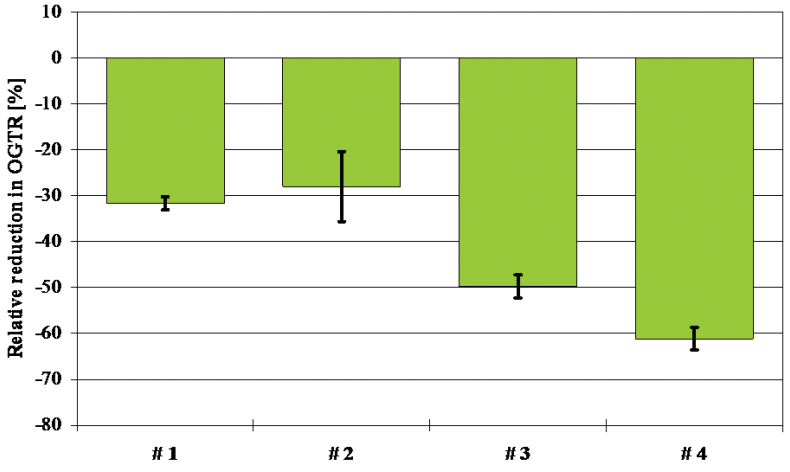


Chart showing the influence of additives on the water vapor permeation rate.

FIGURE 6



Influence of type of pigments on the oxygen transmission rate.

TABLE 3

Excipient	Formulation							
	No. 10	No. 11	No. 12	No. 13	No. 14	No. 15	No. 16	No. 17
Kollicoat® Protect	50%	50%	50%	50%	50%	50%	50%	50%
Talc	35%	35%	35%	35%	35%	35%	35%	35%
Titanium dioxide	5%	5%	5%	10%	13%	14.5%	13%	7%
Myrj® 59	10%							
Brij® 721		10%						
Stearic acid			10%					
Carnauba wax				5%				
Lecithin					2%			
Xanthan gum						0.5%		
SDS							2%	2%
Aerosil® R 972								6%

Formulations to investigate the influence of additives

transmission rate. Furthermore, increasing the pigment contents resulted in film brittleness and cracks that compromised the reduction of oxygen transmission. In addition, the incorporation of lipophylic compounds in the formulations did not significantly reduce the oxygen transmission.[6]

CONCLUSION

Kollicoat Protect, with the formulations containing up to 60% talc and without the use of any lipophilic compounds, can be used as film former to serve dual functions to achieve the moisture barrier coating and reduce the oxygen transmission rate. ◆

ACKNOWLEDGEMENTS

The authors wish to acknowledge Thorsten Agnese and colleagues at the BASF European Pharma Application Lab for generating the data presented in this article.

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BIOGRAPHIES

Maureen Mistry is a Technical Service Manager within the Technical Service team of BASF Pharma Ingredients and services Europe. She has 10 years experience working with BASF s excipients and has worked for more than 20 years in the pharmaceutical and support industries. She is responsible for technical service support for customers in the UK, Ireland, Scandinavia, and the Netherlands.

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Pulmonary Peptide Delivery With a Pharmacokinetic Profile That Closely Mimics Endogenous Peptide Secretion

By: Andrea Leone-Bay, PhD; Robert A. Baughman, PhD; Chad Smutney, and Joseph Kocinsky

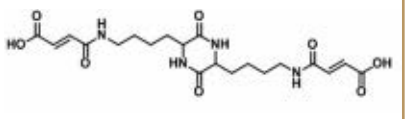
INTRODUCTION

Endogenous peptide and protein hormones regulate many biological functions. Prior to the advent of the biotechnology industry, therapeutic use of these hormones was limited because the hormones themselves could be obtained only by isolating them from animal tissue. Probably the most notable example is insulin, which was isolated from pig pancreas for diabetes treatment. Insulin was first used to treat diabetes in the 1920s, but the first ex vivo synthesis of insulin did not occur until the early 1960s, and the first recombinant insulin synthesis was reported in the late 1970s.[1,2] Biotechnology now routinely produces peptide and protein drugs that manage disease by replacing absent endogenous hormones or as distinct therapeutic agents without endogenous counterparts. For example, exogenous desmopressin is used to replace the absent endogenous hormone in patients with diabetes insipidus, and exogenous insulin replaces absent endogenous insulin in diabetes mellitus. Both parathyroid hormone and calcitonin are peptide hormones that are used to treat osteoporosis.

Unfortunately, the use of peptide hormones has been limited because they must be administered by injection. Regular injections are inconvenient and can be a source of non-compliance. To mitigate this risk, the development of peptide hormone therapeutics has focused on long-acting analogs of the natural peptides that can be injected only once daily or once weekly. While this approach may provide patient convenience and facilitate compliance, the pharmacokinetic profiles for long-acting peptide hormones can be radically different from those of endogenously secreted hormones. Growth hormone, which controls adult height, is a case in point. In healthy individuals, growth hormone is secreted in a pulsatile circadian pattern. To mimic this pattern with exogenously administered growth hormone, several injections would be required overnight for an extended period of time. Repeated overnight injections are not practical, so daily injection regimens and long-acting growth hormone formulations for once-weekly injection were evaluated. Thus, in this case, mimicking the normal, pronounced circadian pharmacokinetic profile of human growth hormone was abandoned in favor of a convenient and acceptable (once daily) dosing regimen. This regimen is effective but rarely results in the attainment of ideal predicted height.[3]

Insulin therapy in diabetes treatment follows a similar paradigm focused on long-acting insulin analogs to replace basal insulin. Recently, however, prandial administration of rapid-acting insulin analogues demonstrated better glucose control than long-acting insulin analog therapy, presumably because the pharmacokinetic profiles of rapid-acting insulin analogs more closely mimic the insulin response in healthy individuals.[4] Thus, both growth hormone and insulin injection therapies show that hormone replacement in a non-physiological regimen is unlikely to achieve normal function. For this reason, and also to eliminate the inconvenience of injection, alternative delivery routes for peptide therapeutics continue to be explored.

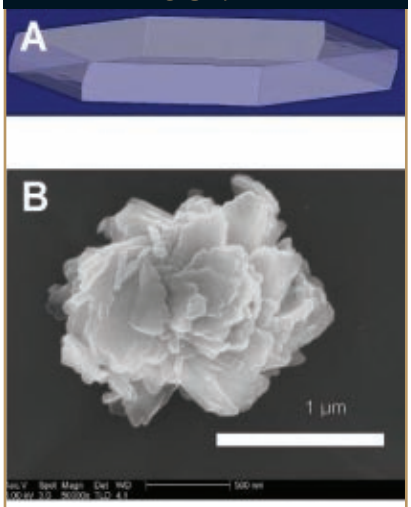
FIGURE 1



Chemical Structure of FDKP

Peptide delivery by inhalation is one alternative to peptide injection. The lung is an excellent portal for systemic drug delivery because it provides a very large surface area for drug absorption with direct access to the cardiovasclular system.

FIGURE 2



Morphology of FDKP Crystal & Technosphere® Particle

A) Plate-like Crystal Morphology

B) Technosphere® Particle

Thus, drugs absorbed through the lung avoid first-pass metabolism, a potential advantage for protein and peptide therapeutics. In addition, agents delivered through the lung enter the arterial circulation directly and reach target organs before returning through the venous stem to pulmonary capillary beds, where endopeptidases are extensively expressed. Paradoxically, this may result in a higher target organ exposure to active peptides than a comparable administration by injection.

FORMULATION TECHNOLOGY

Technosphere® technology is a dry powder inhalation system designed to administer protein and peptide therapeutics. It is based on the novel excipient, fumaryl diketopiperazine (FDKP, Figure 1). FDKP is a substituted diketopiperazine that, upon precipitation from solution, has the ability to self-assemble into discrete particles called Technosphere particles.[5-10] In practice, Technosphere particles are prepared by the acid-induced crystallization of FDKP and subsequent self-assembly of those crystals to form particles with a compact, approximately spherical shape (Figure 2), high-specific surface area, and open architecture. Technosphere particles have a narrow size distribution centered near 2 to 2.5 microns. The FDKP that forms the particles is readily soluble at physiological pH so the particles dissolve in the lungs. Following inhalation, FDKP is absorbed and excreted intact primarily in urine, with no evidence of metabolism.[11] FDKP does not facilitate drug absorption, but functions solely as the particle matrix.[12] Taken together, these unique features contribute to the distinctive pharmacokinetic profile of insulin administered as TI powder.[13]

Protein or peptide drugs can be adsorbed onto these particles to produce dry powders. For example, to prepare insulin and GLP-1 Technosphere powders for inhalation, insulin and GLP-1 were adsorbed onto the surfaces of pre-formed Technosphere particles by adding a solution of the appropriate drug to an aqueous suspension of Technosphere® particles.[14] The resulting suspensions were flash frozen in liquid nitrogen and lyophilized to remove water and produce dry powders. These powders are inhaled to effect systemic delivery of the drugs.

DEVICE TECHNOLOGY

Patients self-administer dry powders using inhalation devices. In general, drug delivery through inhalation has been conducted using three basic systems, including pressurized metered-dose inhalers, dry powder inhalers, and nebulizers. Each of these systems has evolved over the years to improve on dose uniformity and efficiency.[15-18] Dry powder inhalers have gained increased prominence for drug delivery because they do not use propellants, they do not require patient coordination, and dry powder formulations provide the potential for improved drug product stability.[19]

FIGURE 3

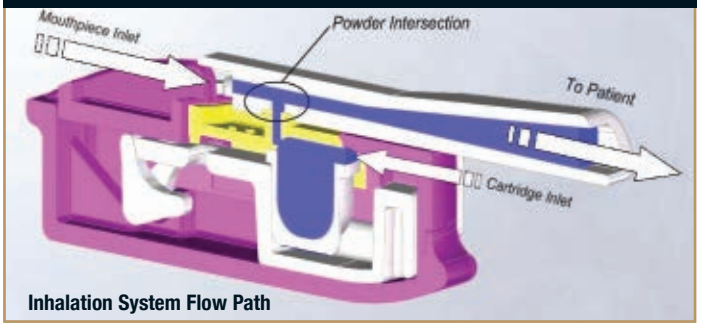
Technosphere® powder inhalation system showing device (left panel), device with single-use, pre-metered cartridge containing drug powder (center panel), and device with cartridge installed (right panel).

Technosphere powders are inhaled using breath-powered inhalers (Figure 3). Patients simply insert the single-use disposable cartridge into the device and inhale. The cartridge contains a pre-metered dose of powder formulation so dosing is controlled by the cartridge contents. Devices of this type have the advantage that they do not require patients to synchronize a device activation step with a sequential inhalation step. Instead, the devices are activated by the patient's inhalation alone. The delivery system designed to administer Technosphere powder formulations incorporates several key features including re-usability and high resistance. While the device itself is reusable, the cartridge containing the powder formulation is based on a single use and is prefilled with a discrete quantity of powder. The general concept of air flow balance was employed in the design to effectively disperse and de-agglomerate the powder. Other characteristics included in the design were small size for portability and discreetness and simple intuitive operation.

For this reason, breath-powered delivery systems must efficiently harness the patient's inhalation effort. This is accomplished by controlling several factors, including particle dispersion. Human anatomy dictates that particles with aerodynamic diameters between 1 and 10 microns have the highest probability of reaching and depositing in the lung.[19] Larger particles may be filtered by the tortuous path from mouth to alveolus, and smaller particles are likely to be exhaled because they may not settle or impact. Particles sized between 1 and 10 microns are defined as the respirable fraction or as being in the respirable range. As a result of the need for micron-sized particles, the normally insignificant static and van der Waals forces cannot be ignored because they have the potential to affect the "dispersability" of the powder leading to cohesion and agglomeration. Particles that are agglomerated or stuck together become larger than 10 microns, are no longer in the respirable range, and cannot be inhaled into the lung. To ensure maximal powder dispersion and minimal powder agglomeration, a breath-powered inhaler must focus the air flow from patient inhalation to lift and separate individual particles but not impart too much velocity onto any single particle. Particles with too much momentum cannot change direction quickly enough to follow the twists and turns of the bronchial airways. Consequently, they impact airway structures in the mouth and upper respiratory tract and never reach the lung tissue. An effective dry powder inhalation system must also consistently deliver the same mass of powder and adequately protect it from deleterious environmental factors prior to use. Moisture, for example, can quickly change a particle's morphology or permanently link it to neighboring particles to form large agglomerates. Finally, users of inhalation systems will range in age, dexterity, and cognitive ability. The most limited of users must still be able to operate the inhaler or the device is rendered useless.

Powder dispersion is ensured by an air flow that is balanced through and around the cartridge. Air flow through the cartridge de-agglomerates and lifts the powder from the bottom of the cartridge to the top exit port. Air flow around the cartridge pushes the powder into the mouthpiece as it exits the

FIGURE 4



Inhalation System Flow Path

cartridge. Here it is sheared to complete the de-agglomeration process as it exits the mouthpiece (Figure 4). This air flow balance allows complete discharge of the cartridge contents as well as providing forces that are sufficient to de-agglomerate the powder into particles sized within the respirable range. These flow contributors, together with their associated inlet/outlet areas, define the principle characteristic of the system called flow resistance. Based on the inhalation pressure supplied by the patient, the resistance determines the available air flow that drives powder delivery/performance. Importantly, pressure differentials across the inhalation system produce flow rates that are consistent with the Bernoulli principle as in the following equation.

Equation 1.

$$\varnothing P^{1/2} = \Phi R$$

Where ∅P is pressure drop, Φ is flow rate, and R is resistance.[20, 21] According to Equation 1, device system resistance is defined as the slope of the line produced by the relationship between the square root of pressure and flow (Figure 5). A high resistance was established to help increase flow turbulence at critical de-agglomeration points within the device system while simultaneously effecting slow average plume velocities to minimize throat deposition. Other researchers have found similar benefits from high resistance in delivery of dry powder inhalers.[22-24]

To refine flow mechanics within the inhaler system, resistance, flow balance, and system geometry were tuned to obtain optimal powder performance. Inhaler mouthpiece and cartridge components possessing dimensional variation were prototyped to explore their respective contributions to flow balance and resistance. For a constant mouthpiece area at the powder shear location, increasing the cartridge outlet area directs more air through the cartridge. Consequently, less air is available to shear the powder as it leaves the cartridge. Cartridge emptying (CE) and geometric particle size as defined by volumetric median geometric diameter (VMGD) of the emitted plumes were used as performance metrics. A laser diffraction test using a Sympatec® instrument was developed for these performance assessments in which the powder was pushed from the inhaler at a 4 kPa peak pressure. This pressure was chosen because it represents a patient inhalation effort.

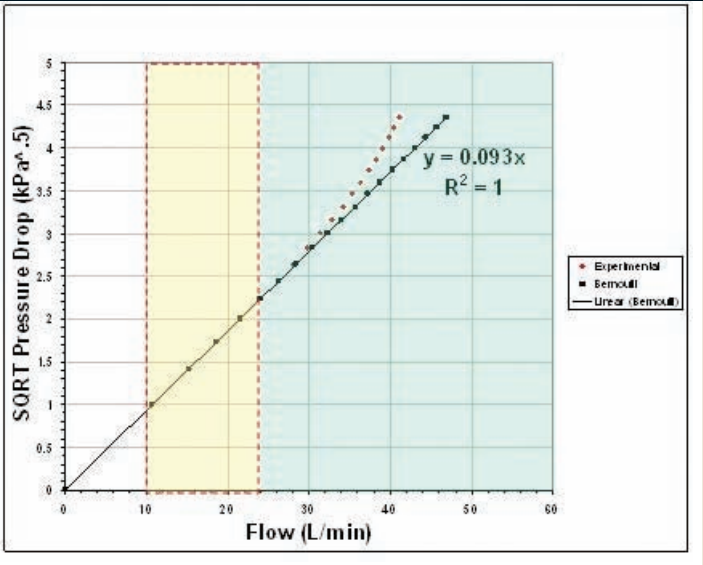
In the development of dry powder inhaler systems, particle size of the powder exiting the inhaler mouthpiece remains the single most important quality attribute for measuring inhaler performance. Additionally, particle size has shown a relationship to in vivo performance. Several review articles on this subject describing measurement techniques and relationships have been published.[19] Two of these techniques were used to develop the inhaler system for the Technosphere powders: laser diffraction and cascade impaction. The sensitivity of inhalation system performance was evaluated at various air flow rates selected to represent different patient inhalation profiles. Figure 6 shows the cumulative geometric particle size distributions for a range of fill masses and pressure drops (air flow rates) in the device system. The inhalation system demonstrated consistent performance across the range of fill masses and applied flow rates. This consistent performance across a diverse range of pressure drops shows that this inhalation system is suitable for broad patient populations, including pediatric, geriatric, and compromised pulmonary function populations.

CLINICAL STUDIES WITH TECHNOSPHERE FORMULATIONS OF INSULIN & GLP-1

Drugs administered as Technosphere dry powder formulations demonstrate rapid absorption profiles, with some (GLP-1) essentially comparable to intravenous injection.[25-27] Based on these pharmacokinetic profiles, both Afrezza™ (Technosphere Insulin) and MKC 253 (GLP-1 Technosphere) represent novel prandial diabetes therapies. The rapid absorption profiles of these drugs following inhalation mimic endogenous responses in healthy individuals and, coupled with the simplicity of the delivery system, are ideally suited to mealtime dosing.

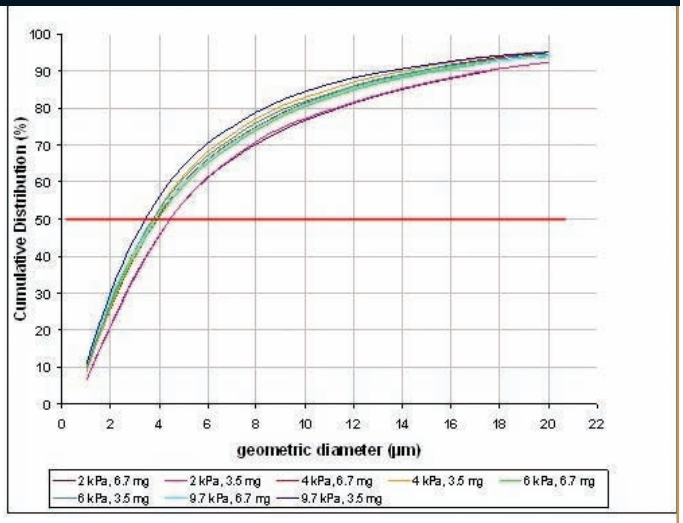
As part of Afrezza development, the pharmacokinetics and relative bioavailability of insulin inhaled as Afrezza were assessed in multiple crossover studies.[25,28,29] Insulin appears rapidly in the systemic circulation following Afrezza administration, usually detectable within 3 to 5 minutes after inhalation. The time of the maximum concentration (T_{max}) of insulin occurs approximately 10 to 15 minutes after dosing, and is comparable in healthy subjects and subjects with type 1 or type 2 diabetes.[25,29,30] The T_{max} for insulin after TI Inhalation Powder dosing occurs earlier than that of the subcutaneous (sc) rapid-acting analogs (Figure 7) and significantly faster than sc human insulin. This pharmacokinetic profile more closely mimics mealtime insulin secretion in healthy individuals than the available insulins.[31] The dose-normalized relative

FIGURE 5



Experimental (measured) and predicted (Bernoulli) behavior of inhalation system resistance: square root of pressure drop versus flow rate.

