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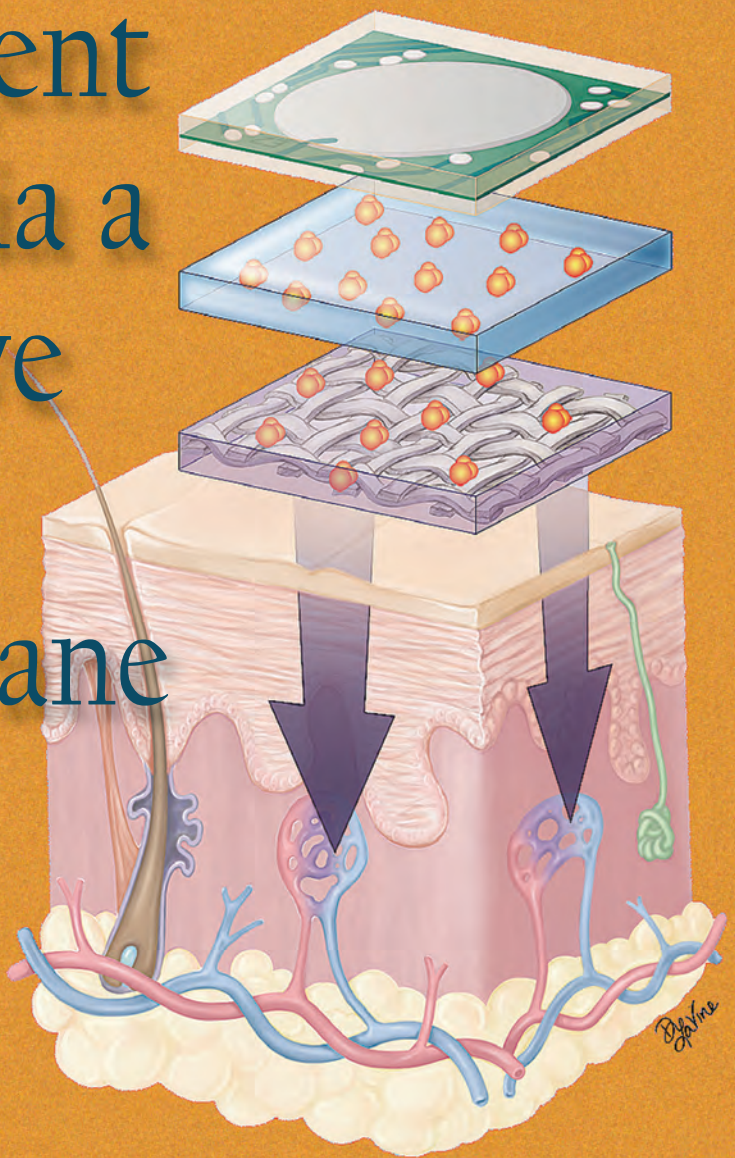