FIGURE 6



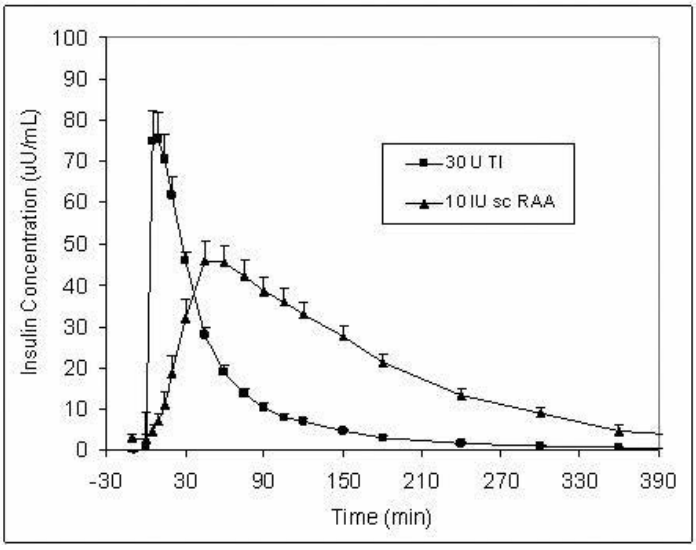
Cumulative geometric particle size distributions over a range of cartridge fill masses and pressure drops in the device system.

bioavailability (geometric means) of 30 U insulin administered as Afrezza was approximately 21% when compared to insulin lispro administered subcutaneously and ranged from 14% to 27% when compared to sc injected (regular) insulin.[25,28] Comparable relative bioavailability (21% to 25%) was obtained over a four-fold increase in insulin dose (25 U, 50 U, and 100 U).[29] Dose-dependent insulin pharmacokinetic parameters were assessed in two studies in which more than one dose strength of Afrezza was administered and pharmacokinetic parameters calculated. In the first study, conducted in healthy subjects, both the maximum concentration of drug (C_{max}) in plasma and the area under the concentration-time curve from t = 0 to 360 minutes ($AUC_{0\text{-}360\ min}$) of insulin were proportional over the dose range of 25 U, 50 U, and 100 U, with an approximate doubling of both C_{max} and AUC with each doubling of the dose.[29] In the second study (MannKind Corp., unpublished data [MKC-TI-110]), subjects with type 1 diabetes were dosed with one or two 30-U doses of Afrezza. A doubling of the dose from 30 U to 60 U resulted in an approximate doubling of the insulin Cmax and $AUC_{0\text{-}480\ min}$ with no significant difference in T_{max} (7.5 and 10 min, respectively). Afrezza administered as two 15-U doses or as one 30-U dose were bioequivalent. The 90% confidence interval (CI) for the $AUC_{0\text{-}360\ min}$ min and C_{max} ratios fell entirely within the interval 0.80 to 1.25.[28]

The intrasubject variability (CV%) of bioavailability was similar for both insulin inhaled as Afrezza and subcutaneous insulin (16% for Afrezza versus 15% for sc insulin). Intrasubject variability for the extent of insulin absorption (insulin AUC) was lower for Afrezza compared to sc insulin at the earlier time intervals (0 to 120 minutes and 0 to 180 minutes), which coincides with the time when the majority of insulin from Afrezza is absorbed. However these differences in variability between Afrezza and sc insulin were not statistically significant.[25,30] Intersubject variability for $AUC_{0\text{-}540\ min}$ was significantly greater for Afrezza than sc insulin (26% versus 10%). Additionally, in a study evaluating insulin kinetics when Afrezza was administered from two different cartridge prototypes, similar intrasubject variability for plasma insulin C_{max} and $AUC_{0\text{-}240\ min}$ was observed, ranging from 20.5% to 23.9% (MannKind Corp. unpublished data [MKC-TI-025]).

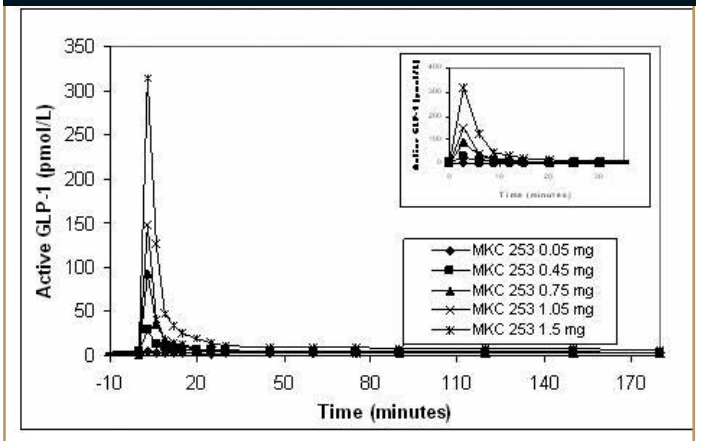
The pharmacokinetic profile of insulin inhaled as Afrezza and the early insulin response in healthy individuals are comparable. This similarity becomes apparent when one considers the normal, biphasic pattern of insulin secretion in healthy individuals. Basal insulin secretion occurs continuously to maintain steady glucose levels for extended periods between meals. Prandial insulin secretion produces increased plasma insulin concentrations in response to meals that typically return to basal levels after 3 hours. Together, basal and prandial insulin secretions maintain blood glucose levels within the physiologic range over 24 hours.[32] Insulin release following a meal has been shown to be biphasic. That is, an early insulin release associated with the suppression of hepatic glucose production is followed by a late insulin release. The magnitude of the late insulin release is related to circulating glucose concentrations following absorption of the meal. It is now evident that the early insulin release is a critical factor in the rapid and efficient suppression of endogenous glucose production following a meal.[33] In type 2 diabetes, the early insulin response is lost. The result is decreased suppression of hepatic glucose output causing postprandial hyperglycemia, which worsens to clinical hyperglycemia as the disease progresses.[34] While the existing insulins (human insulin, rapid-acting insulin analogs, and pre-mixed rapid- and intermediate-acting insulins) are effective in lowering elevated glucose levels, none of them replicate the normal early phase insulin response that is critical for suppressing hepatic glucose production.[33,35] In healthy individuals, prandial insulin concentrations peak by 30 minutes after the start of a meal and correspond with glucose absorption from the meal.[35] In comparison, the time to peak insulin concentrations following injected rapid-acting insulin analogs is approximately 45 to 90 minutes.[36-38] Clearly these times are not aligned. Given that a delayed insulin response of even 30 minutes can result in significant increases in postprandial glucose (PPG), it is clear that the misaligned timing of an injected insulin response and mealtime glucose absorption will result in hyperglycemia in patients with diabetes.[39]

FIGURE 7



Serum insulin concentrations after administration of 30 U of TI Inhalation Powder (n = 29) and 10 IU of a rapid-acting insulin analogue (insulin lispro, n = 26).[28]

FIGURE 8



Mean plasma GLP-1(active) concentrations after single inhaled of escalating MKC253 doses in normal human volunteers (n = 24).

Despite the deficiencies of insulin injections in controlling postprandial hyperglycemia, insulin remains the most effective diabetes treatment. There is no other antihyperglycemic agent with a glucose-lowering effect superior to that of insulin in the treatment of hyperglycemia.[40] The goals of an ideal insulin therapy are two-fold: (1) to replicate normal insulin physiology, including a rapid onset and a limited duration of action following a meal; and (2) to ensure basal insulin support throughout the 24-hour day. To evaluate Afrezza's potential to provide the prandial component of the ideal insulin therapy defined here, a prospective, multicenter, double-blind, placebo-controlled study was conducted. This study was designed to characterize the response to four different doses (equivalent to 3.6, 7.3, 10.9, and 14.6U subcutaneous regular human insulin) of prandial Afrezza compared to placebo administered before each of three meals daily. The 227 patients enrolled in this study were also taking insulin glargine to provide the basal component of therapy. This study comprised an 11-week treatment period, and participants were patients with type 2 diabetes with suboptimal glycemic control. Glucose control was measured as % glycosylated hemoglobin, called hemoglobin A1c (HbA1c). Treatment HbA1c targets have been defined by the American Diabetes Association (< 7%), American Association of Clinical Endocrinologists (< 6.5%), and European Association for the Study of Diabetes (< 6.5%).[41] In all dose groups, Afrezza demonstrated statistically significant dose-dependent reductions in HbA1c versus baseline (-0.4, -0.5, -0.5, and -0.6 for 3.6, 7.3, 10.9, and 14.6U equivalents, respectively; $p < 0.05$ in all groups), as well as versus placebo (-0.40, -0.67, -0.70, and -0.78 for 3.6, 7.3, 10.9, and 14.6U equivalents, respectively; $p < 0.04$ in all groups). Afrezza reduced the postprandial maximum glucose concentration within each treatment group (statistically significant in all but the TI 3.6U-equivalent group) and reduced the postprandial area under the glucose curve (statistically significant for the TI 10.9 and 14.6U-equivalent groups) versus placebo. There were no cases of severe hypoglycemia, while mild/moderate hypoglycemia was observed most frequently in the highest dosage groups, as expected. Rates of cough were low and comparable among all groups. A minimal change from baseline spirometry (FEV_1, 2.97 L) was seen in all groups (range: -0.04 ± 0.16 to -0.09 ± 0.20 L) over the 11-week study. However, the changes in pulmonary function tests in this trial, as well as body weight, high-resolution computerized axial tomography and magnetic resonance imaging, were not considered clinically relevant. This study demonstrated that over 11 weeks, TI plus basal insulin glargine is well tolerated and results in dose-dependent reductions in postprandial glucose and HbA1c levels.[42]

In a longer-term, randomized, open-label, parallel-group clinical study, adult patients from 10 countries with type 2 diabetes mellitus and poor glycaemic control despite insulin therapy, with or without oral antidiabetes drugs, were randomly allocated in a 1:1 ratio to receive 52 weeks of treatment with: prandial Afrezza plus bedtime insulin glargine; or twice-daily premixed biaspart insulin (70% insulin aspart protamine suspension and 30% insulin aspart of rDNA origin) (ClinicalTrials.gov, number NCT00309244). The primary endpoint of this study was a comparison of change in HbA1c from baseline to week 52 between treatment groups; the non-inferiority margin was 0.4%. Analysis was by per protocol for non-inferiority testing of the primary endpoint. Findings from 211 patients on inhaled insulin plus insulin glargine and 237 patients on biaspart insulin were included in per-protocol analyses. Change in HbA1c with inhaled insulin plus insulin glargine (-0.68%, SE 0.077, 95% CI -0.83 to -0.53) was similar and non-inferior to that with biaspart insulin (-0.76%, 0.071, -0.90 to -0.62). The between-group difference was 0.07% (SE 0.102, 95% CI -0.13 to 0.27). Patients had significantly lower weight gain and had fewer mild-to-moderate and severe hypoglycaemic events on inhaled insulin plus insulin glargine than on biaspart insulin. These data suggest that Afrezza, as an ultrarapid prandial insulin, along with a basal insulin, provides improved glycaemic control with lower weight gain and rates of hypoglycaemia in many individuals with type 2 diabetes.[43]

Taken together, these clinical studies show that Afrezza, as the prandial component of a type 2 diabetes regimen, has the potential to control postprandial hyperglycemia with a pharmacokinetic profile that more closely mimics normal, endogenous insulin secretion.

In addition to insulin, there are many other endogenous peptides that are released very rapidly in response to stimuli or receptor occupancy. GLP-1, for example, is an incretin hormone secreted by intestinal L cells, which circulates as the 7-36 peptide and the 7-36 amide, stimulates insulin release, decreases gastric motility, and has a role in other metabolic events. GLP-1 receptor (GLP-1R) agonists are currently administered as sterile solutions for injection (subcutaneous) for the treatment of hyperglycemia in type 2 diabetes. While newer GLP-1R agonists are being developed to extend the duration of action, non-solution formulations that deliver GLP-1 in a normal physiologic pattern may have advantages over injection. To investigate this hypothesis, GLP-1 for oral inhalation was formulated as GLP-1 Technosphere Inhalation Powder (MKC253).[14]

The pharmacokinetics and pharmacodynamics of MKC253 were assessed in two clinical trials, one in healthy normal volunteers and the other in patients with type 2 diabetes. Inhaled GLP-1 was absorbed quickly, with peak concentrations occurring within 5 minutes, and concentrations returning to baseline within 30 minutes (Figure 8). Thus, a dose of 1.5-mg GLP-1 inhaled as MKC253 produced peak GLP-1 concentrations of > 300 pmol/L at the first sampling time point (3 minutes) and peak insulin concentrations of 375 pmol/L at the first measured time point (6 minutes). Additionally, fasting plasma glucose was reduced from 85 to 70 mg/dL 20 minutes after dosing. MKC253 was well tolerated and, importantly, did not cause the nausea or vomiting associated with injected GLP-1.

In patients with type 2 diabetes, inhaled GLP-1 produced plasma GLP1 concentrations comparable to those of parenteral

administration and sufficient to induce insulin secretion resulting in attentuation of postmeal glucose excursions in subjects with T2DM.[27,44] In these subjects, MKC253 reduced fasting plasma glucose by ~1 mmol/L from 30 to 120 minutes and by 2 mmol/L at 240 minutes.

CONCLUSION

Peptides inhaled as dry powder Technosphere formulations are absorbed very rapidly, often resulting in pharmacokinetic profiles that mimic the endogenous hormone secretion characteristic of healthy individuals, enabling exogenous hormone administration that is aligned with normal human physiology. The utilization of insulin with this technology has demonstrated therapeutic benefit, which underscores the potential for therapeutic advances with other peptide or protein agents.

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Mr. Joseph Kocinsky, is Senior Vice President, Pharmaceutical Technology Development at MannKind in Danbury, CT. Mr. Kocinsky has expertise in product technologies across pharmaceutical dosage forms and manufacturing technologies leading to product registration and commercialization. Mr. Kocinsky has over 23 years experience in the pharmaceutical industry in technology and product development.

TRANSDERMAL DELIVERY

Formulation & Evaluation of a Transdermal Patch Containing Fluconazole

By: Rakesh P. Patel, PhD; Chirag P. Patel, MPharm; Bhupendra G. Prajapati, MPharm; Chaudhary Varsha, BPharm

ABSTRACT

The purpose of this research was to develop a matrix-type transdermal therapeutic system containing fluconazole (FLZ) with different grades of hydroxy propyl methyl cellulose (HPMC) polymers. The physico-chemical compatibility of the drug and the polymers was studied via differential scanning calorimetry and infrared spectroscopy and suggested absence of any incompatibility. Formulated transdermal films were physically evaluated with regard to thickness, weight variation, drug content, flatness, tensile strength, folding endurance, percentage of moisture content, and water vapor transmission rate. All prepared formulations indicated good physical stability. In vitro permeation studies of formulations were performed using Franz diffusion cells. The formulation prepared with HPMC K4M 3% polymer containing a mixture of DMSO and oleic acid (OA) as a permeation enhancer at optimum concentration showed best in vitro skin permeation through rat skin (Wistar albino rat) as compared to all other formulations. However, the release profile of the optimized formulation F5 indicated that the permeation of the drug from the patches was governed by a diffusion mechanism. Formulation F5 showed the highest flux among all the formulations and better enhancements in drug permeation. These results indicate that the formulation containing 20% glycerol as a plasticizer with 3% of HPMC K4M result in better penetration of fluconazole through rat skin.

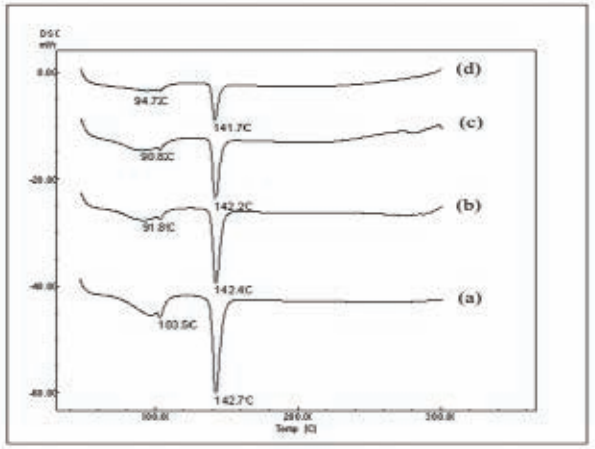
INTRODUCTION

Transdermal drug administration generally refers to topical application of agents to healthy intact skin for localized treatment of tissues underlying the skin or for systemic therapy. For transdermal products, the goal of dosage design is to maximize the flux through the skin into the systemic circulation and simultaneously minimize the retention and metabolism of the drug in the skin.[1] Transdermal drug delivery has many advantages over the oral route of administration, such as improving patient compliance in long-term therapy, bypassing first-pass metabolism, sustaining drug delivery, maintaining a constant and prolonged drug level in plasma, minimizing inter- and intra-patient variability, and making it possible to interrupt or terminate treatment when necessary.[2,3]

Fluconazole (FLZ) interferes with the formation of fungal cell membranes, causing leakage of cellular contents and cell death. It is used in the treatment oropharyngeal and esophageal candidiasis, vaginal candidiasis, prevention of candidiasis in bone marrow transplants; and cryptococcal meningitis.

There are reports describing the use of different grades of HPMC polymers in transdermal patches for controlled release of

FIGURE 1



DSC thermograms of (a) pure drug, (b) drug + HPMC K100M, (c) drug + HPMC K4M, and (d) drug + HPMC K15M.

drugs.[4-6] The transdermal delivery systems were prepared using different grades of HPMC to study the effect of polymer grades on release of FLZ and stability of transdermal films.

A large number of fatty acids and their esters have been used as permeation enhancers. Here, oleic acid and dimethyl sulfoxide (DMSO) have been used. Oleic acid has been shown to be effective as a permeation enhancer for many drugs, for example, increasing the flux of salicylic acid 28-fold and 5-fluorouracil flux 56-fold, through human skin membranes in vitro.[7,8] It has also been used for ketoprofen, flurbiprofen, 5-FU, estradiol, zalcitabine, didanosine, zidovudine, and more.[9-12]

The purpose of this work is to (1) develop a topical formulation that would improve drug bioavailability, reduce dose and frequency of dosing, and improve patient compliance; (2) carry out studies to enhance the permeability of FLZ through rat abdominal skin; (3) compare and evaluate the transdermal systems formulated using different grades of HPMC as film-forming polymers; (4) select and optimize solvents and penetration enhancers; (5) select and optimize polymer systems and plasticizers using 3^2 full factorial design; (6) analyze an optimized batch from 3^2 full factorial design by ANOVA; and (7) conduct in vitro diffusion studies of a selected formulation through cellophane membrane and rat abdominal skin.

MATERIALS

Fluconazole was received as gift samples from Lincoln Pharmaceuticals (Ahmedabad, India). Different grades of HPMC were a generous gift from Colorcon Asia Pvt. Ltd. (Mumbai, India) and Maan Pharmaceuticals Ltd. (Ahmedabad, India), respectively. Oleic acid was procured from Sigma Chemicals Ltd. (Ahmedabad, India). Other materials used in the study (methanol, dichloromethane, glycerin, PEG 400, etc.) were of analytical grade. Double-distilled water was used throughout the study.

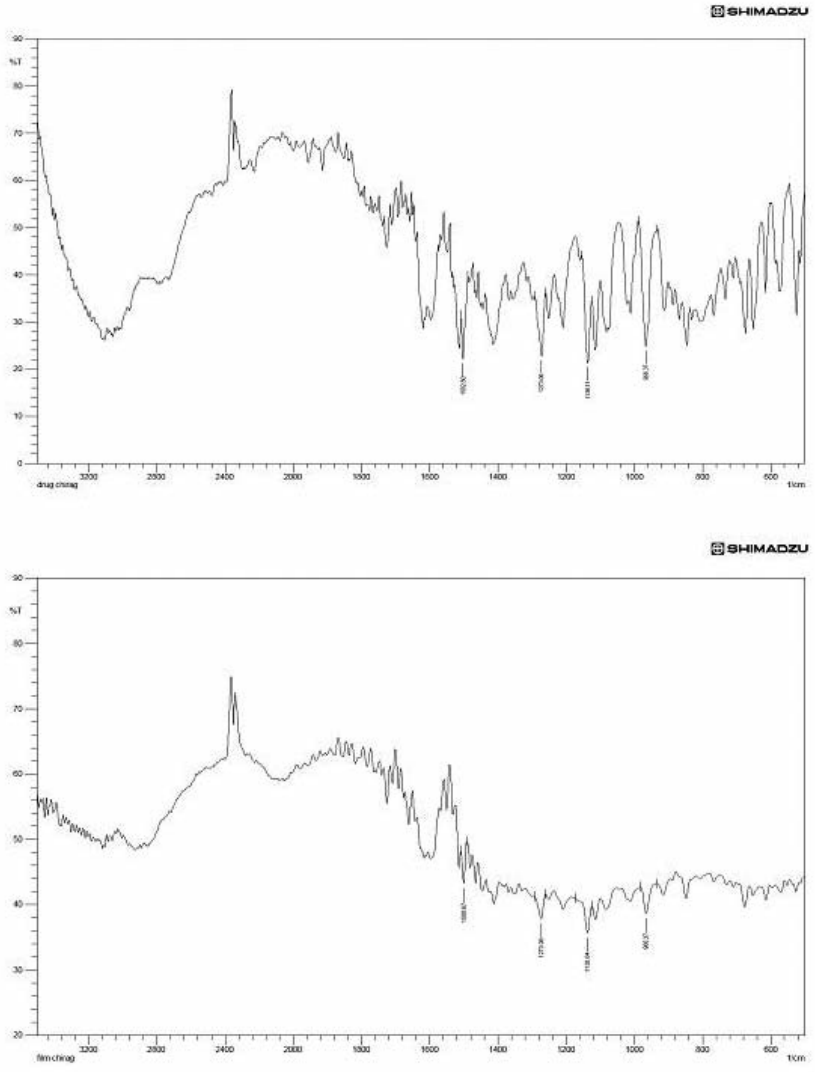
METHODS

Investigation of Physicochemical Compatibility of Drug & Polymer

To investigate any possible interaction between the drug and the utilized polymer (HPMC), IR spectrum of pure drug (FLZ) and its physical mixture was conducted using FTIR. The range selected was from 400 cm^{-1} to 4000 cm^{-1}.[13,14]

DSC thermograms of pure drug (FLZ) and its physical mixture with polymer (HPMC)

FIGURE 2



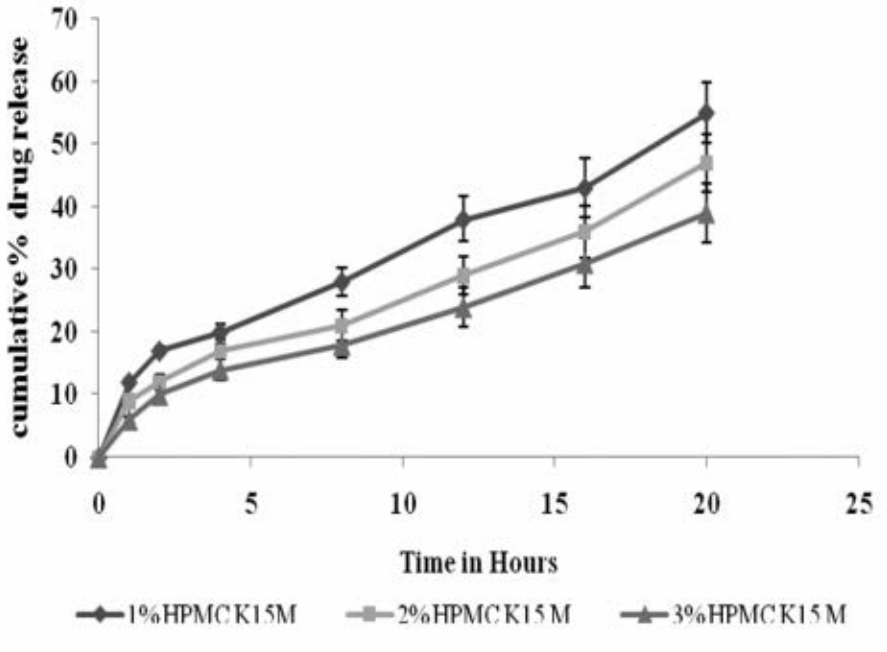
FTIR spectra of (a) pure drug and (b) physical mixture of final formulation of transdermal patch

TABLE 1

No.	Ingredients	Formulation Code					
		A1	A2	A3	A4	A5	A6
1	Drug (mg)	50	50	50	50	50	50
2	HPMCK4M	1%	2%	3%	-	-	-.
3	HPMC K15M	-	-	-	0.25%	0.5%	1%
3	DMSO	1%	2%	3%	1%	2%	3%
4	Glycerol	20%	20%	20%	20%	20%	20%
5	Oleic acid	1.5%	3%	4.5%	1.5%	3%	4.5%
6	Ethanol	8%	8%	8%	8%	8%	8%

Composition of transdermal patches

FIGURE 4



Drug diffusion profile of transdermal film containing various concentrations of HPMC K15M

were carried out to investigate any possible interaction between the drug and the utilized polymer (HPMC). The selected heating rate is from 50°C to 300°C at an increase of 10°C per minute using a Shimanzu DSC.[15,16]

Preparation of Transdermal Films

The solvent casting method was used for the preparation of the films. The required amount of film-forming polymer of different grades of HPMC was allowed to hydrate using minimum amount of ethanol:water (8:2) for about 3 to 4 hours and then uniformly dispersed to obtain a clear solution of film-forming polymer. The required amount of plasticizer (ie, glycerin and PEG 400) was then added to the film-forming solution. Other ingredients, including drug and permeation enhancers such as OA, were dissolved one by one in previously prepared film-forming solutions with constant stirring to form a clear solution. The solution was kept in undisturbed conditions until the entrapped air bubbles were removed. The solution was casted in a glass petri dish and dried at room temperature. The petri dishes were placed on a leveled surface during drying to avoid variation in thickness. The film took approximately 24 hours to dry at room temperature. The dried film was carefully removed from the mould and was cut into appropriate sizes required for testing. The films were stored in airtight plastic bags until further use.

Physico-Chemical Characterization of Films

PHYSICAL APPEARANCE: All the transdermal patches were visually inspected for color, clarity, flexibility, and smoothness.

THICKNESS UNIFORMITY: Discs (1 cm^2 patches) were subjected to measurement of thickness using Digital Vernier Calipers.[17]

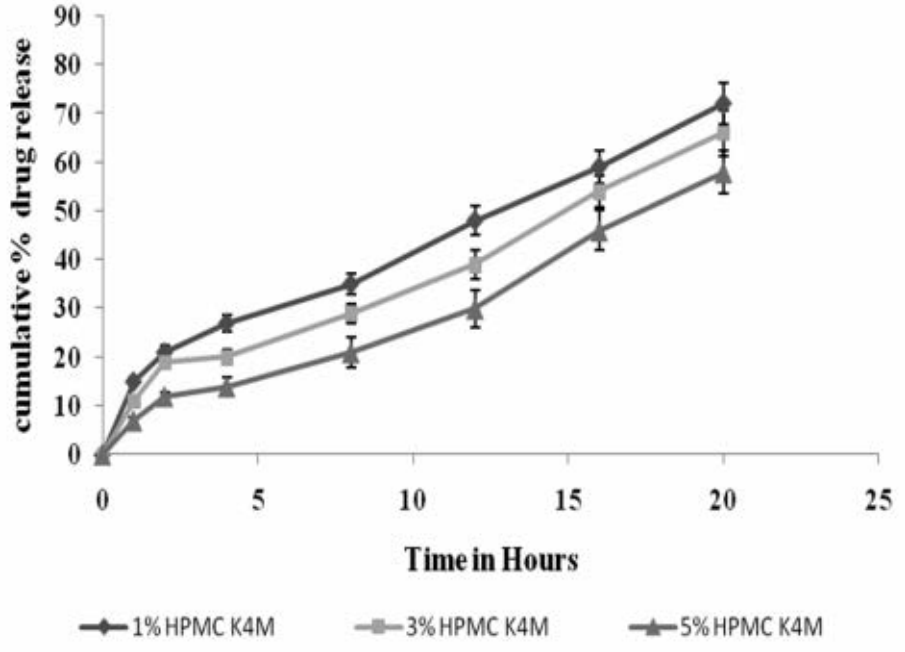
FOLDING ENDURANCE: This was determined by repeatedly folding one film at the same place until it broke. The number of times the film could be folded at the same place without breaking/cracking gave the value of folding endurance.[4]

TENSILE STENGTH & % ELONGATION: The films were casted on mercury and taken in rectangular containers. As the concentration of HPMC increases, the percent of elongation will increase. A proportionate quantity of the solution was calculated on the basis of area.[18] The films were cut into strips (1 cm width x 15 cm length) and were fixed onto the tensile strength apparatus in such a way that the length of film between the jaws was initially 10 cm. The trials where the breakage occurred at the jaw were invalid, and the result was repeated on another strip. The tensile strength was calculated using the following:

$$\text{Tensile Strength} = \frac{\text{Load at Failure}}{\text{Strip Thickness x Strip Width}}$$

The percent elongation was determined by noting the length just before the break point and substituting the following formula:

FIGURE 3



Drug diffusion profile of transdermal film containing various concentrations of HPMC K4M

% Elongation = [Final Length-Initial Length] x 100
Initial Length

PERCENTAGE OF MOISTURE CONTENT: The films were weighed individually and kept in a desiccator containing activated silica at room temperature for 24 hours. Individual films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight.

WATER VAPOR TRANSMISSION RATE (WVTR): WVTR is defined as the quantity of moisture transmitted through a unit area of film in unit time.[19] Glass cells were filled with 2 g of anhydrous calcium chloride, and a film of specified area was affixed onto the cell rim. The assembly was accurately weighed and placed in a humidity chamber (80 ± 5% RH) at 27 ± 2°C for 24 hours.

MOISTURE UPTAKE: Weighed films were kept in desiccators at room temperature for 24 hours. These were then taken out and exposed to 84% relative humidity using saturated a solution of potassium chloride in a desiccator until a constant weight was achieved. Percent moisture uptake was calculated using the following:

% Moisture Uptake =
Final Weight - Initial Weight x 100
Initial Weight

DRUG CONTENT UNIFORMITY: Exactly 1-cm^2 areas of the film were cut, and each was dissolved in a sufficient quantity of methanol. The volume was made up to 10 mL. Then, 1 mL was withdrawn from this solution and diluted to 10 ml .The absorbance was then measured at 208 nm. From the absorbance and the dilution factor, the drug content in the film was calculated.[17]

In Vitro Skin-Permeation Studies

In vitro skin-permeation studies were performed using a Franz diffusion cell with a receptor compartment capacity of 22.5 mL. The excised rat abdominal skin was mounted between the donor and receptor compartment of the diffusion cell. The formulated patches were placed over the skin and covered with paraffin film. The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 50 rpm; the temperature was maintained at 32°C ± 0.5°C. The samples were withdrawn at different time intervals and analyzed for drug content spectrophotometrically. The receptor phase was replenished with an equal volume of phosphate buffer pH 7.4 at each sample withdrawal. The cumulative percentage of drug permeated per square centimeter of patches was plotted against time.

Full Factorial Design

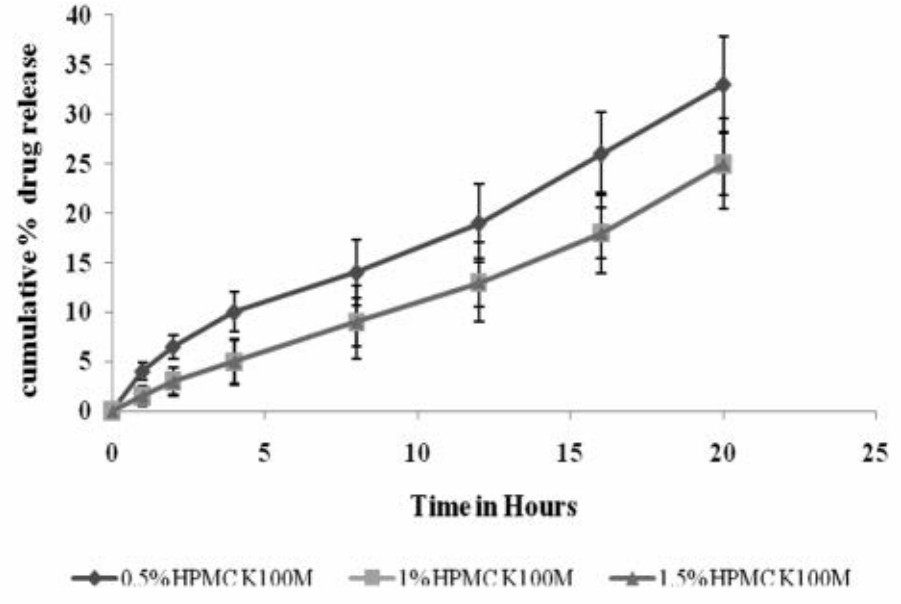
A 3^2 randomized full factorial design was used in the present study. In this design, two factors were evaluated, each at three levels, and experimental trials were performed at all nine possible combinations. The amount of glycerin (X_1) and the amount of HPMC K4M (X_2) were selected as independent variables. The drug release at 20 hours was selected as the dependent variable.

TABLE 2

Parameters	A1	A2	A3	A4	A5	A6
Thickness (micrometers)	121 ± 3.6	134± 4.05	143± 4.26	185 ± 5.58	206 ± 6.18	214 ± 6.45
Weight Variation (mg cm^{-2})	10.61 ± 0.31	12.51± 0.37	14.97 ± 0.44	10.11 ± 0.30	12.74 ± 0.38	15.13 ± 0.45
Drug Content (%)	97.3 ± 2.94	99.0 ± 2.97	99.2 ± 2.94	99.2 ± 2.97	98.7 ± 2.96	97.9 ± 2.93
Folding Endurance	209 ± 6.27	213 ± 6.39	210 ± 6.3	234 ± 7.02	245 ± 7.35	238 ± 7.14
Tensile Strength (kg/cm^{-2})	3.15 ± 0.094	3.51 ± 0.105	3.83 ± 0.114	2.12 ± 0.063	2.25 ± 0.067	2.98 ± 0.089
Moisture Content (%)	2.32 ± 0.56	2.92 ± 0.68	4.02 ± 0.89	1.96 ± 0.39	1.78 ± 0.33	1.64 ± 0.31
WVTR (mg/cm^{-2}/h^{-1})	0.468 ± 0.014	0.482 ± 0.014	0.569 ± 0.017	0.121 ± 0.003	0.268 ± 0.008	0.140 ± 0.004

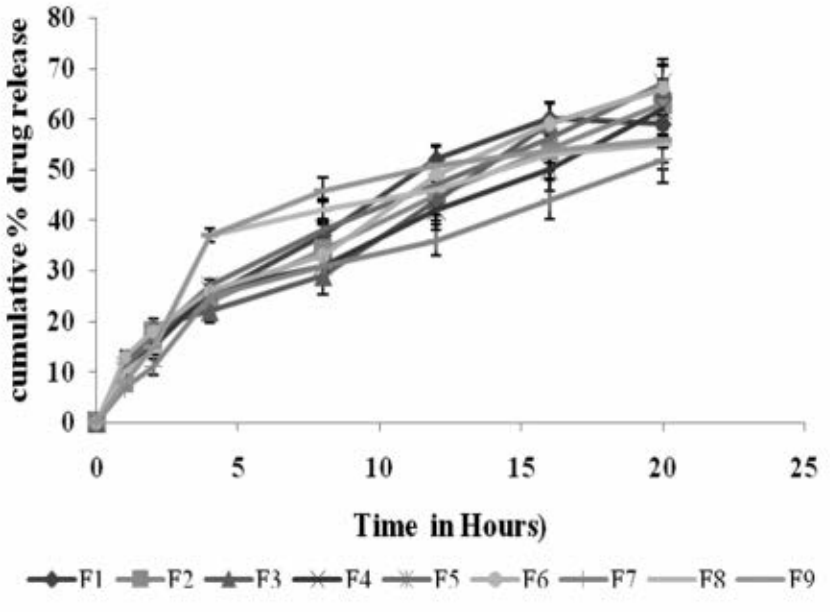
Evaluation of transdermal patches, mean ± SD (n=3)

FIGURE 5



Drug diffusion profile of transdermal film containing various concentrations of HPMC K100M

FIGURE 6



Release profile of ACF from patches containing different concentrations of different grades of HPMC polymer

Stability Study of Optimized Formulation

The stability study was carried out for optimized patch formulation at 40°C in a humidity chamber having 75% RH for 30 days. After 30 days, the samples were withdrawn and evaluated for physico-chemical properties and in vitro diffusion.

Primary Skin Irritation Study

The matrix patches were applied to the shaved skin on the back of three albino rabbits and secured using adhesive tape. A control patch (without drug) was secured on one side of the back, and an experimental patch was secured on the other side. The animals were observed for any signs of erythema and edema for 7 days and scored as repored by Draize et al.[20]

RESULTS & DISCUSSION

Investigation of Physico-Chemical Compatibility of Drug & Polymer

Differential scanning calorimetry enables the quantitative detection of all processes in which heat energy is required or produced (ie, endothermic or exothermic phase transformations). The thermograms of pure FLZ and the patch formulations of FLZ with HPMC K4M, HPMC K15M, and HPMC K100M are presented in Figure 1. The FLZ showed a melting peak at 142.7°C. The melting peaks of FLZ at 142.21°C, 142.42°C, 141.70°C, and 142.71°C were observed at the same position, ie, near the pure drug peak seen in the drug mixtures with the three different grades of HPMC formulation excipients. This confirmed the physico-chemical stability of drug with the formulation excipient used in the study.

Physico-Chemical Characterization of Films

The results of the physico-chemical characterization of the patches are shown in Table 2. The thickness ranged between 121 ± 3.6 and 214 ± 6.45 micrometers, which indicates they are uniform in thickness. The weights ranged between 10.11 ± 0.30 mg and 15.13 ± 0.45 mg, which indicates that different batches of patch weights were relatively similar. Good uniformity of drug content among the batches was observed with all formulations and ranged from 97.9% ± 2.93% to 99.2% ± 2.97%. The results indicate that the process employed to prepare patches in this study was capable of producing patches with uniform drug content and minimal patch variability. The flatness study showed that all the formulations had the same strip length before and after their cuts, indicating 100% flatness. Thus, no amount of constriction was observed. All patches had a smooth, flat surface, and that smooth surface could be maintained when the patch was applied to the skin. Folding endurance test results indicate the patches would not break and would maintain their integrity with general skin folding when applied. Moisture content and moisture uptake studies indicate the increase in the concentration of hydrophilic polymer was directly proportional to the increase in moisture content and moisture uptake of the patches. The moisture content of the prepared formulations was low, which could help the formulations remain stable and reduce brittleness during long-term storage. The moisture uptake of the formulations was also low, which could protect the formulations from microbial contamination and reduce bulkiness.[21]

TABLE 3

Time (hrs)	HPMC K4M (w/v)			HPMC K15M (w/v)			HPMC K100M (w/v)		
	1%	3%	5%	1%	2%	3%	0.5%	1%	1.5%
0	0	0	0	0	0	0	0	0	0
1	15.1±0.8	11.3±0.6	7.4±0.7	12.3±0.6	9.10±0.8	6.42±0.5	4.11±0.9	2.4±0.7	1.5±0.9
2	21.4±1.5	19.1±1.3	12.3±0.8	17.7±0.7	12.5±1.2	10.3±1.6	6.5.3±1.2	4.5±1.4	3.3±1.4
4	27.5±1.7	20.5±1.5	14.2±1.7	20.8±1.3	17.7±2.4	14.2±1.7	10.1±2.0	8±2.3	5.5±2.2
8	35.9±2.1	29.8±1.9	21.6±3.2	28.9±2.2	21.8±2.9	18.4±2.2	14.5±3.3	12.2±3.7	9.6±2.4
12	48.3±3.2	39.7±2.9	30.5±3.9	38.4±3.6	29.9±4.1	24.9±3.1	19.7±3.9	16.4±3.9	13.7±2.4
16	59.1±3.4	54.5±3.3	46.6±4.1	43.2±4.7	36.2±4.2	31.6±3.9	26.3±4.1	22.9±4.1	18.2±2.5
20	72.4±4.3	66.1±4.6	58.7±4.3	55.1±4.9	47.4±4.6	39.3±4.7	33.4±4.6	30.4±4.6	25.1±3.2

Cumulative percent drug release of polymer batches

In Vitro Skin Permeation

Three different polymers grades of HPMC (HPMC K4M, HPMCK15M, and HPMC K100M) were used at three different concentrations, and the prepared transdermal films were checked for their folding endurance and in vitro drug release using cellophane paper in 7.4 phosphate buffer using a Franz diffusion cell at 37°C. Table 3 and Figure 6 show different concentrations and different grades affect drug-release patterns. As the amount of concentration increases for HPMC K4M from 1%, 3%, and 5%, the concentration of drug release decreases simultaneously due to a higher gel strength formed due to the matrix system. In the same manner, as the viscosity grade increases from HPMC K4M (4000 cps) to HPMC K100M (100000 cps), drug release decreases. HPMC K4M in 3% concentration resulted in a more than 50 folding endurance, which was good for handling during packaging and transportation purposes, and drug release was under a controlled manner up to 20 hours. So 3% HPMC K4M exhibited good results compared to the other grades and concentrations. Further optimization of plasticizer was carried out in subsequent sections.