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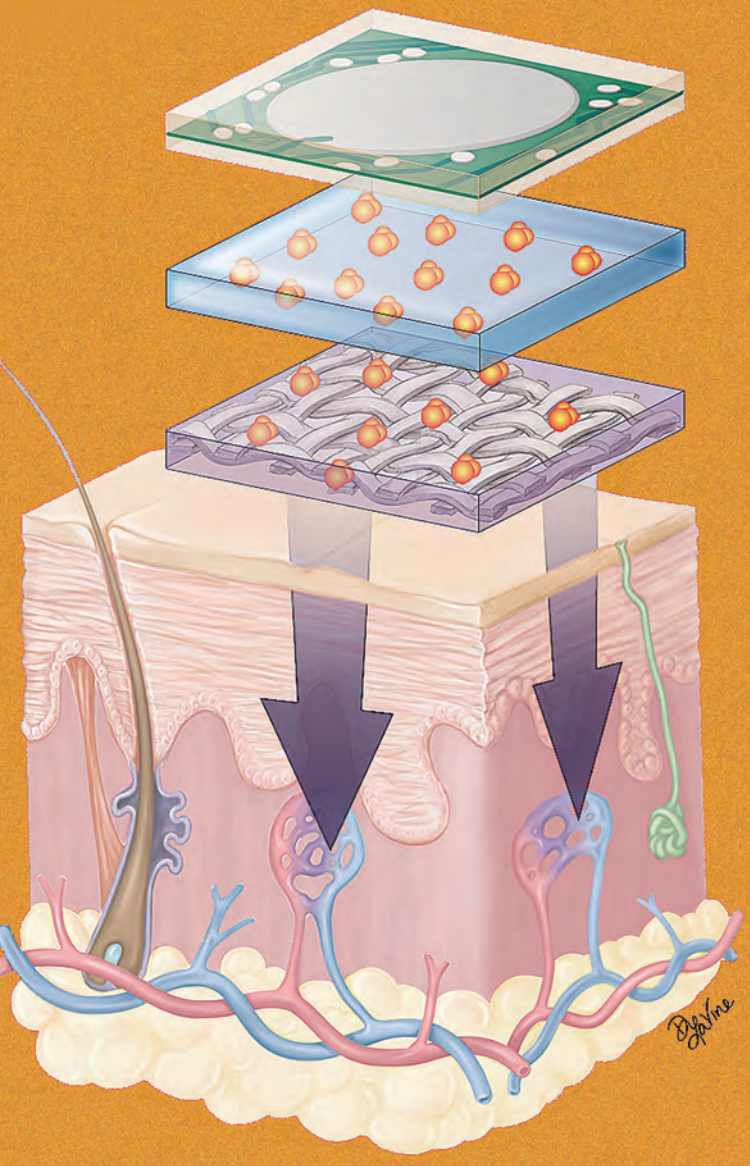

"The Isis Biopolymer approach to transdermal drug delivery via an iontophoretic patch addresses many of these aforementioned shortcomings. By utilizing proprietary, polymer thick film conductive inks, adhesives, and dielectrics, along with advanced RFID, Bluetooth LE, and battery technology, the Isis approach allows for a more practical application of the transdermal patch in clinical settings."

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"The growing market for peptides can cause capacity issues. Between 2002 and 2007, the market CAGR exceeded 10%. Given the time required to acquire large-scale equipment and qualify this, some companies no doubt found that they had more projects on their hands than they could comfortably cope with. The answer is to be found in diligent analysis of customers' requirements and then careful planning."

p.66

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Market News and Trends

Dow Completes Acquisition of Rohm and Haas, Creating a Leading Global Specialty Chemicals & Advanced Materials Company

The Dow Chemical Company recently announced it has completed its acquisition of Rohm and Haas. The acquisition is a major step in Dow's strategy of growing its performance products and specialty portfolio to deliver more consistent earnings growth. Combining the two organizations' best-in-class technologies, broad geographic reach, and strong market channels will create a $14-billion diversified business portfolio, which will be called Dow's Advanced Materials division. The division is intended to achieve $3 billion in additional value growth opportunities, as well as annual cost synergies of $1.3 billion.

"The closing of this transaction strongly positions Dow for the future by transforming our business portfolio," said Dow Chairman and CEO, Andrew N. Liveris. "This is an exciting day for all of Dow's stakeholders, and we are committed to delivering on a clear and measurable plan designed to meet the needs of our investors, employees, customers, and suppliers, even in this current challenging macroeconomic environment. Our first critical task is to ensure a seamless integration of Rohm and Haas that maximizes the synergies and opportunities offered by this transaction."

Rohm and Haas is the key element in Dow's new Advanced Materials division. Pierre Brondeau has been named president and CEO of this division, which includes Coatings, Building and Construction; Specialty Materials, Adhesives and Functional Polymers; and Electronic Materials.