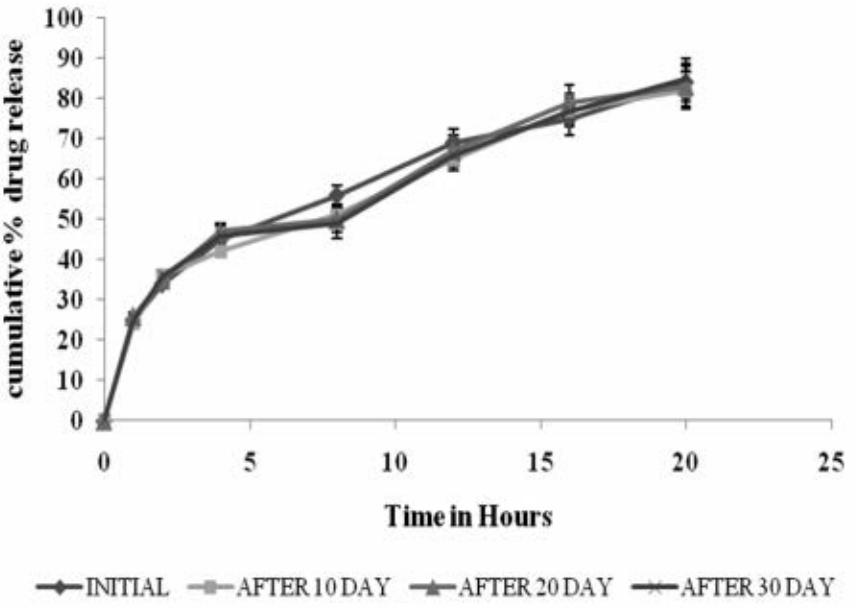
In Vitro Drug Release Study of Factorial Design Batches

Optimization of HPMC K4M and glycerin were carried out via 32 full factorial designs taking both independent variables at HPMC K4M at 1.5%, 3%, and 4.5% concentrations and glycerin at 17%, 20%, and 23% concentrations. In addition, all film formulations were evaluated in terms of folding endurance, tensile strength (N/mm^2), percent elongation, percent drug release after 2 hours (Q_{2hr}), and percent drug release after 20 hours (Q_{20hr}). Results are shown in Table 4.

The tensile strength for all nine batches F1 to F9 shows a good correlation co-efficient of 0.9695. It is shown that variable X_1 has a p value of 0.005531 ($p < 0.05$). variable X_2 has p value of 0.013212 ($p < 0.05$). Variables that have a p value less than 0.05 significantly affect. So here, both X_1 (concentration of HPMC) and X_2 (concentration of glycerin) significantly affect the tensile strength of the film. The positive sign of X_1 and X_2 coefficients indicate that as the concentration of HPMC increases, so will the tensile strength. X_{11} has a p value of 0.053481 ($p > 0.05$), thus the square of X_1 does not produce a significant effect on tensile strength. X_{22} has p value of 0.093033 ($p > 0.05$) so the square of X_2 does not produce significant effect on tensile strength, but has a negative effect on tensile strength. Interaction of X_{12} has p value of 0.597593 ($p > 0.05$), so interaction of X_{12} has no significant effect on tensile strength.

The percent elongation for all 9 batches F1 to F9 shows good correlation coefficient of 0.9789. From Table 4, it is shown that variable X_1 has p value of 0.002543 ($p < 0.05$), and variable X_2 has p value of 0.017565 ($p < 0.05$). Variables that have a p value less than 0.05 significantly affect. So here, both X_1 and X_2 variables significantly affect the percent elongation of the film. A positive sign of X_1 and X_2 coefficients indicates that as the concentration of HPMC increases so will the percent elongation. X_{11} has p value of 0.02625 ($p < 0.05$) thus, the square of X_1 produces significant effect on percent elongation. X_{22} has

FIGURE 7



In vitro diffusion study of transdermal patches kept under normal conditions

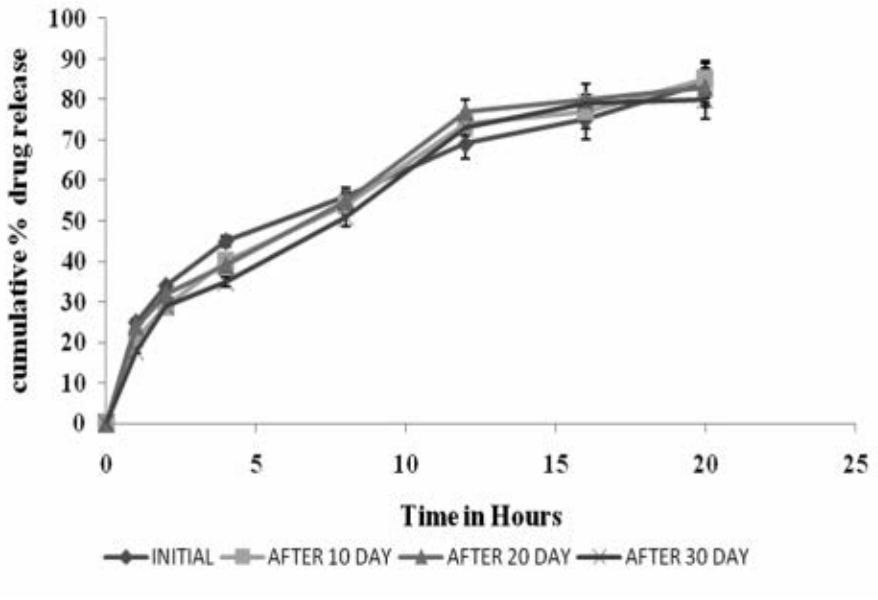
TABLE 4

X1	X2	Tensile Strength	% Elongation	Folding Endurance	Q_2	Q_8	Q_{20}
17	1.5	3.2	76	65	16	31	59
17	3	4.4	145	112	18	34	63
17	4.5	4.55	155	103	19	36	66
20	1.5	4.7	189	83	15	34	62
20	3	6.8	247	135	17	30	67
20	4.5	6.4	219	138	18	31	68
23	1.5	5.3	198	102	11	24	52
23	3	6.35	246	163	14	26	55
23	4.5	7.09	250	175	15	27	56

Translation of Coded Levels in Actual Units			
Variables Level	**Low (-1)**	**Medium (0)**	**High (+1)**
Amount of glycerin (% w/w of drug) X_1	17	20	23
Amount of HPMC K4M. (% w/w of drug) X_2	1.5	3	4.5

Optimization of polymer & plasticizer both by 3^2 factorial design

FIGURE 8



In vitro diffusion study of transdermal patches kept under accelerated stability conditions (40°C and 75% RH)

p value of 0.048261 ($p < 0.05$), so the square of X_2 produces a significant but negative effect on percent elongation. Interaction of X_{12} has p value of 0.400004 ($p < 0.05$), therefore interaction of X_{12} has a significant but negative effect on percent elongation.

The folding endurance for all 9 batches F1 to F9 shows good correlation coefficient of 0.999437. From Table 4, it is shown that variable X^1 has p value of 0.0000198 ($p < 0.05$) and variable X_2 has p value of 0.000017 ($p < 0.05$). Variables that have a p value less than 0.05 significantly affect on the response. So here, X_1 and X_2 variables produce significant affects on the folding endurance of the film. The positive sign of X_1 and X_2 coefficients indicates that as the concentration of HPMC increases so does the folding endurance. X_{11} has p value of 0.258 ($p > 0.05$), so the square of X_1 does not produce a significant effect on folding endurance. X_{22} has p value of 0.0001 ($p < 0.05$), thus the square of X_2 produces a significant but negative effect on folding endurance. Interaction of X_{12} has p value of 0.0010 ($p < 0.05$), so interaction of X_{12} has a significant effect on folding endurance.

Stability Study

The optimized batch was studied for its stability in two different conditions, room temperature and accelerated temperature (40°C) and relative humidity (75% RH). Transdermal films of FLZ were evaluated for their in vitro drug release initially and after every 10 days throughout a 1-month period. Results are shown in Table 5 and Figures 7 and 8. The results indicate there were no release profile problems for the transdermal film of FLZ at room temperature, but it was very slightly changed in the presence of higher temperature and humidity. However, the release profile was not significantly altered to doubt the stability of our final optimized transdermal patch of FLZ.

TABLE 5

Stability Condition	Ordinary Condition				Accelerated Condition (400°C and 75% RH)			
Days After Testing	0	10	20	30	0	10	20	30
0	0	0	0	0	0	0	0	0
1	25.3±0.8	24.4±0.6	26.1±0.9	25.3±0.7	25.5±0.6	21.3±1.0	24.5±0.5	18.9±0.6
2	34.1±1.2	36.2±1.3	35.3±1.2	36.7±1.4	34.3±0.7	29.2±1.2	32.3±1.6	29.1±0.7
4	45.5±1.2	42.6±1.5	47.5±2.0	46.6±2.3	45.1±1.3	40.0±1.2	39.0±0.7	35.6±1.3
8	56.7±2.4	51.6±1.9	50.3±3.3	49.3±3.7	56.9±2.2	54.3±2.5	55.6±1.3	51.3±2.2
12	69.8±3.5	65.2±2.9	67.1±3.9	66.1±3.9	69.7±3.6	74.4±2.9	77.8±2.2	73.4±3.6
16	75.1±4.1	77.1±3.3	79.5±4.2	77.3±4.1	75.4±4.7	77.2±4.1	80.1±3.6	79.2±4.7
20	84.3±4.6	82.3±4.6	83.1±4.9	85.3±4.8	84.3±4.9	85.5±4.6	83.4±4.9	80.3±4.9

In vitro diffusion study of stability indicating batch

Primary Skin Irritation Test

A primary skin irritation test of the transdermal formulation batch F5 showed a skin irritation score (erythema and edema) of less than 2. According to Draize et al, a compound producing a score of 2 or less is considered negative (no skin irritation).[20] Hence, the developed transdermal formulation is free of skin irritation.

CONCLUSION

Based on the results obtained in this study, it can be concluded that HPMC K4M 3% w/v with 20% w/w glycerol as a plastisizer shows promise as a controlled-release transdermal drug delivery system for FLZ. Incorporation of DMSO and oleic acid as permeation enhancers into the polymeric patch enhanced the permeability of FLZ. The results of the skin-permeation study show the feasibility of formulating a rate-controlled transdermal patch of FLZ for effective management of microbial infection. The primary skin irritation study on albino rabbits for the optimized transdermal patch showed no allergic symptoms. Further in vivo investigation is required to correlate the in vitro permeation study for the development of suitable transdermal system of FLZ.

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BIOGRAPHIES

Dr. Rakesh Patel is currently working as an Associate Professor and Head of Pharmaceutics and Pharmaceutical Technology Department at the S.K. Patel College of Pharmaceutical Education and Research (SKPCPER), Ganpat University, Gujarat, India. He earned his PhD in Pharmaceutical Sciences from Hemchandrachrya North Gujarat University, Patan, and his MPharm in Pharmaceutical Technology from M.S. University, Baroda. His current research interests include formulation and development of novel and conventional pharmaceutical products, dissolution enhancement techniques, drug delivery, regulatory affairs, industrial pharmaceutical manufacturing, and antimicrobial plant screening. He has prepared more than 100 dossiers for product registration in various countries for a pharmaceutical company, and has more than 80 research publications and 70 presentations in international and national journals and conferences to his credit. He is working as an Advisory Editorial Committee Member of Dissolution Technologies and Pharmaceutical Manufacturing, USA. He has guided more than 30 students for their MPharm projects, and 4 students are currently working toward their PhD under his valuable guidance.

Chirag P. Patel has completed his MPharm from the Department of Pharmaceutics and Pharmaceutical Technology, S.K. Patel College of Pharmaceutical Education and Research (SKPCPER), Ganpat University, Gujarat, India. Currently, he is working as a Production Executive in Wellable Pharmaceuticals Ltd, Mehsana, Gujarat, India. His area of research includes transdermal drug delivery systems.

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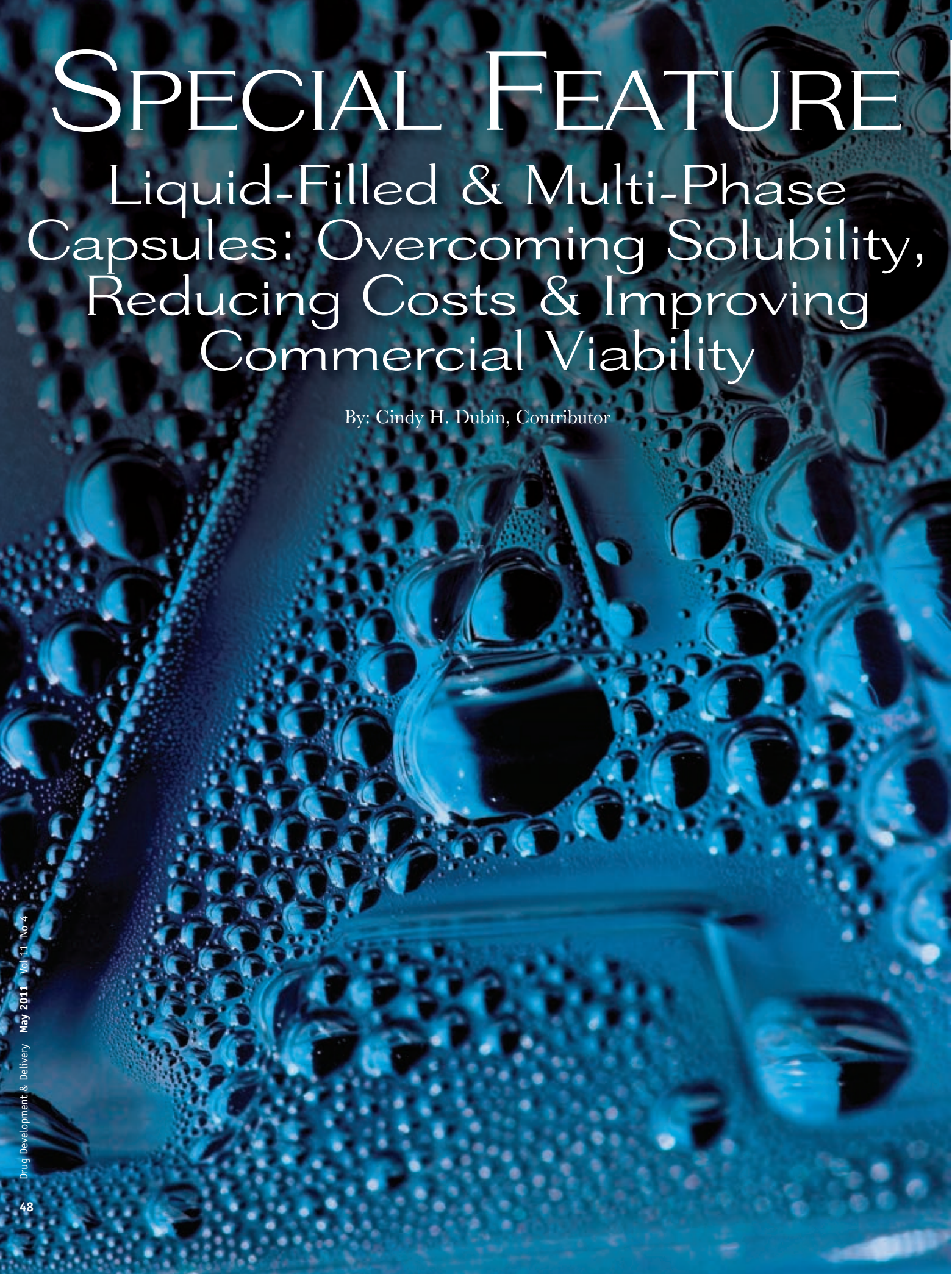
Chaudhary Varsha is persuing her post-graduate degree in the Department of Pharmaceutics and Pharmaceutical Technology at the S.K. Patel College of Pharmaceutical Education and Research (SKPCPER), Ganpat University, Gujarat, India. Her area of research focuses on folic acid conjugate drug delivery systems.

Special Feature

Liquid-Filled & Multi-Phase Capsules: Overcoming Solubility, Reducing Costs & Improving Commercial Viability

By: Cindy H. Dubin, Contributor



It is estimated that more than 40% of new chemical entities (NCEs) currently coming out of the drug discovery process have poor bioavailability properties, such as low aqueous solubility and/or permeability. These suboptimal properties pose significant challenges for the oral absorption of the compounds and for the development of orally bioavailable dosage forms. Liquid-filled capsules offer a unique advantage of delivering these types of poorly aqueous soluble compounds in a solubilized form using non-aqueous vehicles that are proven to be safe for human consumption. Also, through selection of suitable excipients in the liquid fill, challenges arising from the poor permeability properties of these types of molecules can be reduced or eliminated.

According to Rampurna Prasad Gullapalli, PhD, Vice President of Drug Delivery Technologies at Pharmaceutics International Inc. (Pii), liquid-filled capsule technology offers Pharma and Biotech line extensions to currently marketed products and the intellectual property protection that comes with it. "This is an important factor for a company to survive and thrive, especially under current market conditions and competitive pressures," he says.

Liquid-filled capsule technology refers to soft gelatin and hard gelatin/non-gelatin capsules. In the past 25 years, the launch of several soft capsule products (cyclosporine, etoposide, bexarotene, calcitriol) has provided benefits and life-saving medications to patients. On the other hand, liquid-filled hard capsule technology is still in its infancy, but emerging as a solution to overcome formulation challenges associated with soft-gel manufacturing. Filling and sealing of the liquids into two-piece hard gelatin capsules is now easier than ever with more sophisticated equipment. Several pharmaceutical products currently under development are expected to reach the market within the coming years.

Compartmentalized or multi-phase capsules are also being developed to deliver a "cocktail" of drugs simultaneously in one vessel. The idea is to develop a drug delivery system in which a single oral dosage unit comprises a capsule-in-a-capsule; two independent compartments form one dosage unit that can target incompatible drugs to different regions of the body. The outer capsule normally contains a liquid or semi-solid formulation with the inner capsule housing the more delicate powder formulation. The multi-layer aspect of the structure fosters sustained-, pulsed-, or delayed-release delivery.

In this exclusive *Drug Development & Delivery* report, liquid-filled and multi-phase capsule developers discuss how their formulation strategies have helped overcome solubility issues, reduce costs, and improve commercial viability. Participants include W. Stephen Faraci, PhD, Senior Director and Site Head, BioPharmaceutical R&D, Capsugel Product Development Center; Robbie Stewart, Encap Sales Director; Fred Miller, CEO, Innercap Technologies; Rampurna Prasad Gullapalli, PhD, Vice President of Drug Delivery Technologies at Pharmaceutics International Inc. (Pii); and Paul F. Skultety, PhD, Director, Pharmaceutical Development Services, Xcelience, LLC.

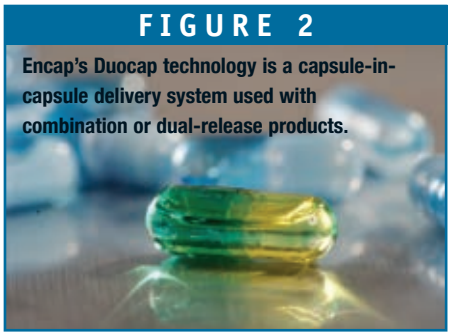
FIGURE 1

Capsugel's Licaps® two-piece capsules are designed to be sealed for secure containment of liquids and semi-solids without banding.

CAPSUGEL—SOLUTIONS FOR CHALLENGING COMPOUNDS

Discovering viable and profitable new drugs today often requires working with NCEs that are poorly water soluble. These NCEs require time-consuming experimentation and analysis to achieve satisfactory drug absorption from a solid oral dosage form, a challenge that can sometimes take years of development without yielding positive results. By formulating in lipid-based liquid or semi-solid formats, bioavailabilty and content uniformity may be improved. Formulating in liquid-based liquid or semi-solid formats is also a way to reformulate existing drugs to extend patent protection or create new line extensions for OTC drugs.

FIGURE 2



Encap's Duocap technology is a capsule-in-capsule delivery system used with combination or dual-release products.

To help clients achieve these goals, Capsugel Product Development Center, a leading global investment firm, created the Licaps® Drug Delivery System, a suite of products, services, and patented technologies for liquid formulations. These two-piece capsules for liquid and semi-solid formulations are available in both gelatin and HPMC (Hydroxypropyl Methylcellulose) capsules specially designed to be sealed for secure containment of liquids and semi-solids without banding.

A six-dimple design maintains uniform clearance between the cap and body around the entire capsule's circumference, ensuring uniform distribution of sealing fluid in the sealing zone. The body design acts as a primary seal barrier to reduce leakage before sealing.

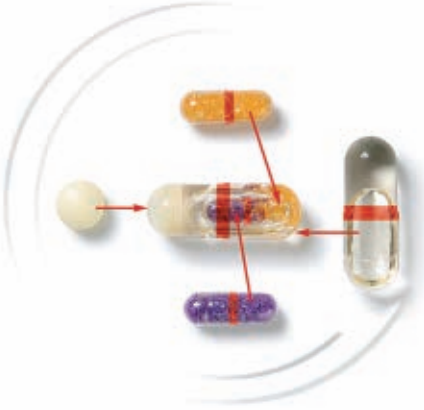
"We have an expertise in lipid formulations, in particular for poorly soluble compounds (BCS Class II). This involves using unique ternary diagrams to enhance stable microemulsion formulation, thus leading to better oral absorption," says Dr. Faraci.

Licaps capsules are used in Capsugel's R&D liquid filling and sealing machine and its commercial-scale sealing LEMS (Liquid Encapsulation Microspray Sealing) machine.

"Our lipid-based formulations provide enhanced oral absorption over traditional tableting when the compound has solubility issues," explains Dr. Faraci. "Our technology allows one to take a compound that has poor solubility and formulate it in such a way that we can increase oral bioavailability to a significant level, which may be the difference in the compound becoming a drug or not. The technology is not dependent on a specific therapeutic area and can be used for any compound that has absorption issues."

Capsugel sees itself not just as a capsule manufacturer, but also a drug delivery company, actively working on new technology platforms. Dr. Faraci says, "We believe our

FIGURE 3



INNERCAP's Multi-Phase Controlled-Release Combination Delivery System separates different physical phases.

work in lipid-based formulations and solid lipid microparticles will lead to enhanced bioavailability of poorly soluble compounds."

ENCAP–EXCLUSIVELY FOCUSED ON LIQUID-FILL HARD CAPSULES

The Pharmaceutical and Biotech industry appears to recognize that liquid-fill encapsulation is a well-established and proven method of drug delivery. It can provide many advantages over traditional oral drug formulations, such as tablets, powders, or pellets in capsules, particularly within early drug development. Encap Drug Delivery's pharmaceutical development business has tripled in size in the past 3 years as more drug formulators turn to liquid-fill hard capsules to address many issues, such as improvement of API solubility and bioavailability, reducing content uniformity variability, or poor API stability. In addition to these API challenges using liquid fill technology, drug developers are also using liquid-fill capsules as a fast and effective tool for early development. Phase I supplies can be produced very quickly, using minimal API quantities, making it a great way to quickly assess compounds in the clinic. Controlled, sustained, and multi-phase release profiles are all possible.

Encap has been involved with liquid-fill capsules for more than 20 years, specializing exclusively with liquid-fill hard capsules. In addition to providing contract development and commercial manufacturing services, Encap also has several proprietary technologies, including Duocap, a capsule-in-capsule delivery system used with combination or dual-release products; Abusolve, a range of formulations designed for preventing abuse of Opioid products; and Encode, designed for targeting drug delivery to the colon.

In the past 12 months, Encap has brought online a new facility dedicated to the manufacture of liquid-fill products that require high containment.

"Liquid fill has been of interest to companies developing highly potent, cytotoxic or cytostatic compounds as it can reduce containment or processing issues associated with manufacturing tablets or powders," explains Dr. Stewart. "Encap is the only company with a high containment facility dedicated to liquid-fill hard capsule products. In the past year, we have begun collaborations with six new clients who are using this facility."

Looking ahead, Dr. Stewart says that as the industry switches to biological molecules, not normally associated with oral drug delivery, Encap is now actively focused on developing several proprietary technologies related to the oral delivery of large molecules.

"Our pharmaceutical development business should help bring several new products to the market throughout the next 5 years."

INNERCAP–COMBINATION PRODUCTS IMPROVE CARE & REDUCE COSTS

Innercap Technologies, Inc. and its affiliate, Liquid Capsule Manufacturing LLC, have seen the level of interest and focus on liquid-filled two-piece hard-shell capsules increase throughout the past 5 years, says Mr. Miller. As a result, Innercap is seeing a lot of interest in its controlled-release multi-phase, multi-compartment, two-piece hard-shell capsules increase for combination products.

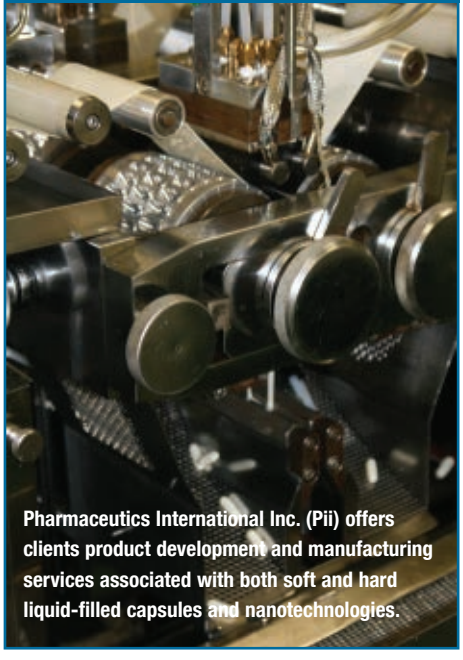
"This interest is to due to the fact that many actives in currently commercialized products contain a single or combination of soluble actives and are delivered as solid dosage forms," he explains. "As a greater number of poorly soluble or potent actives and biopharmaceuticals are formulated as liquids, it increases the possibilities for new combination products combined with soluble actives that are currently on the market as solid dosage forms. When these soluble actives products can be converted to combination products and combined with synergistic insoluble actives where the most viable option is to formulate these insoluble actives as liquids formulations, you end up with a product that requires a multi-phase, multi-compartment capsule to develop these types of advanced and unique products."

This patented delivery system also provides a life-cycle management option for successful products going forward. Innercap has focused its resources around research to support its core patented multi-phase multi-compartment delivery technology that makes difficult, if not otherwise impossible, combination products possible. Innercap has set up a new R&D and manufacturing facility with Liquid Capsule Manufacturing to work with potential licensees in developing new products and is working on potential combination products to license using the multi-phase, multi-compartment technology. The company is also working on projects that will show how the technology can protect oxygen- or moisture-sensitive compounds from oxidation or moisture by creating a barrier around the interior capsule.

"This novel use can benefit many biopharmaceuticals and sensitive APIs by protecting the active within the delivery system by using supporting actives as well as coatings," says Mr. Miller.

In March 2010, Innercap was granted its first US Patent for the multi-phase, multi-compartment technology. The delivery system can be used for numerous therapeutic areas, such as cardiovascular, oncology, neurology,

FIGURE 4



Pharmaceutics International Inc. (Pii) offers clients product development and manufacturing services associated with both soft and hard liquid-filled capsules and nanotechnologies.

infectious diseases, and psychiatric therapies.

"There are many therapeutic areas in which there are soluble APIs and synergistic insoluble actives that would benefit by using the multi-phase delivery system to provide the most advantageous pharmacokinetic profile for each active within the dosage form," explains Mr. Miller. "One example in the cardiovascular area would be the combination of a statin that is known as a soluble active with the poorly soluble active fenofibrate."

Innercap Technologies and Encap Drug Delivery have similar delivery systems that are used for different types of products. Innercap's NOVACAP delivery system has a granted patent for multi-phase multi-compartment combination capsule products whereas Encap's DUOCAP multi-phase multi-compartment delivery system has a granted patent for delivering a single active in different phases.

Mr. Miller is confident the Innercap delivery system will create an entirely new class of combination products and bring advanced therapies to market, which he says will be welcomed "by a healthcare system that is looking to increase patient outcomes and decrease costs." He continues, "Healthcare professionals and consumers are looking to combination products to decrease the pill burden associated with many therapies. As the demand for therapies that decrease healthcare costs increases, combinations products should also increase."

Pii–OPTIMIZING CLINICAL PROFILES & COMMERCIAL VALUE

As a CDMO, Pharmaceutics International Inc. (Pii) offers clients product development and manufacturing services associated with both soft and hard liquid-filled capsules and nanotechnologies. These technologies are being applied for NCEs, which are still in the investigational stage of development, and for developing generic formulations for currently marketed products. According to Dr. Gullapalli, each area has its own challenges and requirements.

"While NCEs require formulating dosage forms that can overcome the poor biopharmaceutical properties and attain higher bioavailability, generic formulations require mimicking the bioavailability of currently marketed products," he says. "Having access to multiple technologies enables us to better meet our clients' needs and provide them with comprehensive formulation services."

Though the liquid-filled capsule technology offers solutions to many challenges posed by molecules with less than optimal biopharmaceutical properties, its uniqueness also poses significant challenge from the client perspective.

"The technology is not as well understood as other dosage forms, such as tablets and capsules," Dr. Gullapalli explains. "Even in the case of Big Pharma, which tends to be very familiar with the technology, those companies use it as a final option as it requires outsourcing to an external CMO, and only few providers are available in the field with the experience and scientific expertise to develop a successfully product." Often considered a last resort, development time is constrained.

"We encourage our clients to consider the technology early, especially if the compound exhibits less than optimal biopharmaceutical properties. In the end, companies will save substantial amounts of development time, costs, and other resources from early conducting of bioavailability and bioequivalency studies related to change in the dosage form rather than at the later stages of the clinical program."

As part of its Drug Delivery Solutions program launched in 2009, Dr. Gullapalli stresses that Pii is dedicated to offering liquid-filled capsules as a technology for compounds with poor solubility, low melting point, or those susceptible to oxidation or UV degradation.

XCELIENCE, LLC–LIPID-BASED FORMULATIONS FOR SMALL MOLECULES

Liquid-fill technology is a good fit for compounds requiring low dosage strength, for those with challenging physical and chemical properties (poor bioavailability, low melting point, poor stability), or for those that naturally exist in liquid form. And, now more than ever, there is an increased demand for liquid-fill capsule dosage forms now that the technology for liquid fill in hard gelatin capsules has made this a more accessible and affordable option. Xcelience liquid-in-capsule services provide an approach that enables small-molecule developers to exploit the potential of lipid-based formulations to overcome poor aqueous solubility and improve compound bioavailability.

FIGURE 5

Xcelience's liquid-fill services use Capsugel's CFS 1200™ system for filling and sealing.

Relative to traditional dosage forms, liquid-in-capsule has the advantages of shortened development time, assisting in eliminating challenging API characteristics (such as poor flowability or taste) and helping to eliminate the potential for content uniformity issues. In addition, delivering the API as a solution usually helps to increase bioavailability, explains Dr. Skultety. The developed liquid formulation is filled into appropriately sized gelatin or HPMC capsules to provide a stable prototype formulation that accelerates development timelines to Phase I studies.

For manufacturing liquid-filled hard gelatin capsule formulations for clinical supplies, Xcelience uses Capsugel's CFS 1200™ with LEMS (Liquid Encapsulation Microspray Sealing) technology.

"This has definitely made liquid-filled formulations more accessible, driving down costs," explains Dr. Skultety. "In addition, hot-melt technology may be utilized, as an alternative to liquid-fill, as a means to improve stability, bioavailability, and provide controlled release, and we use CFS 1200 for this as well."

Dosing requirement obstacles for liquid fill may include low or high dosage strengths. For the former, Xcelience applies liquid-fill technology to ensure content uniformity. For the latter, lipid material is evaluated and selected to achieve the solubility necessary for the higher dosage strength.

In addition to the CFS 1200 encapsulation system, Xcelience recently added the MG Futura Capsule Filler and a high-speed, versatile encapsulator that enables powder dosing, pellet dosing, and over-encapsulation of existing drug products. ◆

COLONIC DELIVERY

Colonic Delivery of Metronidazole Tablets Using a Double-Coating Technique

By: Nitesh Shah, MPharm; Tejal Shah, MPharm, PhD; Avani Amin, MPharm, PhD

ABSTRACT

The aim of the present investigation was to develop colon-targeted drug delivery for metronidazole using a double-coating technique. In preparation, the core tablets of metronidazole were first coated with time-dependent polymethacrylate, Eudragit RS/RL 100, and then with pH-dependent polymethacrylates, Eudragit FS 30D. Before applying a double coat of polymethacrylate on a single-core tablet, each coat of polymethacrylate was checked individually for its effect of polymer concentration and coating level on in vitro drug release. The individual effect of each coat of Eudragit RS/RL and Eudragit FS resulted in a synergistic effect rather than a combination effect. The combination of Eudragit RL and FS resulted in a more sustained effect. Thus, a novel time- and pH-based drug delivery system for potential colonic delivery was developed using multiple coatings of polymethacrylates, and the present delivery system may be ideal for chronic treatment of Crohn's disease.

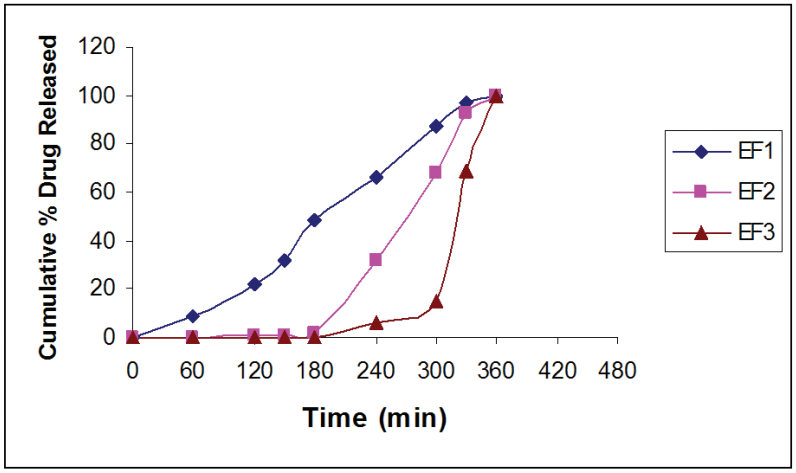
INTRODUCTION

In recent years, colonic drug delivery has gained increased importance for the treatment of local diseases of the colon, such as irritable bowel syndrome and inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis.[1]

The major function of the colon is to absorb water and electrolytes (each day up to 2000 ml of fluid enters the colon through the ileocecal valve). Although the absorption capacity in the human colon is lower than that in the small intestine (surface area is 0.3, 120 m^2, respectively), the residence time of formulations in the human colon is 2 to 3 days. This long colonic residence time provides a significant opportunity for the absorption of drugs.[2]

The basic challenge for designing oral colon-specific drug delivery is twofold: (1) robustness of dosage form to prevent drug release in the upper gastrointestinal regions and (2) sensitivity for the trigger mechanism to ensure prompt drug release in the colon. While the former is relatively simple to achieve, the difficulty comes in ensuring that drug release occurs promptly and completely once the dosage form arrives in the colon.[3] Such dosage forms have relied on a unique physiological feature of the colon to act as

FIGURE 1



Comparative Release Profile of Batches Enteric Coated With Eudragit FS30D

a trigger for drug release, and those investigated thus far include pH gradient, colonic bacterial enzymes, gastrointestinal transit time, and pressure arising from intestinal contractions.[4-10] Amongst the various approaches, the time- and pH-dependent systems are highly explored by researchers. A time-controlled release formulation for colon delivery is designed to release the active ingredient at a specified time after it passes through the pylorus of the stomach based on its residence time in the small intestine.[11,12] Therefore, the formulation might disintegrate in the small intestine when its residence time is longer than expected, and could be excreted out of the body when its residence time in the small and large intestine is shorter than expected. Therefore, the drug release from a time-controlled release formulation for colon delivery is strongly affected by its residence time in the intestines, decreasing its colon specificity. Enteric-coated systems are the most commonly used for colonic drug delivery, but the disadvantage of this system is that the pH difference between small intestine and colon is not very pronounced. These delivery systems do not allow reproducible drug release.[13,14] Recent investigations are focused to simultaneously exploit both these approaches, ie, site- and time-controlled drug delivery.[15]

Eudragit FS30D dissolves at a pH above 6.8. Thus, it can be used to prepare enteric-coated tablets. Eudragit RS100 and Eudragit RL100 are composed of poly (ethylacrylate-methylmethacrylate-trimethylammonioethyl methacrylate chloride) copolymers with ratio of 1:2:0.1. Both Eudragit RS100 and Eudragit RL100 are water-insoluble polymers, and the drug delivery systems prepared from it show pH-independent drug release. They are insoluble at any physiological pH.[16]

The objective of this study was to prepare colonic tablets of metronidazole using a combination of time- and pH-dependent polymethacrylate polymers that offer protection to the drug until it leaves the small intestine (provided by the outer coat of pH-dependent polymer, Eudragit FS30D) and avoid major drug release in small intestine (provided by inner pH-independent polymer, Eudragit RS100/Eudragit RL100). Before combining the two coats on a single tablet, each enteric coat (Eudragit FS30D) and time-dependent coat (Eudragit RS/RL) was checked individually for its effect on drug release.

MATERIALS & METHODS

Metronidazole was obtained as a gift sample from J.B. Chemicals (Ankleshwar, India). Eudragit FS30D, Eudragit RS100, and Eudragit RL100 were generously gifted by Evonik Pharma Polymers (Darmstadt, Germany). Plasdone K90 was gifted from Anshul Agencies (Mumbai, India). Crosscarmellose Sodium was obtained as a gift sample from Gujarat Microwax Pvt. Ltd. (Ahmedabad, India). Polyvinyl Pyrollidone K30 (PVP K30) and lactose were purchased from S.D. Fine-Chem Ltd. (Mumbai, India) and CDH (New Delhi, India), respectively. Double distilled water was used throughout the study, and all other chemicals used were of analytical reagent grade.

Preparation of Core Tablets of Metronidazole

Core tablets of metronidazole (200 mg) were prepared via the wet granulation technique. Solution of PVP K30 and PVP K90 (1:1 ratio) in iso-propyl-alcohol was used as a granulating agent. Lactose was used as a diluent. Crosscarmellose sodium (10%) was used as a super disintegrant. Talc (2%) and magnesium stearate (1%) were used as glidant and anti-adherant, respectively. Tablets were prepared using a rotary tablet machine (Rimek, Karnavati Engineering Pvt. Ltd.) using a 11-mm concave punch. Total tablet weight was 400 mg. The tablets had a hardness of 6 kg/cm^2 and disintegration time of 4 mins.

TABLE 1

Eudragit RS-Coated Tablets

Polymer Solution Concentration	% Weight Gain (Coating Level)				
10%	RS1	RS2	RS3	RS4	RS5
	10	12.5	15	17.5	20
15%	RS6		RS7	RS8	
	10		12.5	15	

Eudragit RL-Coated Tablets

Polymer Solution Concentration	% Weight Gain (Coating Level)				
10%	RL1	RL2	RL3	RL4	RL5
	10	12.5	15	17.5	20
15%	RL6		RL7	RL8	
	10		12.5	15	

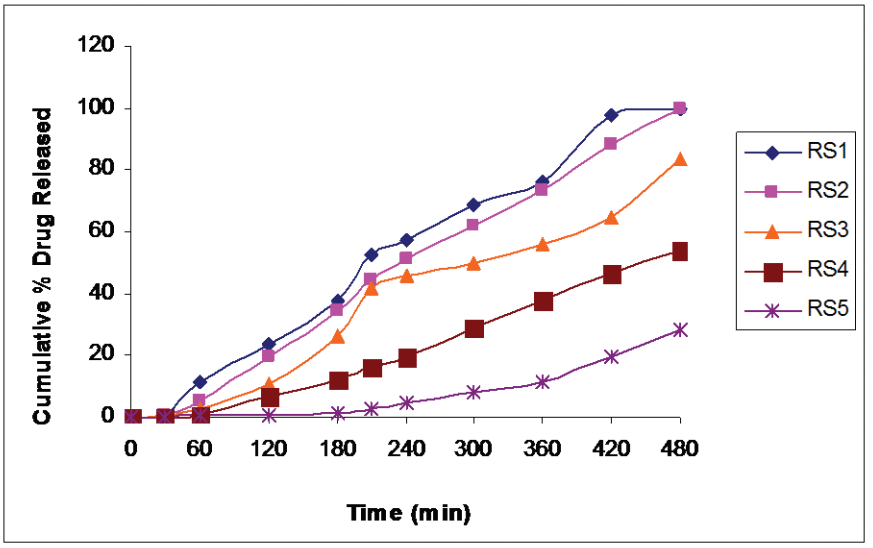
Core Tablets Coated With Eudragit RS/RL

Preparation of Coating Solution & Coating of Core Tablets

Eudragit FS30D is a ready-made dispersion; it was used after diluting it to 60%. The coating solution consisted of castor oil (10% of polymer weight) as a plasticizer, talc (0.1% w/v) as antiadherant, titanium dioxide as opacifier (0.05 % w/v), and coloring agent. The solution was stirred for 15 mins.