The creation of Dow's new Advanced Materials division is expected to deliver significant cost and revenue synergies. Based on work that has been ongoing since July 2008, Dow has increased its annual cost synergy estimates to $1.3 billion, capitalizing on additional expected cost savings in the areas of combined purchasing and centralized business services.

It is also expected to leverage Rohm and Haas' strengths and drive growth for the combined company. Dow's Advanced Materials division will provide deeper geographic reach, increased channels to market, and complementary technologies. In addition, the combined company will have one of the largest research and development programs in the chemical industry.

The deal will also enable Dow's transformation into an earnings growth company. By expanding its specialty chemicals and advanced materials businesses, Dow has shifted the balance of its portfolio to this higher growth, higher margin area. The Advanced Materials division is strongly positioned in more resilient markets, as well as businesses that are poised for growth in the economic upturn, including coatings, adhesives, and electronics.

Dow has decided to exercise its option to have the Haas Family Trusts make an additional $500 million investment in Dow equity. This is consistent with Dow's disciplined plan to retire the bridge loan for the financing of the Rohm and Haas transaction by the end of 2009. This will be accomplished through the sale of assets, issuance of equity and debt, and the previously announced reduction in the company's dividend to preserve cash.

On January 23, 2009, Dow entered into a consent order with the United States Federal Trade Commission (FTC) that permitted the completion of the acquisition, provided that certain actions to address potential anticompetitive effects are implemented within 240 days of the deal closing. Specifically, under the terms of that agreement, Dow is required to divest the following businesses: Clear Lake, Texas, acrylic acid and esters plant and the related glacial acrylic acid, butyl acrylate, and ethyl acrylate businesses in North, Central, and South America; UCAR Emulsion Systems specialty latex businesses in North America; and North American hollow plastic pigment business (also referred to as the hollow sphere particle business).

The consent order also includes an Order to Hold Separate which requires Dow to maintain the competitiveness of these businesses pending their divestiture and to ensure that confidential information is not transferred between these businesses and the other businesses of Dow. Dow has already initiated procedures to comply with the FTC consent order and has been actively seeking buyers for the impacted businesses. The acquisition previously received regulatory clearance from the European Commission on January 8, 2009.

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PPD Acquires Magen BioSciences; Divests Piedmont Research Center

PPD, Inc. recently announced it has acquired Magen BioSciences, Inc., a biotechnology company focused on dermatologic therapies based in Waltham, MA. The acquisition expands PPD's compound partnering program into dermatology, initially in the indications of psoriasis, atopic dermatitis, and acne.

With the acquisition, PPD gains a pipeline of compounds through Magen's exclusive license to develop and commercialize preclinical compounds discovered by Eli Lilly & Co. for dermatologic therapeutics. The acquisition also provides PPD state-of-the-art research and development capability to screen dermatologic compounds to determine efficacy and safety.

"By combining Magen's unique dermal biology expertise and innovative pipeline of compounds with our extensive development experience, we hope to develop compounds that address unmet needs for major dermatological disorders," said Fred Eshelman, CEO of PPD. "The market is strong and growing for dermatologic products, which generally present fewer development hurdles than other therapeutics and have a more straightforward path to regulatory approval."

Sandra Luikenhuis, PhD, who was integral in founding and growing Magen and who joined PPD with the acquisition, will oversee development of these compounds in her role as executive director, dermatology.

"We see significant potential for the discovery and development of new treatments in dermatology, where few novel products are currently being developed," said Dr. Luikenhuis. "Magen's experience will be valuable in helping PPD evaluate future opportunities in this growing therapeutic area."

Under the terms of the deal, PPD purchased Magen for $14.5 million in cash. For the remainder of 2009, PPD anticipates that Magen's research and development activities will generate a loss from operations of approximately $15.2 million, or a diluted loss per share of $0.09. The quarterly 2009 diluted loss per share from the operations of Magen is expected to be as follows: Q2 - $0.03; Q3 - $0.03; and Q4 - $0.03.

As announced earlier, PPD has also entered into a definitive agreement to sell its Piedmont Research Center business, subject to various closing conditions. Assuming it is consummated as expected in the second quarter, the net impact of this sale and the acquisition of Magen on PPD's full year 2009 financial guidance will be a reduction of projected discovery segment revenues by approximately $19.0 million and an increase in projected diluted earnings per share of approximately $0.03. The net impact of these transactions on PPD's projected quarterly diluted earnings per share is expected to be as follows: Q2 - $0.11; Q3 - ($0.04); and Q4 - ($0.04).

PPD is a leading global contract research organization providing discovery, development, and post-approval services as well as compound partnering programs. Its clients and partners include pharmaceutical, biotechnology, medical device, academic, and government organizations. With offices in 33 countries and approximately 10,500 professionals worldwide, PPD applies innovative technologies, therapeutic expertise, and a commitment to quality to help its clients and partners maximize returns on their R&D investments and accelerate the delivery of safe and effective therapeutics to patients.

Hovione's TwinCaps® Inhaler in Phase III Clinical Trials for Influenza

Hovione recently announce that its licensee Daiichi Sankyo (Tokyo, Japan) has informed that it intends to use Hovione's TwinCaps dry powder inhaler device in the launch of the compound CS-8958, an inhaled long-acting neuraminidase inhibitor active against the influenza virus. Daiichi Sankyo has completed patient enrolment for Phase III clinical trials in Japan and other Asian countries and results are expected to be released mid year, including data to confirm the device switching. TwinCaps was specifically developed by Hovione for the indication and licensed to Daiichi Sankyo and Biota Holdings Ltd (Victoria, Australia).

The announcement follows the recent publication of data indicating the compound is as effective as Relenza and Tamiflu against various influenza strains. Significantly, this efficacy is achieved with a single dose, as opposed to a treatment over 5 days for the established drugs.

A 20-mg dose of CS-8958 is inhaled from powder compartments in the TwinCaps inhaler, which is made of just two plastic parts. Hovione believes this is currently the simplest inhaler being tested in clinical trials and once approved, will be the simplest in the market and have the lowest cost of goods. TwinCaps has no moving parts to deaggregate the dose of powder and only requires a low inspiratory airflow to achieve optimal delivery to the lung. This means that children and the elderly will find it easier to inhale the full dose.

The design challenge for Hovione was to make TwinCaps extremely simple to use, as in the case of a pandemic requiring immediate treatment of large populations, there is an obvious advantage for simple operation. The TwinCaps DPI (to be manufactured in Japan and Europe) is a two-piece unit comprising body and shuttle components. The shuttle has two prefilled dose chambers, left and right. In use, the shuttle is moved to one side by the patient to align one chamber of the shuttle with the mouthpiece to allow the first inhalation, creating turbulence within the dose chamber and drawing the dry powder into the lung of the patient. The process is then repeated for the second dose chamber, as the shuttle is moved to the opposite side to permit another inhalation to take place.

Daiichi Sankyo has indicated they are planning to file NDA in Japan in March 2010 and get approval within 2010, while Daiichi Sankyo and Biota are seeking licensees for the drug product collaboratively for the rest of world market. Hovione retains the right to commercialize TwinCaps outside the field of influenza.

"The unique design benefits of TwinCaps, including high-dose capability, disposability, and low cost are predicted to drive growth in Hovione's inhalation business and further leverage our already proven track-record in developing inhalation APIs, formulation development, and manufacturing services," said Peter Villax, Hovione's Vice President Pharma Business Unit.

Hovione is an international company with 50 years of experience in Active Pharmaceutical Ingredient development and compliant manufacture. With four FDA-inspected sites in the US, China, Ireland, and Portugal, the company focuses on the most demanding customers, in the most regulated markets. The company also offers integrated API, particle design, and formulation development and manufacturing. In the inhalation area, Hovione is the only independent company offering such a broad range of services.