Eudragit RS100 and RL100 (polymers) were dissolved in methylene chloride using a magnetic stirrer. Following complete solubilization of polymer, 15% of polymer weight of castor oil (plasticizer) was added to the Eudragit RS/RL coating solution. Talc, titanium dioxide, and coloring agent were also mixed in the solution in the aforementioned concentration and manner. The solution was

FIGURE 2



Effect of Coating Level at 10% Eudragit RS Concentration

stirred for 15 mins. Eudragit RS and RL solution were tried at two different concentration levels, 10% w/v and 15% w/v, to check the effect of polymer concentration on drug release.

In the present study, the tablets were coated using the dip-coating method. The coated tablets were air dried for 15 mins at room temperature, after which they were cured for 30 mins at 40°C in a hot air oven (Sun Instruments Pvt. Ltd., Ahmedabad).

Preparation of Enteric-Coated, Time-Dependent Coated & Colonic Tablets of Metronidazole

The aim of the present work was to prepare colonic tablets of metronidazole using a double-coating technique. Thus, the enteric coat of Eudragit FS30D, and the time-dependent coat of Eudragit RS/RL100 were optimized individually by applying them separately on core tablets. Colonic tablets were prepared by coating the core tablets initially with Eudragit RS/RL. The coat was allowed to dry for 30 mins, then the second coat of Eudragit FS30D was provided. Both coats of Eudragit FS30D and RS/RL were optimized for polymer concentration and coating level (coating thickness).

In Vitro Drug-Release Studies

In vitro drug-release studies were carried out using a USP XXIII dissolution test apparatus Type II, paddle apparatus (100 rpm, 37°C ± 0.5°C). The in vitro release study for the enteric-coated tablets was carried out by keeping the tablets for 2 hrs in 0.1 N HCl (900 ml), ie, simulated gastric fluid (SGF) solution. The dissolution medium was then replaced with pH 7.4 phosphate buffer solution (900 ml), ie, simulated intestinal fluid (SIF) solution, and tested for 3 hrs.

The time-dependent coated tablets were evaluated by exposing them to 900-ml SIF for 3 hrs, which was later replaced by pH 6.8 phosphate buffer solution (900 ml), simulated colonic fluid (SCF) solution, and tested for release for an additional 3 hrs.

The colonic tablets containing enteric- and time-dependent coats were evaluated by keeping them in 900-ml SGF for 2 hrs, which was then replaced with 900-ml SIF, wherein it was kept for 3 hrs, and lastly, SIF was replaced with 900-ml SCF wherein it was kept for 3 hrs. The drug release at different time intervals was analyzed via a UV double-beam spectrophotometer (Electrolab TDT-06 T) at 276.5 nm in SGF, 319.4 nm in SIF, and 320.4 nm in SCF. Each test was performed in triplicate.

RESULTS & DISCUSSION

Optimization of Enteric Coat (Eudragit FS)

The tablets coated using undiluted readymade dispersion of Eudragit FS had a very high viscosity, resulting in the formation of hard and brittle films. Thus, a 60% diluted form of the dispersion was used for enteric coating.

Batch EF1 (5% coating level) showed premature drug release due to low coat thickness. Batch EF2 (10% coating level) and EF3 (15% coating level) protected the drug release in SGF (Figure 1). The coats dissolved after exposing them to alkaline pH due to interaction of anionic groups of Eudragit

TABLE 2

Combination of Eudragit RS & Eudragit FS				
Polymer Solution Concentration	% Weight gain (Coating Level)			
	RSFS1	RSFS2	RSFS3	RSFS4
10% Eudragit RS	15	15	10	5
60% Eudragit FS	10	7.5	10	10

Combination of Eudragit RL & Eudragit FS					
Polymer Solution Concentration	% Weight gain (Coating Level)				
	RLFS1	RLFS2	RLFS3	RLFS4	RLFS5
10% Eudragit RS	15	12.5	10	7.5	5
60% Eudragit FS	10	10	10	10	10

Colonic Tablets Prepared Using Eudragit RS/RL & Eudragit FS

FS30D with simulated intestinal fluids. This fact was reported by Gupta et al.17 Here, batch EF2 and EF3 can be considered promising batches as they kept drug release below 2% for 2 hrs in SGF.

Drug release from the enteric-coated systems occurs due to dissolution of coat at neutral or alkaline pH. In fact, with this system, the drug delivery to the terminal part of the small intestine can be ensured as a majority of the drug is released between the fourth and fifth hour for batch EF3. However, release could not be sustained for a long enough time to reach the colon. Thus, there was a need for the addition of a time-dependent polymer to this system, which could prevent major drug release in SIF as the basic aim is to deliver a majority of drug to the colon.

Optimization of Time-Dependent Coat (Eudragit RS/RL)

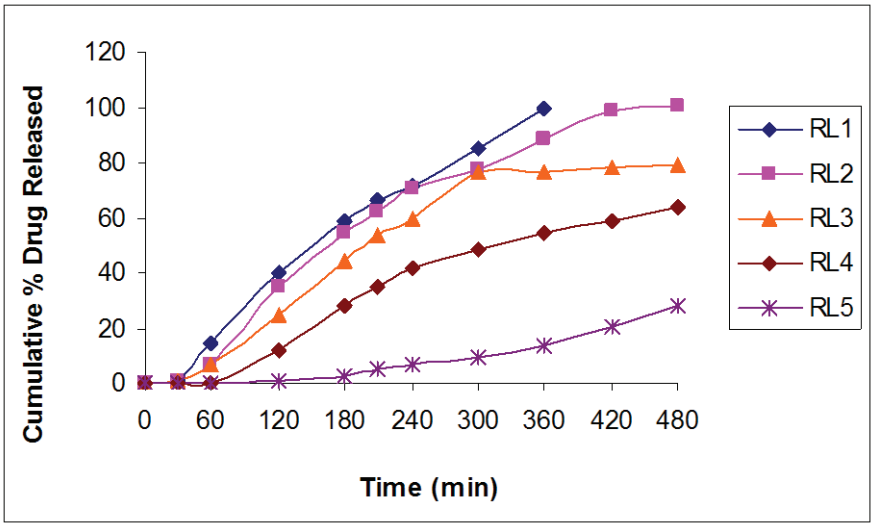
As pH-dependent (enteric coated) tablets alone were unable to deliver drug to the colon, an additional time-dependent coat was incorporated in between the core tablet and enteric coat. Acrylic copolymers have been used not only as an enteric coating material but also as a sustained-release coating polymer in the pharmaceutical industry due to their biological safety. Because Eudragit RS and Eudragit RL are insoluble at all physiological pH, they were used as time-dependent coating materials. Both polymers were tested individually, as coats, for their effect on drug release.

Both Eudragit RS and Eudragit RL were tried at two different polymer concentrations (10% w/v and 15% w/v) of coating solution and were then coated at different coating levels as shown in Table 1.

Effect of Coating Level of Eudragit RS/RL

Upon increasing the coating level, the drug release was retarded. The batches that showed less than 10% release at the end of the third hour, which is intestinal emptying time, were considered to be the promising batches. At 10% polymer concentration of Eudragit RS, only batches RS4 and RS5 met the criteria (Figure 2), whereas in the case of Eudragit RL, only batch RL5 at 20% coating level prevented drug release in SIF for a lag phase of 3 hrs (Figure 3).

FIGURE 3



Effect of Coating Level at 10% Eudragit RL Concentration

With a view to reduce coating thickness, a higher polymer concentration of 15% was tried at three different coating levels (10%, 12.5%, and 15%) for both Eudragit RS (RS6 to RS8) and RL (RL6 to RL8). As anticipated, the drug release at the higher coating levels was slow for batches containing 15% polymer concentration. At the end of 3 hrs, all the batches of Eudragit RS and RL (RS6 to RS8 and RL6 to RL8) failed to keep drug release below 10% as the coating levels were low, and it was also found (unexpectedly) that the sustained effect was prolonged, ie, 100% of the drug did not release even following 8 hrs. Eudragit RS and RL provided successful time dependency to the drug release at higher coating levels. Eudragit RS and RL contain quaternary ammonium groups in their chemical structure, which play an important role in controlling drug release because they relate to water uptake followed by swelling of Eudragit RS and RL.[18] The active ingredients are gradually dissolved by penetrating dissolution media, and release is primarily diffusion controlled.[19] The release rate was slower at higher coating levels because of the increased diffusion path-length and tortuosity at higher coating levels. Moreover, the coating layer of all the tablets containing Eudragit RS and RL did not disintegrate by the end of the dissolution run, indicating an apparent intactness of the coat. The drug release can be attributed from the openings of the coating layer visible at the end of dissolution study.

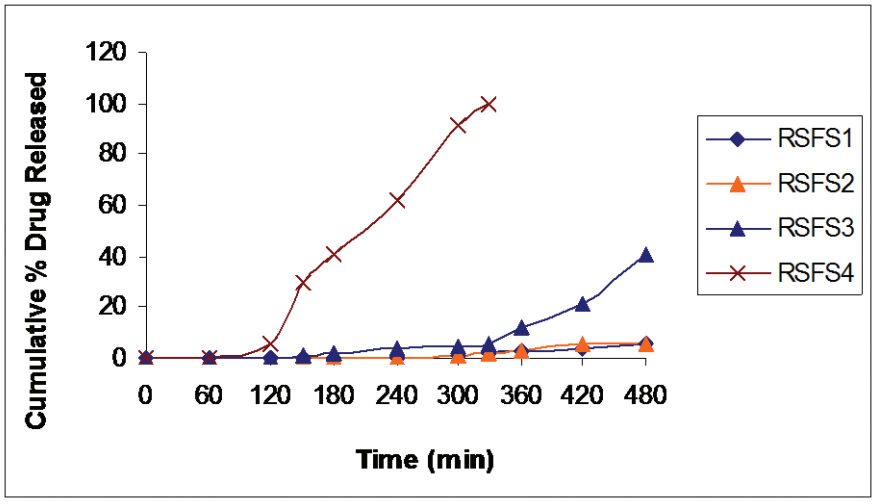
Effect of Polymer Concentration of Eudragit RS/RL

As the polymer concentration increases, the films become more rigid, and the coating solutions become more viscous. The effect of polymer concentration can be seen clearly by keeping the coating level the same. Batch RS1 and RS6, with similar coating levels of 10%, can be compared. In the case of batch RS1, 100% release is found at the end of the eighth hour, whereas for batch RS6, only 84% of drug is released at the end of the eighth hour. This indicates that polymer concentration plays a vital role in retarding drug release.

Selection of Promising Batches Prepared Using Eudragit RS/RL 100

At both 10% and 15% polymer concentrations (RS1 to RS8, RL1 to RL8), drug release decreases as the coating level increases. Tablets coated with Eudragit RL

FIGURE 4



Colonic Tablets Prepared Using a Combination of Eudragit RS & Eudragit FS

(10% polymer concentration, 17.5% coating level) showed comparatively faster release than Eudragit RS. For example, batch RS4 showed 53% drug release at the end of the eighth hour, whereas at similar polymer concentration and coating level, batch RL4 showed 63% drug release at the end of the eighth hour. However, as the coating level increased, the effect of the type of polymer used almost vanished because both RS5 and RL5 coated at 20% coating levels showed a 28% release at the end of the eighth hour. Drug release at lower coating levels was faster using Eudragit RL than Eudragit RS due to double the number of hydrophilic ammonium groups in Eudragit RL.[20,21]

From all the batches using Eudragit RS and RL (RS1 to RS8, RL1 to RL8), batch RS4, RS5, and RL5 can be considered promising batches as the drug release is below 10% in SIF.

Colonic Tablets of Metronidazole

From the individual results of Eudragit RS/RL, it was found that a 10% polymer concentration of Eudragit RS/RL was sufficient for protecting drug release in SGF and SIF. Eudragit FS, which is supplied as a ready-made dispersion, was diluted to 60% in preliminary trials, where it gave satisfactory results. It was speculated that Eudragit RS at 15% coating levels was necessary to prevent drug release in SIF. Thus initially, only coating levels of Eudragit FS was changed in this combination approach (Table 2).

When Eudragit RS was taken at a fixed coating level of 15%, and Eudragit FS was varied from 10% (batch RSFS1) to 7.5% (batch RSFS2), drug release was sustained to an extent that there was only about 5% drug release after the lag time of 8 hrs.

In order to decrease the delay in drug release in batch RSFS3 and RSFS4, Eudragit RS coating level was decreased to 10% and 5%, respectively, and Eudragit FS coating level was kept fixed to 10%. Batch RSFS3 showed about a 40% release after the lag time of 8 hrs, whereas batch RSFS4 showed 100% drug release within 4 hrs (Figure 4). The reason for 100% release at a 5% coating level of RS can be attributed to poor film-forming properties at such low levels.

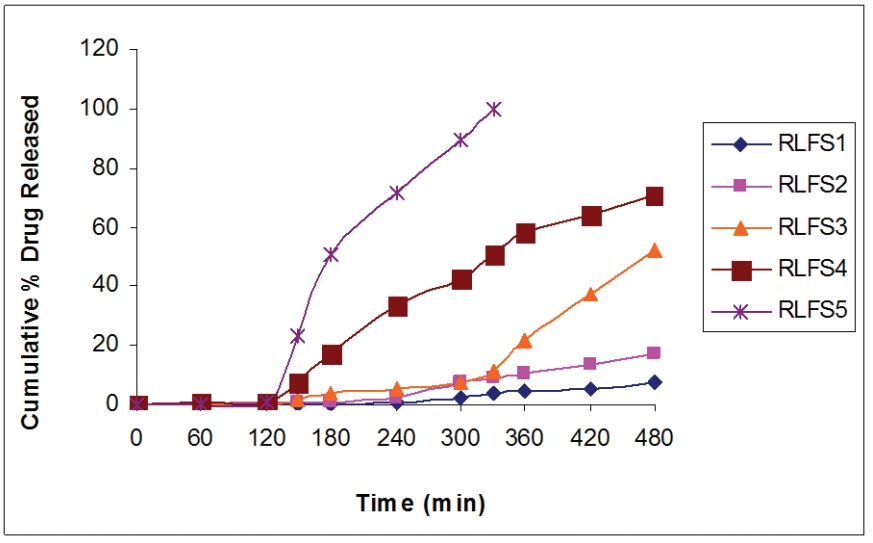
From the aforementioned speculations, it was concluded that coating levels of Eudragit RS played a major role in delaying drug release rather than Eudragit FS. From this combination, it can be concluded that even at low coating levels of 10% for both Eudragit RS and FS, drug release was excessively delayed. In order to decrease drug delay, Eudragit RS was replaced with a more permeable polymer, Eudragit RL. Various combinations of Eudragit RL with Eudragit FS are shown in Table 2.

All the batches (RLFS1 to RLFS4) were able to withstand the acidic condition of the stomach. Here, lag time to reach the colon is taken as 5 hrs. Batches RLFS1, RLFS2, and RLFS3 showed only 7%, 17%, and 52% release, respectively, even after 3 hrs in SCF (Figure 5). Batches RLFS4 and RLFS5 showed excessive release (> 40%) in SIF. Thus, they are unsuitable for colonic delivery as they give premature drug release.

The coats did not dissolve even at the end of the dissolution run when Eudragit FS was combined with Eudragit RS and Eudragit RL.

Apparent intactness of most of the combinations of Eudragit FS with Eudragit RS

FIGURE 5



Colonic Tablets Prepared Using a Combination of Eudragit RL & Eudragit FS

and Eudragit RL (batches RSFS1 to RSFS4 and batches RLFS1 to RLFS5) was probably due to possible ionic interaction between cationic ammonia groups of Eudragit RL with carboxylic groups of Eudragit FS, which protects anionic groups of Eudragit FS from rapid ionization retarding pH dependency of Eudragit FS.[20,21]

Thus, amongst these batches, RLFS3 coated with 10% Eudragit RL and 60% Eudragit FS30D at a 10% coating level can be considered the best batch releasing drug in a controlled fashion in colon.

CONCLUSION

A novel time- and pH-based drug delivery system for potential colonic delivery was developed using multiple coatings of polymethacrylates. The delivery system might prove successful for delivery of drug to the colon in a sustained-release fashion. Because Crohn's disease needs a long-term treatment with metronidazole, colonic tablets of metronidazole prepared using Eudragit RL as a primary coat and Eudragit FS as a secondary coat can be used for chronic treatment of Crohn's disease.

For successful colonic delivery, any possible change in the residence time of dosage forms in the GI tract of a patient suffering from IBD or Crohn's disease must also be borne in mind. The delivery system developed in this study will not be seriously affected by an increase or a decrease in the residence time because the outer coat is pH-dependent and not time-dependent. Changes in pH values in the colon will not prevent drug delivery because the pH-dependent polymethacrylate will dissolve at intestinal pH, and when the delivery system reaches the colon, the pH-independent coat governs drug release from the delivery system.

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BIOGRAPHIES

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DRUG DELIVERY Executive

DBV TECHNOLOGIES: PIONEERING THE SAFE DESENSITIZATION OF PATIENTS SUFFERING FROM DANGEROUS FOOD ALLERGIES

Pierre-Henri Benhamou, MD

Co-Founder & CEO

DBV Technologies

The goal of DBV Technologies is to make food allergy therapy a simple pharmaceutical treatment. DBV Technologies is focused on using a patient's own skin to solicit a desired immune system reaction, thus avoiding the risk of life-threatening anaphylactic reactions. Its VIASKIN® platform exposes a controlled quantity of a given allergen to the skin of the patient. The skin then naturally prevents the allergen from entering the bloodstream, making this a safe therapy. DBV's strategy is to focus on peanut and milk allergies. These products have already been tested on patients and make possible a $2-billion revenue opportunity for DBV Technologies. The company's initial commercialization effort is VIASKIN Peanut, whose development is supported by the NIH-funded Consortium of Food Allergy Research (CoFAR) and some of the most recognized opinion leaders for peanut allergy in the US. Drug Development & Delivery recently interviewed Pierre-Henri Benhamou, MD, Co-Founder & CEO of DBV Technologies, to discuss the VIASKIN platform and how it will whet the appetite of Big Pharma to lead an entirely new pharma franchise as big as statins or vaccines.

"We believe our VIASKIN® platform will stimulate the interest of the Pharma industry to build an entirely new franchise - a new paradigm in the treatment of allergy, even the most severe food allergies, bringing to patients a non-invasive and safe approach in specific immunotherapy. Pharma companies can now enter this multi-billion-dollar market, where there is no significant competition."

Q: What is VIASKIN and how is it a platform for allergy-immunotherapy?

A: The safe immunotherapy of patients suffering from dangerous food allergies has not been possible in clinical practice until now, due to the high risk of anaphylactic reactions. DBV Technologies has developed the VIASKIN epicutaneous delivery system, a technology platform designed to safely desensitize children and adults who have allergies. DBV is especially/currently involved in food allergies. The breakthrough and patented design of VIASKIN presents an allergen onto intact skin via a skin patch while significantly reducing the risk of the allergen's free passage into the bloodstream. VIASKIN thus safely triggers the desired immune reaction via specific immune cells so the body can gradually become desensitized to the allergen - while avoiding the risk of a life-threatening anaphylactic reaction.

Q: Why is DBV Technologies focused on food allergies?

A: Allergy is a growing disease, and food allergies represent the segment where life can be directly threatened - but no treatment is available. Until now, avoidance of the culprit food has been the primary acceptable solution. Treatment of food allergies is a significant worldwide unmet medical need. Indeed, there are 12 million food-allergic people in the US alone, and incidence of peanut allergy has doubled throughout the past 5 years in children. Because there are no treatments for food allergies, many children and their families live with the constant fear of ingesting a life-threatening food.

Q: How is DBV's approach unique?