Altea Therapeutics Announces Development & Commercialization Agreement With Amylin & Lilly

Altea Therapeutics recently announced it has entered into an agreement with Eli Lilly and Company and Amylin Pharmaceuticals, Inc. to develop and commercialize a novel daily transdermal patch delivering sustained levels of exenatide utilizing the Altea Therapeutics proprietary PassPort Transdermal Delivery System. Altea Therapeutics, supported by Lilly and Amylin, recently completed an initial Phase I clinical study of the exenatide transdermal patch in people with type 2 diabetes.

The exenatide transdermal patch is an investigational product designed to be applied once per day to provide sustained levels of exenatide for people with type 2 diabetes. The potential benefits for patients from the exenatide transdermal patch include eliminating injections, which may increase therapy compliance.

Under the terms of the agreement, Altea Therapeutics has granted Lilly and Amylin exclusive worldwide rights to develop and commercialize transdermal exenatide utilizing the Altea Therapeutics proprietary PassPort Transdermal Delivery System. Lilly and Amylin will fund all product development, manufacturing, and commercialization activities for the product. In addition, Altea Therapeutics will receive from Lilly and Amylin an up-front license payment and may receive clinical, regulatory, and sales milestones of up to $46 million, and royalties on future product sales. As part of the agreement, an equity investment in Altea Therapeutics is included.

"This agreement continues the validation of the Altea Therapeutics transdermal patch technology for medicines that currently can be administered only by needle injection or infusion, including water-soluble proteins, carbohydrates, and small molecules," said Dr. Eric Tomlinson, PhD, DSc, President and CEO of Altea Therapeutics. "We believe the diabetes care experience of Lilly and Amylin, combined with the transdermal expertise of Altea Therapeutics, creates an excellent partnership for the potential development of the world's first transdermal GLP-1 receptor agonist, transdermal exenatide."

"At Lilly, we are fully committed to improving outcomes for patients with diabetes," added David Vondle, Lilly's global brand development leader for exenatide. "Broader application of the exenatide molecule is a valuable part of that mission. We are excited to be partnering with Altea Therapeutics and Amylin on this innovative program."

"The agreement to develop a transdermal patch for exenatide is aimed at responding more broadly to the needs of the patients we serve by offering more treatment choices, such as the Altea Therapeutics non-injectable delivery option, for this important medicine," said Orville G. Kolterman, MD, Senior Vice President of Research and Development at Amylin Pharmaceuticals.

Altea Therapeutics is privately held clinical-stage pharmaceutical company with a proprietary platform technology broadly applicable to the transdermal delivery of biological drugs (proteins and carbohydrates) that otherwise would be administered by needle injection or infusion.

The company's PassPort Transdermal Delivery System also is uniquely suited for delivering highly water-soluble low molecular weight drugs that otherwise could not be delivered transdermally. These include ionic salt forms of drugs that can be delivered more safely and effectively than by the existing transdermal product, and other low molecular weight drugs with potencies too low to be delivered using conventional transdermal patches.

The company is conducting several clinical trials in the US for its products, including for a Transdermal Basal Insulin Patch designed to provide continuous delivery of insulin for people with type 1 and type 2 diabetes, and for a Transdermal Fentanyl Citrate Patch that enables rapid and safe management of moderate-to-severe pain. The company is in preclinical development with a number of product candidates, including a Parathyroid Hormone Transdermal Patch for the prevention and management of osteoporosis.

Altea Therapeutics has entered into several collaborations with pharmaceutical companies to assess the feasibility of transdermal delivery of certain drugs using its PassPort Transdermal Delivery System. It announced in July 2008 that it entered into a partnership with Hospira, Inc., a global specialty pharmaceutical and medication delivery company, to develop and commercialize an undisclosed transdermal product utilizing the PassPort System.

Abeille Licenses AB-1001 to Prostrakan for North America, Europe & Other Territories

Abeille Pharmaceuticals, Inc. is pleased to announce the signing of an exclusive license agreement with ProStrakan Group plc to develop and sell AB-1001, Abeille's transdermal patch for emesis, in all territories excluding Japan, China (including Hong Kong), Korea, Taiwan, and Singapore, the rights for which were earlier granted to SymBio Pharmaceuticals (Japan). For the right to develop and sell AB-1001 in the aforementioned territories, ProStrakan has paid Abeille an up-front licensing fee, and will make certain payments based on achievement of specific milestones, in addition to royalty payments on commercial sales.

AB-1001 is a transdermal patch for chemotherapy-induced nausea and vomiting (CINV). AB-1001 is designed to deliver a commercially available 5HT3-antagonist through the skin for a continuous period of up to 5 days, thereby providing the patient with sustained relief for CINV.

"We are extremely pleased with the signing of this license agreement with ProStrakan, which has a presence in Europe and the US, and with partners in most other major countries," said Suresh Borsadia, President and CEO of Abeille. "AB-1001 is Abeille's first product, and with this announcement, we have successfully licensed it on a worldwide basis to two very capable partners, ProStrakan and SymBio Pharmaceuticals, who are committed to its successful commercialization. This is further validation of our product-focused business strategy and represents a significant milestone in the evolution of Abeille."

Abeille Pharmaceuticals, Inc. is a privately held pharmaceutical company based in Princeton, NJ. The company is focused on the formulation of products by applying advanced delivery technologies to existing drugs. Abeille is dedicated to the development and commercialization of products that address unmet medical needs and improve the quality of life for patients. The company's initial focus will be on drugs used to treat oncology-related discomforts (such as CINV), diabetes and metabolic disorders, and CNS.

Pantec Biosolutions Reports Successful Phase I Study Into the Delivery of Triptorelin Using P.L.E.A.S.E.® Technology

Pantec Biosolutions AG, a privately owned company developing innovative transdermal drug delivery products, recently announced it has achieved excellent results in a Phase I clinical trial of a triptorelin patch used in conjunction with the company's novel P.L.E.A.S.E. (Painless Laser Epidermal System) technology.

The purpose of the study was to investigate the safety and tolerability of the newly developed triptorelin patch as well as the primary pharmacokinetic characteristics in healthy male volunteers. Due to its size and physicochemical properties, triptorelin cannot permeate passively across intact skin. Therefore, prior to patch application, the skin was microporated using Pantec Biosolutions' P.L.E.A.S.E. laser device. This pre-treatment created microchannels in the skin's outermost layer (stratum corneum) and facilitated triptorelin administration, accelerating release from the patch and uptake into the dermis, where the molecule entered the systemic circulation.

All of the volunteers considered the method to be convenient and simple and there were no reports of any adverse events. Results showed that serum levels of triptorelin exceeded those required for therapeutic effect. Triptorelin is administered daily by subcutaneous injection in the induction phase of in vitro fertilization protocol. Triptorelin is also used to treat prostate cancer, endometriosis, and precocious puberty. The serum profiles further demonstrated that the P.L.E.A.S.E. - triptorelin patch combination was able to achieve reproducible pharmacokinetics with little inter-individual variability.

"This pilot study shows that our novel technology is an effective and safe method for the transdermal delivery of triptorelin, which is currently administered only by injection. This validation of P.L.E.A.S.E. is an extremely important milestone that puts the company on a different level with respect to partnering opportunities." said Christof Boehler, CEO of Pantec Biosolutions.

Pantec Biosolutions AG is a private drug delivery company specialized in using laser microporation technology to deliver large molecular weight drugs into the epidermis for local or systemic uptake. Its proprietary P.L.E.A.S.E. platform enables efficient, needle-free, and painless administration of biopharmaceutical drugs, in varying and individualized dosages, through partnered patch technology. The technology is currently in clinical trials for the delivery of IVF hormone therapy, a market with an estimated value of $1.5 to $2 billion. Pantec Biosolutions' P.L.E.A.S.E. platform is available both for the development of the company's own pipeline and for penetration into new markets through strategic partnerships. Pantec Biosolutions is based in Ruggell, Liechtenstein.