A: Allergen-specific immunotherapy is the major strategy that treats the underlying cause of an allergic disorder. However, the conventional approaches of specific immunotherapy, using subcutaneous administrations, are associated with high risk of systemic life-threatening allergic reactions, such as anaphylaxis, and their use in food allergy is therefore limited. DBV Technologies is the only company in the world whose products are designed to epicutaneously deliver an allergen via a skin patch without any specific preparation of the skin. This process allows the allergen to reach directly the specific immune system through the wide immune network of the skin. DBV's proprietary skin patch technology, VIASKIN, involves maintaining an allergen on the intact skin of an allergic subject for repeated and prolonged periods in order to achieve clinical desensitization.

Q: How does your VIASKIN platform differ from conventional approaches to desensitization?

A: The goal of desensitization is to increase the amount of allergen the patient can eat or breathe without any symptom. Ultimately, the patient could become tolerant to the allergen and live normally. Conventional immunotherapy in the form of drops, pills, or injections (used for airborne allergens, such as pollens, and venom, such as bee stings) consists of exposing a patient to a controlled amount of allergen; but these conventional treatments are too dangerous for desensitizing food-allergic patients because their mechanism of delivery requires entering the bloodstream. A novel technology combining safety and efficacy is desperately needed by food allergists and patients. When the VIASKIN patch containing a specifically designed protein extract is applied on the skin of a patient with an IgE-mediated allergy, such as peanuts or milk, the allergens are deposited locally on the intact skin, ie, no specific preparation of the skin is needed before the application of the VIASKIN. Proteins do not pass the intact skin and do not reach the bloodstream, but are captured locally by the skin's immuno-competent cells, the Langerhans cells. These specialized cells, particularly efficacious in inducing or regulating immunity, uptake protein allergen and migrate to lymph nodes where they trigger the modulations of the immune responses. This epicutaneous exposure is non-invasive and thereby significantly reduces the risk of anaphylaxis. Epicutaneous delivery is also visually monitored: if necessary, its application can be simply halted with the instant removal of the VIASKIN patch containing the offending allergen. The VIASKIN patch is designed to be easily and painlessly applied by healthcare professionals and by patients or their parents/caregivers at home, which facilitates compliance with the treatment.

Q: Is there clinical data that suggests VIASKIN is safe and effective?

A: Results of a pilot study of VIASKIN that were published in a recent issue of the *Journal of Allergy and Clinical Immunology* opened a new path: patients severely allergic to cow's milk were able to ingest 10 to 600 times more milk after 3 months of VIASKIN treatment, whereas in the placebo-treated patients group, almost nothing changed. DBV Technologies is the only company whose products are designed to deliver an allergen via an epicutaneous patch to safely diagnose

and treat food allergies. DBV is developing two therapeutic products. Our first product in development, VIASKIN Peanut, is the first desensitization product for peanut allergy, a life-threatening and lifelong food allergy that is a major unmet medical need and thus an important healthcare concern. An IND has been granted to DBV by the FDA, and a safety 1b clinical study is underway at five select centers in the US. Additionally, the AFSAPPS in France has approved a pilot efficacy study sponsored by the AP/HP. Finally, the NIH allocated to the CoFAR a grant that will include a clinical study conducted with VIASKIN Peanut in the US.

Our second product in development, VIASKIN Milk, is specifically designed to treat patients with cow's milk protein allergy (CMPA), the most common food allergy in infants and young children. A pilot clinical study has been successfully completed in France.

Q: What is the mechanism of action for VIASKIN?

A: By contrast to conventional desensitization methods, such as drops, pills, or injections, which are too dangerous because of the risk of systemic allergen exposure, VIASKIN is non-invasive. VIASKIN creates an occlusive chamber on the skin that rapidly generates moisture and releases the allergens from the support onto the skin, allowing adequate diffusion of the proteins toward the more superficial layers of the skin without any passive passage through the skin, thus avoiding a systemic delivery. The allergen is captured by the skin resident specialized immune cells, the Langerhans cells. In preclinical studies, it has been shown that the capture of proteins activates these Langerhans cells and prods them to migrate to the afferent lymph nodes where they can activate specific immune responses able to modulate the inappropriate response against allergen and so start the tolerance process.

Q: What can your VIASKIN delivery platform offer the pharmaceutical industry?

A: We have developed a true pharmaceutical approach to allergy. DBV's VIASKIN technology is a disruptive platform in the treatment of allergy: it uses the skin route in a very unique way. This opens new possibilities for allergy treatment - in the short-term, the "safe" treatment for food allergy and a +$2-billion opportunity and in the medium-term, making mass desensitization as prevalent as vaccination is to infections in order to eradicate most atopic diseases like asthma and eczema. Every detail in DBV's work is focused on developing a business that is "pharma" compatible, ie, a business that can either be marketed and operated in partnership or acquired by large pharma companies.

Q: Why should the pharmaceutical industry be interested in DBV's manufacturing technologies at this time?

A: VIASKIN is a unique technology platform ready for mass production and well-protected by numerous patents. Although elegant in its concept, VIASKIN requires a very unique process technology to control the small amounts of allergen administered. DBV Technologies has developed and patented two proprietary manufacturing processes able to fix active dry compounds onto a polymeric backing film by electrostatic forces alone - (1) Static Powder and (2) Electrospray Deposit. DBV's technology incorporates many technology components, including its Electrospray Deposit Technology, a very precise means of layering a controlled solution of the allergen on the patch so that it is ultimately dry and stable. The US-FDA has reviewed our Electrospray Deposit Technology and has been satisfied with it to grant DBV an IND for clinical use in the US. The clinical equipment is pharmaceutically qualified and can be operated easily in a GMP environment. Our patented technology is adapted for large-scale production.

Q: How does DBV's Static Powder manufacturing process work?

A: DBV's novel Static Powder manufacturing process allows for the precise deposition of powdered compounds onto the polymeric backing of delivery systems, such as VIASKIN. The Static Powder manufacturing process creates a suspension of particles that are attracted and adhere to the polymeric backing film, resulting in a thin and uniform layer of powder. Bound to the backing of the patch

by electrostatic forces, these particles remain active as long as the delivery system is kept under dry conditions, but are easily released when the device is applied on the skin. Static Powder fits particularly for compounds that can be deposited onto polymeric backing films without any formulation. The only preparation is a fine grinding of the compound in order to get small particles. There are four critically important benefits of DBV's Static Powder manufacturing process: (1) there is no intermediate liquid formulation, as our Static Powder process fits with many active powdered compounds; (2) the active agent is deposited homogenously; (3) the whole localized dose is available to the skin; and (4) our process permits the deposit of chemical and biological substances alike.

Q: How does DBV's Electrospray Deposit manufacturing process work?

A: DBV's novel Electrospray Deposit is a manufacturing process that produces dry deposits of substances from liquid formulations. DBV Technologies has developed a pharmaceutical multi-nozzle production tool to deposit a mass ranging from a few to several hundred micrograms per cm2 to be deposited onto a wide variety of raw materials, such as backings, films, and glue. In adapted formulation, both chemical and biological substances are able to be deposited. Our proprietary manufacturing process is ideal for cutaneous devices requiring an immediate release of an active ingredient. Deposits can be either a spot or a homogenous layer. There are five critically important benefits of our Electrospray Deposit process: (1) the active agent is deposited homogenously; (2) accuracy of the deposit's mass is high - from 0 to 400 ng/cm2; (3) the process permits flexibility of the size and the mass of the deposit; (4) there is instant drying of the deposit; and (5) the deposit is highly soluble.

Q: Can you tell us more about you and how you started DBV Technologies?

A: After studying medicine in Paris, I graduated with a medical degree in Pediatrics and went on to specialize in pediatric gastroenterology. I have held a number of senior clinical positions, including Senior Consultant at St. Vincent de Paul Hospital in Paris. In 1989, I founded the first Pediatric Center for Digestive Disease in the Paris area. I also founded a clinic for digestive diseases in Pediatrics with Dr. PY Vannerom. I was extremely fortunate to receive the Altran Foundation Prize for Innovation in 2003 for my work on the development of patch tests for the diagnosis of cow's milk allergy.

Food allergies can cause death. It has been frustrating to me as a medical doctor and pediatrician that the safe desensitization of food-allergic children and adults has not been possible in clinical practice, until now. The reason for that is simple: conventional treatment methods, such as injections, drops, and pills, get into the bloodstream and may cause a systemic, life-threatening anaphylactic reaction in food-allergic people. As a pediatrician involved in gastroenterology and food allergy, I was very concerned by the absence of treatment for the children suffering from severe food allergy. I was especially obsessed by the consequences on their health and social life as well as the parents' difficulties for managing the daily risk of systemic reaction and their incredible demand for a safe treatment.

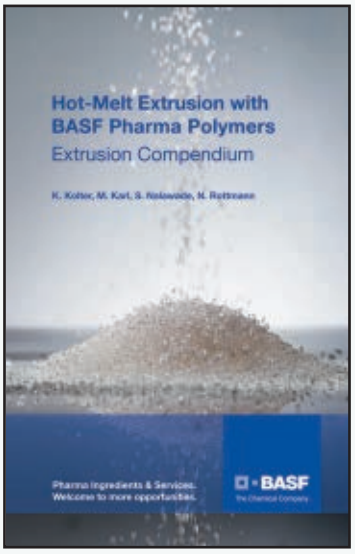
Along with my Co-Founders (Professor Christophe Dupont, MD, PhD, Head of Pediatric Gastroenterology Dept., Hôpital Necker, Paris, who also serves as Chairman of the DBV scientific board; and Bertrand Dupont, DBV's Chief Technology Officer) we have invented a very special skin patch technology that enables the body to safely develop immunity against a particular allergen, such as peanut or milk, while preventing the allergen from getting into the patient's bloodstream. We hope that when our products receive regulatory approvals that the positive impact on the lives of millions of food-allergic children and adults will be greatly enhanced and safeguarded. And if we can gain the support of the Pharmaceutical industry, the clinical benefits will be enormous. ◆

Technology & Services Showcase

Performance Materials

Avantor Performance Materials renamed its Mallinckrodt® Chemicals product line Macron™ Chemicals, effective March 7, 2011. The name change does not involve any product or manufacturing changes. The Macron Chemicals product line, identical to the previous Mallinckrodt line, includes high-purity solvents, acids, salts, minerals, and sugars. Macron brand products are produced in the same facilities under the same manufacturing processes, and share the same product numbers, names, and code numbers as the previous Mallinckrodt brand products. Avantor products have a legacy of safety and trust, with a 140-year tradition for delivering the highest standards of quality, purity, and consistency. Today, Macron Chemical's focus is on providing products for cGMP pharmaceutical production and everyday laboratory use in environmental testing, university research, and industrial manufacturing. For more information visit Avantor Performance Materials at **www.avantormaterials.com/macron-DDD**.

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**.

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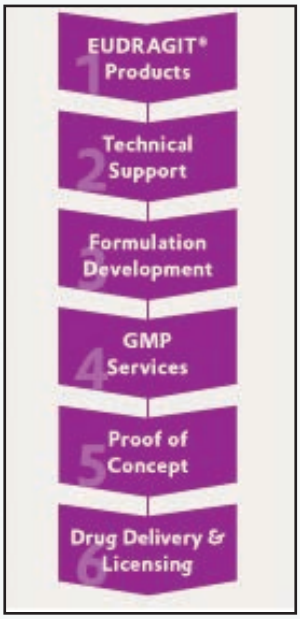
Pharma Polymers



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Technology & Services Showcase

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Recent Therapeutic Advances Targeting Toll-Like Receptors

By: Alcide Barberis, PhD

Introduction

Toll-like Receptors (TLRs) are key players in the innate immune system and are a major class of proteins that activate immune cell responses in the presence of microbial infections. They have been known since the 1990s and as more has been discovered about them, it has become apparent that they would make viable therapeutic targets for a whole range of diseases. There are already several agonists or antagonists of TLRs that are currently under development for the treatment of a broad variety of illnesses and diseases. The following will provide an overview of the products under development as well as the main functions of TLRs and their relevance to the treatment of, for example, infection, cancer, and autoimmune diseases.

What Are TLRs?

Throughout the past decade, there has been a growing interest in targeting TLRs for therapeutic purposes in the prevention and treatment of cancer and autoimmune diseases. TLRs are a major class of proteins that play a key role in the innate immune system by activating immune cell responses in the presence of microbial infections.

TLRs are a type of pattern recognition receptor, which recognize configurations of molecules typically associated with microbes. These are known as pathogen-associated molecular patterns (PAMPs) or microbe-associated molecular patterns (MAMPs).

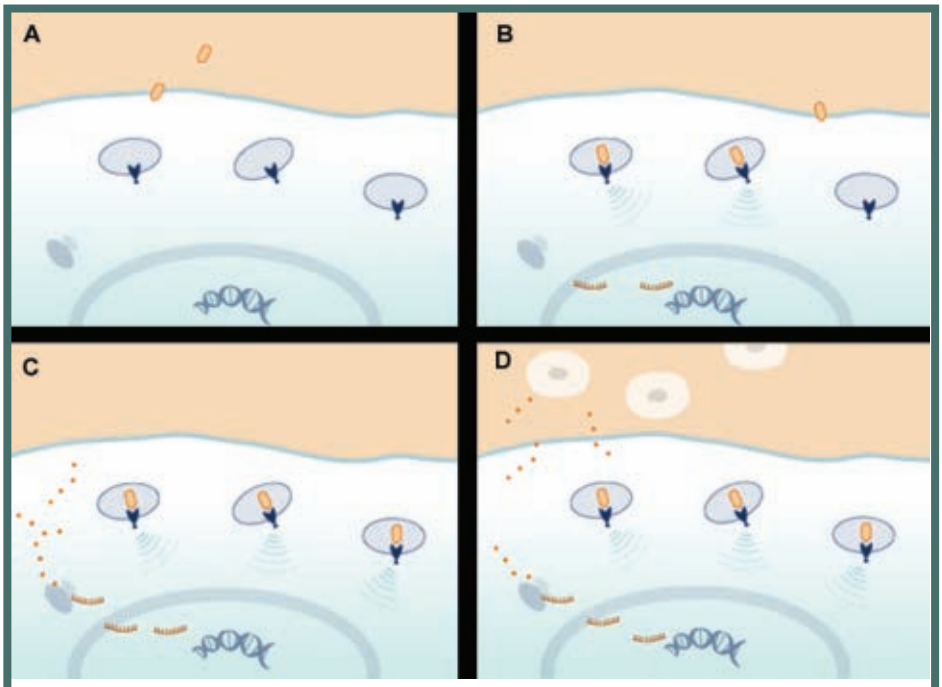

Figure 1. TLR Mechanism (A) Small molecule drug penetrates the plasma membrane of the cell (or is endocytosed by the cell) and then the endosome membrane. (B) The drug binds to TLR7 and activates a cell signalling process to the nucleus, which stimulates transcription of cytokine genes in the genomic DNA. (C) Large numbers of cytokines are produced continually. (D) Cytokines exit the cell and attract pro-inflammatory cells. Pro-inflammatory cells induce an immune response that can eliminate cancer cells and/or infected cells.

Pathogen-encoded TLR ligands fall into three broad categories: lipids and lipopeptides (TLR1, TLR2, TLR4, TLR6), proteins (TLR5), and nucleic acids (TLR3, TLR7, TLR8, TLR9).[3] Pathogen recognition via TLRs serves three distinct functions:

- Sensing the presence and type of the pathogen
- Provoking an immediate anti-pathogen response
- Stimulating the development of long-lasting adaptive response with effect or functions appropriate to the type of pathogen.[3]

They are able to recognize any microbe, regardless of its degree of pathogenicity; it is this ability to initiate and generate inflammation that makes TLRs attractive therapeutic targets.

Initial discoveries involving the biology of TLRs have provided scientists with evidence regarding their therapeutic potential, and several companies have already begun to develop modulators targeting TLRs in specific diseases. Current preclinical and clinical data support the idea that specifically targeting key processes in innate immunity might help prevent uncontrolled infection and limit inflammation in multiple diseases.[2]

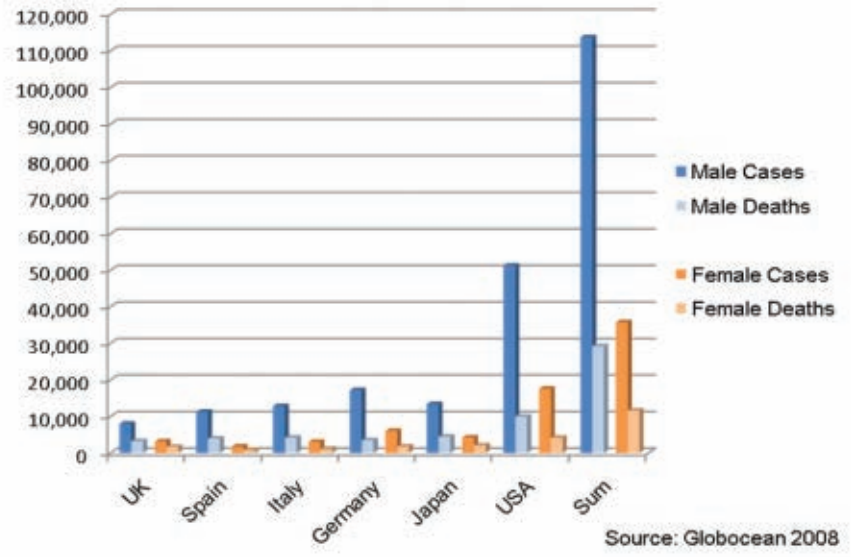

Figure 2. The incidence of bladder cancer in the US and four major markets in Europe (Germany, UK, Italy, and Spain - excluding France) is approximately 150k cases p.a. for both males and females. Men are approximately 3 times more likely to be affected by bladder cancer. Approximately 80% of newly diagnosed cases in both men and women occur in people aged 60 years and older. The incidence of bladder cancer is therefore expected to increase due to the aging population.

Therapeutic Importance of TLRs

In order to be considered as potential therapeutic targets, molecules must fulfil several different criteria. Some of these criteria include over expression in disease, knock-out mice being resistant to disease in disease models, ligands exacerbating inflammation in disease models, and genetic differences in TLRs (or their signalling proteins) correlating with risk of disease.[2] TLRs successfully fulfil many of these criteria, and extensive scientific research has already indicated that TLRs can be used effectively as therapeutic targets for a number of diseases.

Currently, studies in human genetics have shown the strongest evidence that TLRs represent good therapeutic targets. Scientists have been able to associate human disease progression and susceptibility with polymorphisms in genes that encode TLRs and their signalling molecules.[2] It is still unclear whether or not these genetic differences will be useful in determining the role of a given TLR as a drug target for inflammation or infection. However, it is clear that understanding such polymorphisms and their role in innate immune signalling and associated pathologies will greatly help researchers to develop novel therapies for patients.

The role TLRs play in human disease is still not fully understood, but significant in vitro and animal data exists that supports roles for particular TLRs in disease initiation and progression. For instance, it is widely known that TLR activation occurs early in the cascade of events that give rise to inflammation. This stereotypic inflammatory response has prompted speculation that there may be an advantage to blocking TLR activation, as they are likely close to the initiating events that give rise to chronic inflammation. Blocking TLR activation would thus be a highly effective strategy to limit inflammation.

The discovery that synthetic molecules can bind specific TLRs has generated a great deal of enthusiasm for the development of novel therapeutics targeting diseases that

involve innate immunity.[1] In recent years, scientists have begun identifying antagonists and agonists in order to enhance the immune response, particularly in the context of vaccine adjuvancy in infectious disease and therapeutic vaccine potential in cancer.[2] Several new compounds targeting TLRs, mainly TLR7 and TLR9, are currently in development and clinical testing for infection, cancer, and inflammatory diseases.

Previous Challenges in Developing TLRs

Before TLRs were discovered almost 13 years ago, it was difficult to target a single protein within the complex signalling cascades responsible for autoimmune diseases, cancer, infection, and inflammation. Scientists today have a better understanding of the molecular components that regulate innate immunity and inflammation, which means they are now able to target a single protein within a certain signalling cascade and achieve a desired therapeutic effect.

At present, it is still unclear as to whether or not there is a downside to systemically activating any TLR. Although no ill-effects have been reported in animal models or clinical trials, it is possible the over-activation of pathways could give rise to unwanted effects, including autoimmunity and tissue fibrosis.[2] Because TLRs also interact with endogenous ligands released by necrotic cells, the process can intensify autoimmune diseases, such as rheumatoid arthritis.[1] In addition, a single administration of a TLR agonist has the ability to initiate a profound "sickness" response due to cytokine release.[1] Despite these issues, scientists now know that repeated exposure to low doses of TLR agonists can induce tolerance and reduce subsequent inflammatory responses over time.

Current Therapeutic Developments in TLRs

There are several companies currently conducting research on TLRs in autoimmune diseases and oncology, including Ireland's Opsona Therapeutics Ltd. and Idera Pharmaceuticals. Opsona Therapeutics Ltd. is focused primarily on targeting TLRs for chronic autoimmune and inflammatory diseases, while Idera Pharmaceuticals Inc. has a lead TLR9 agonist targeting renal cancer. Partnered with Merck KGAA, Idera also has a TLR7 and TLR9 antagonist in preclinical development for autoimmune diseases and several research-stage TLR7 and TLR8 agonists for oncology and infectious disease indications. Additionally, Anadys Pharmaceuticals Inc. has developed a Phase I hepatitis C compound, which acts via the TLR7 pathway. The company also began a Phase I trial of this same compound in advanced cancer patients, but stopped recruiting in early 2009 due to resource issues.

TLRs are also highly relevant to vaccine development. TLR activation amplifies and directs the antigen-specific acquired immune response and, because of this, molecules that stimulate TLRs can be used as potential adjuvants. Dynavax Technologies Corp., a company focused on infectious diseases, signed a significant option-based deal with GlaxoSmithKline PLC in December 2008 around four endosomal TLR inhibitors. The company currently has two clinical-stage therapeutic programs in hepatitis, and its lead product is a hepatitis B vaccine. Likewise, Juvaris BioTherapeutics Inc. is developing adjuvanted vaccines and immunotherapeutics for infectious disease and cancer. Their product, immunotherapeutic JVRS-100, stimulates TLRs and is currently in the clinic as a systemic treatment for acute leukaemia.

Recent Developments Targeting Bladder Cancer & Autoimmune Diseases

Telormedix, a clinical-stage biopharmaceutical company based in Bioggio, Switzerland, has also been targeting TLRs for use in fighting cancer and treating autoimmune diseases. The company's main focus has been the innate immune system and modulating the immune response via TLR7, which contributes to the control of cancerous tumors as well as viruses. TLR7 receptors are present on dendritic cells, macrophages, and monocytes, and they play an important role in the immune response leading to inflammation, one of the immune system's first reactions to infection. TLR7 has emerged as a particularly interesting target for the development of drugs that modulate the innate immune system, as this receptor has been shown to recognize both naturally occurring single stranded RNA and synthetic low molecular weight ligands with classical drug-like properties, such as imidazoquinolines and purine-like molecules.[1]

Telormedix's lead product, TMX-101, is a targeted small molecule for the treatment of superficial bladder cancer. The active ingredient in TMX-101 is a known immunomodulatory molecule with a favorable safety profile and a demonstrated clinical efficacy in oncological and viral diseases. The company has taken advantage of existing regulatory data and clinical experience to bring TMX-101 quickly through non-clinical development and into Phase I/II clinical trials. Growing awareness of bladder cancer means more companies are now working on treatments for the disease, but Telormedix is the only company developing a compound for this indication

that targets TLR7. Telormedix expects this targeted therapy will have a shorter treatment protocol than other cancer therapies, with a dosing regimen suited specifically to bladder cancer.

It should also be noted that although bladder cancer is the fourth most common cancer in men and ninth most common in women (around 70,000 diagnosed each year in the US), there are to do date no specific therapeutics for the disease itself. If successful, TMX-101 should be the first targeted drug developed to treat bladder cancer.

Telormedix also has an additional compound in development. TMX-202 is a small molecule TLR7 agonist that has been selected for preclinical study in the topical treatment of skin cancers, bladder cancers, and other indications. Its advantage is that, unlike existing topical skin cancer treatments, it binds highly specifically to TLR7. This means it is far easier to predict and eventually control potential side effects, which is significant because current topical treatments for skin cancer are not highly specific for selected targets. For instance, in basal cell carcinoma, patients can only receive treatment with the leading topical therapeutic twice a week, otherwise they will suffer from a strong inflammatory response. However, TMX-202 has the potential to achieve comparable or higher efficacy at a lower dose.

Finally, the company is also developing TMX-201 and other second-generation TLR7 molecules as possible vaccine adjuvants and has an additional pipeline of programs for autoimmune disease, which includes TMX-30X. TMX-30X is a so-called "partial agonist" of TLR7. In various animal models of autoimmune diseases, TMX-30X has shown significant anti-inflammatory effects. This seems to be due to the induction of an inhibitory condition in the TLR7-signalling pathways.

Summary

TLR receptors have only recently been fully described, and their functionality is still under investigation. However, early indications of immune modulatory effects have made them desirable targets for pharmacotherapy. In particular, agonists and antagonists of TLR7, TLR8, and TLR9 are being developed by a number of companies, including Telormedix, as primary therapeutics in cancer and autoimmune diseases or as vaccine adjuvants.◆

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Alcide Barberis, PhD

Head of Research & Collaborations
Telormedix

Dr. Alcide Barberis has over 12 years of management experience in the biotechnology industry, as well as many years of scientific experience in the academic and corporate research sector. Dr. Barberis has been the scientific founder and Chief Scientific Officer of two Swiss biotech companies, ESBATech AG and Oncalis AG, where he directed highly innovative research teams. Dr. Barberis earned his PhD in Molecular Biology and Biochemistry from the University of Zürich. He was a scientist at Harvard University as well as the San Raffaele Research Institute, and recently, he has been a lecturer and group leader at the University of Zürich. He is the author of more than 50 scientific publications and inventor of more than 10 patents. He can be reached at abarberis@telormedix.com.

Executive Summary

Michael C.Pohl, PhD
Vice President, HORIBA Scientific

Robert Lee, PhD
Vice President, Pharmaceutical Development Particle Sciences, Inc.

Particle Sciences & Horiba Instruments: Providing Clients a Total Solution

Particle Sciences, Inc. (PSI), located in Bethlehem, PA, is a full-service CRO specializing in nano-based and rational solubility systems design approaches to formulation. PSI brings this skill set to bear on all dosage forms ranging from oral to parenteral to topical and drug/device combinations. In addition to industry-leading formulation capabilities, PSI has GLP/GMP analytic, bioanalytic, and characterization labs and class 100 clean room facilities. Providing an integrated suite of services aimed at minimizing the time and risks of drug development, PSI is expert in fine-particle and nanotechnology approaches and regularly deals with challenging APIs, high-potency compounds, and controlled substances. They work with a variety of APIs, including small molecules, peptides, proteins, and oligos. The company brings 2 decades of expertise providing an expansive suite of preformulation, formulation, analytic, and GLP/GMP manufacturing services - including sterile products. A responsive and collaborative approach ensures the objectives of all clients, large and small, are successfully met on-time and on-budget with the highest degree of quality.

The HORIBA Group of worldwide companies provides an extensive array of instruments and systems for applications ranging from automotive R&D, process and environmental monitoring, in vitro medical diagnostics, semiconductor manufacturing, and metrology, to a broad range of scientific R&D and QC measurements. Proven quality and trustworthy performance have established widespread confidence in the HORIBA Brand. HORIBA's current R&D efforts are directed toward nanotechnology instrumentation and its application to the field of Life Sciences. From Microscopic Raman Imaging to Fluorescence Spectroscopic mapping to miniaturized Water Quality measurements, the analysis of small, biological materials is a key focus. In the area of Particle Characterization products, a number of new technologies have been introduced to support industrial R&D initiatives. One recent example would be Dynamic Light Scattering (DLS) for the determination of size and Zeta Potential for small particles in dilute systems. Acoustic spectroscopy is also offered for similar types of measurements in more concentrated samples. Both Static and Dynamic Image Analysis has been developed to provide size and shape information for small particles in wet and dry systems. This provides a nice arsenal of weapons to characterize particles that are of major concern to the Life Sciences Industry.

Specialty Pharma recently spoke with Robert Lee, PhD, Vice President of Pharmaceuticals and Quality, Particle Sciences, and Michael C. Pohl, PhD, Vice President, Horiba Instruments, Inc. to discuss their recent strategic alliance to provide their clients with the most up-to-date physical characterization tools with operational expertise in a fully GLP/GMP-compliant setting.

Q: ***For the benefit of our readers who are not familiar with HORIBA, what does HORIBA bring to the Pharmaceutical Industry?***

Dr. Pohl: HORIBA Instruments is an analytical instruments company headquartered in Kyoto, Japan, with its US operations situated in Irvine, CA, and Edison, NJ. The company has a number of core competencies that range from X-ray Fluorescence to Raman Spectroscopy to Atomic Emission Spectroscopy. While all of these are of great interest to the Pharmaceutical Industry, our collaboration with Particle Sciences currently focuses on our Spectroscopic and Particle Characterization Products. These products focus on Microscopic Raman Imaging, Particle Sizing, Surface Area Determination, Zeta Potential Measurement, and Particle Shape Characterization. While these instruments are provided by a few other suppliers, HORIBA offers some unique accessories, algorithms, and applications to meet the needs of this industry.

Q: ***What is unique about Particle Sciences and their capabilities?***

Dr. Lee: PSI differs from many CROs in that our genesis was as a formulation group and that remains our core competency. We continue to grow deeper and deeper in our core skill set and are intentionally not trying to be all things to all people. This is one of the drivers to form an alliance with HORIBA. Increasingly, the regulatory characterization burden placed on drug developers is becoming gating. Solutions often require deep understanding of the techniques and devices used in establishing specifications. Particle Sciences is a leading expert in physical characterization and by establishing this close relationship with HORIBA, a scientific instrumentation company that will listen and use our feedback to improve their equipment, our clients will ultimately reap the benefits. Our goal is to solve our clients' problems, and we are not wed to any given drug delivery technology or characterization methodology. To that end, we have designed or acquired multiple drug delivery technologies so that we can best serve our clients. We view ourselves as technology consolidators, and our role is to offer our clients a complete solution. This includes both the actual drug delivery techniques as well as the analytic and characterization components.

As our name implies, we have special expertise in particulate-based systems. This encompasses both microparticles and nanoparticles. We are well versed in several technologies, including encapsulation, particle size reduction - both top down (including high energy milling and high pressure homogenizers, such as Microfluidizers®) and bottom-up (solvent/antisolvent precipitation, including Microfluidics PureNano Continuous Crystallizer) approaches, and particle engineering. In addition, we have developed a proprietary approach, termed DOSE™, to maximize the solubilities of the APIs we work with. These techniques are all employed as appropriate for a client's specific delivery goal, independent of dosage form, and PSI has worked on most routes of administration, including non-sterile, sterile, oral, vaginal, topical, ophthalmic, inhalation, injectables, etc. Additionally, and unique to PSI, is our capability to develop combination drug-eluting devices, which flows naturally from our sweet spot in particulates and solubilization techniques. Our focus on particulate-based and unique solvent systems differentiates PSI from other CROs, and we believe this better serves our clients, and it seems like this is in sync with a vast majority of our clients' requirements. Not to be minimized and a key aspect of our business strategy is our initial interaction with our clients. Early in our discussions, we strive to understand exactly what our clients' goals are - we want to

make sure we hear and understand their needs and design our programs to satisfy these goals. For example, an early question is whether our clients are interested in a formulation approach using proprietary intellectual property (IP). In some cases, our clients have strong IP surrounding their new chemical entity or use for their molecule and are interested in a straight line to some value-inflection milestone, such as in vivo evaluation or human proof-of-concept. In these cases, PSI will employ, whenever possible, a non-proprietary drug delivery approach. We remain agnostic when it comes to using either our existing proprietary or non-proprietary drug delivery technology - it is based on our clients' requirements and often, a simple emulsion or non-proprietary nanoparticulate approach fulfills our clients' requirements. In other cases, our clients may be seeking to reposition a marketed drug or may have mediocre or no IP protection for their product concept or may be seeking life cycle management for one of their currently marketed products. In these cases, PSI can draw upon our existing IP or create new IP to better protect our clients' products. As you can see, it is critical to understand our clients' needs, and PSI is uniquely positioned to support their development strategies - both from a technical and business perspective.

Q: ***What will the recent collaboration between HORIBA and Particle Sciences provide that is new to the industry?***

Dr. Lee: What this collaboration provides to PSI's clients is access to state-of-the-art equipment and, because of the close relationship between PSI and HORIBA, the ability to fully leverage today's best technology to most efficiently get to a clinic-ready product. This also provides a seamless path, from a product characterization perspective, from research to preclinical to clinical and ultimately, into commercial production. We offer full cGLP and cGMP development services, not only bioanalytical and manufacturing, but also analytical and physicochemical characterization. We can fully develop and validate methods plus conduct testing in support of regulatory filings, such as INDs and NDAs.

Dr. Pohl: As previously mentioned, HORIBA has instruments with unique features widely applicable to Pharmaceutical R&D. A great example of this is our LA-950, which offers a versatile Auto Sampler, a temperature-controlled measurement cell, a paste cell, and a variety of other accessories. Due to our corporate headquarters being located on the West Coast, it is challenging for us to make this technology accessible to the major Pharmaceutical companies headquartered on the East Coast. The ideal location of Particle Sciences makes this much more available to our core customers.

What this collaboration provides to potential HORIBA customers is access to HORIBA instrumentation so they can evaluate it in a lab setting before committing to purchase of the equipment. Additionally, PSI is expert in the use of the HORIBA equipment they currently own and will become expert in those they will acquire through the collaboration. This will provide HORIBA clients with a valuable resource for method development and validation. Additionally, if our clients desire to use our equipment strictly for research and not to support cGLP and cGMP studies, then PSI can also provide this service.

Q: ***What new services do HORIBA and PSI see the industry needing?***

Dr. Pohl: The tough times in the Pharmaceutical Industry are far from over. Patent expiration, healthcare reform charges, limited new drug pipelines, and other headwinds are not likely

to dissipate in the near future. Faced with these challenges, the industry will be faced with more rounds of cost cutting and retrenchment. A major area for cost containment is surely capital spending for analytical instrumentation in R&D, production, and Q&C. HORIBA's goal is to provide application-specific equipment to the Pharmaceutical Industry at cost-effective pricing.

HORIBA believes it has been doing this for the industry for many years now. Our collaboration with Particle Sciences now provides a ready means for the industry to test their application on this equipment. This can be done safely and confidentially with a group of industry experts in a very convenient geographic location. Particle Sciences will further elaborate on the capabilities that are available in Bethlehem, PA.

Dr. Lee: Pharmaceutical development is highly regulated and is getting more stringent on a continuing basis. This translates into Pharma and BioPharma having to adopt higher standards for characterizing their formulations. One potential example is the integration of optical microscopic image analysis coupled with spectroscopic analyses in order to identify particles using Raman spectroscopy in a semisolid formulation. PSI is working with HORIBA on just such a project and sees the value of this to our clients - the ability to not only determine morphology and particle size of discrete particles, but to then couple that to the generation of the associated Raman fingerprint for that specific particle amongst a sea of particles in a formulation. This will allow the client to see which particles are growing as a function of storage condition or formulation.

Q: *What are some of the challenges facing the Pharmaceutical Industry?*

Dr. Lee: Recent challenges have been imposed by the downsizing experienced across the Pharmaceutical Industry; resources have evaporated, companies are getting leaner, and talent is reshuffled or lost. Still work has to get done to support product development. Some of the gap has been filled by outsourcing. There is pressure, which will continue to grow across the industry to more accurately characterize products. This stems from both safety and efficacy perspectives. The question is a how to balance doing the appropriate level of testing and managing a shrinking budget. Hopefully, as better analytical tools become accessible, there will not be any question of compromising.

Q: *Where does HORIBA see the industry heading?*

Dr. Pohl: The Pharmaceutical Industry has proven throughout the years to be very resourceful when it comes to developing new delivery systems for drugs. Measuring the properties of these systems in order to predict performance has proven to be a serious challenge for the analytical instruments industry. HORIBA has always been striving to develop new instruments and accessories to meet these challenges. As the industry moves forward, HORIBA will be attempting to keep pace with instruments to properly characterize them. It may range from the development of totally new techniques to increasing the capabilities of current instruments to designing new accessories for older instruments. HORIBA will continue to strive to provide the Particle Characterization solutions required by this very innovative industry ■

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The Escalator Test

By: John A. Bermingham

A while back I wrote an article on *The Marketing Strategy Elevator Test*. This was an article based on a CEO's responsibility to ensure every person in the company knows the CEO's vision for the company and what role each person plays in achieving that vision. The theoretical test occurs when the CEO and a person employed by the company get on an elevator together to descend to the lobby. After the elevator doors close, the CEO turns to the other person and asks, "Can you tell me what my vision is for the company and what role you play in achieving that vision?" If the person cannot answer those two questions posed by the CEO before the elevator doors open in the lobby, then the CEO has failed to properly articulate his or her vision for the company to every person in the company.

This past February, I joined a biotech start-up as COO and have been preparing the company for investor meetings to finance the company. Part of that preparation was to develop my "elevator pitch." That is, my very brief overview of the company as my opening statement, followed by a detailed Power Point presentation.

The elevator pitch is a very clear, concise, descriptive, and interesting explanation of what your company does. In the case of a job interview, it is the answer to the question from a prospective employer or new boss, "So tell me about yourself?" Either answer should last no more than 2 or 3 minutes. After that, you have lost the listener.

So I began to agonize over how I am going to describe our company, which is a manufacturer of a product that has uses in the agriculture, pharmaceutical, cosmetic, military, and auto glass markets to name a few. I considered speaking at warp speed or skimming over the description at a high level, but no one would understand what I just said. Then it hit me!

I am going to be making presentations to investors and seeking millions of dollars in financing. So while I need to be clear, concise, etc., I do not have to make a 2- or 3-minute opening elevator pitch.

How about an "escalator pitch?" A little bit longer than an elevator pitch but still accomplishes what needs to be done. It's certainly not as slow as taking the stairs. So I have allocated 4 to 5 minutes to my escalator pitch. Still clear, concise, descriptive, and I hope interesting but not rushed or at too high of a level. The same may hold true for you when you get that dreaded question, "So tell me about yourself."

Sometimes taking a little more time to answer that question can be to your benefit as long as you do not drone on and on. Five minutes of clear, concise, descriptive, and interesting personal detail can be much more effective with a perspective employer or new boss than 3 minutes of intense babble. Sometimes more is better. ◆

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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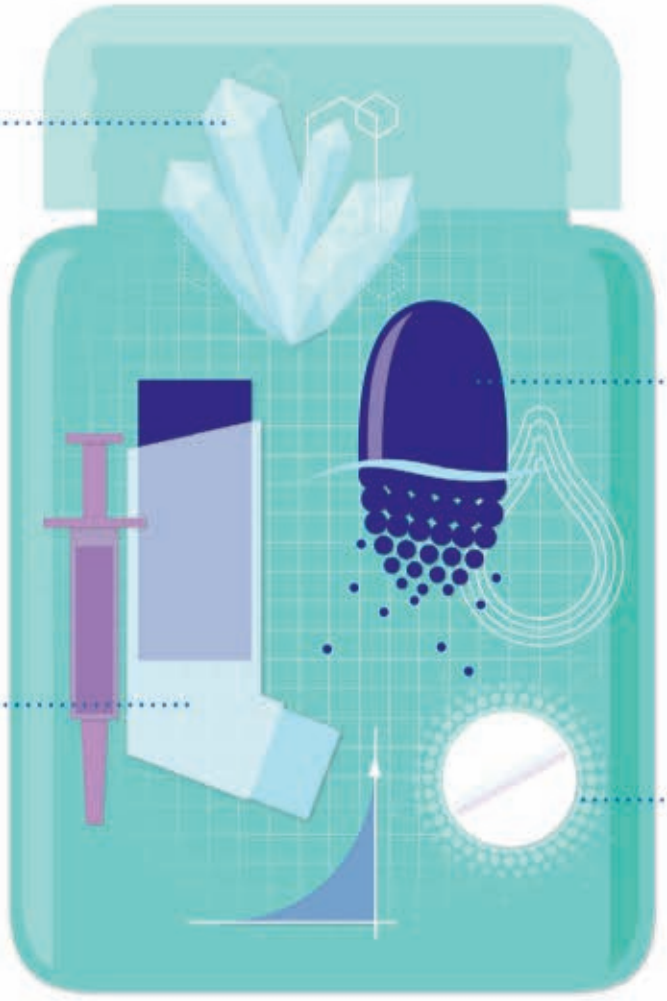

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