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Allan Hoffman, University of Washington, U.S.A.
The Early History and Evolution of the Controlled Drug Delivery Field

Robert Kiss, Belgian National Fund of Scientific Research, Belgium
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MonoSol Rx & Strativa Pharmaceuticals Submit NDA for Ondansetron Orally Dissolving Film Strip

MonoSol Rx, the developers of PharmFilm technology and a drug delivery company specializing in dissolving thin film pharmaceutical products, and Strativa Pharmaceuticals, the proprietary products division of Par Pharmaceutical Companies, Inc., recently announced the submission on April 7, 2009, of a New Drug Application to the US FDA for the orally dissolving film strip (ODFS) formulation of ondansetron.

The NDA is supported by positive data from completed pivotal studies in which ondansetron ODFS demonstrated bioequivalence against GlaxoSmithKline's Zofran ODT anti-emetic product. The ondansetron ODFS product has been developed as an anti-emetic therapy for the prevention of chemotherapy-induced nausea and vomiting (CINV), nausea and vomiting associated with radiotherapy, and post-operative nausea and vomiting.

"The submission of the NDA for our ondansetron orally dissolving film strip marks another key milestone for MonoSol Rx and our licensing partner, Strativa Pharmaceuticals," said A. Mark Schobel, President and Chief Executive Officer of MonoSol Rx. "This sets the stage for a promising new therapy to combat nausea resulting from chemotherapy, radiotherapy, and surgical procedures. For patients in need of anti-emetic drugs, such as ondansetron, the burden of ingesting a tablet or swallowing a liquid medication can be significant because it has a tendency to exacerbate the nausea. Our PharmFilm technology offers the potential to improve the convenience and compliance of ondansetron by delivering the drug through a quick orally dissolving film strip that requires no water."

In June 2008, MonoSol Rx and Strativa entered into an exclusive licensing agreement under which Strativa acquired the US commercialization rights to the ODFS formulation of ondansetron from MonoSol Rx. Under terms of the agreement, MonoSol Rx will receive pre-commercialization and sales-based milestone payments that could total $23.5 million, as well as payments for the purchase of product supply and royalties on net sales. The anti-emetic market totaled 4.1 million prescriptions in 2008. Ondansetron was the prescription leader in the category, accounting for 95% of prescriptions.

MonoSol Rx is a specialty pharmaceutical company leveraging its proprietary PharmFilm technology to deliver drugs in quick dissolving films. PharmFilm is designed to benefit patients by improving the convenience, efficacy, and compliance of new and currently marketed drugs. The company's leadership in thin film drug delivery is supported by strong intellectual property, a portfolio of commercialized OTC drug products, and a development pipeline of prescription formulations based on PharmFilm technology. With a vertically integrated development and production infrastructure, MonoSol Rx has the capacity to manufacture OTC drug products for near-term revenues that fund prescription product development programs that will generate long-term value.

The company's commercialization strategy for all PharmFilm products is to partner with the innovator, other specialty Pharma, or leading consumer products companies that can sell-in and manage product sales and marketing. For existing and future partners, PharmFilm formulations represent revenue life cycle extensions for products with patent lives that have expired or are approaching expiration. PharmFilm is also a tool to help sales and marketing partners differentiate in competitive markets while offering unique advantages over drugs dosed by traditional tablets, capsules, and orally disintegrating tablets (ODTs).

Strativa Pharmaceuticals is the proprietary products division of Par Pharmaceutical, Inc. Strativa is committed to developing and marketing novel prescription drugs. Its initial focus is on supportive care therapeutics in HIV and oncology. Drawing on the specialty products expertise of its staff, Strativa possesses the resources to prepare products for commercialization and to help ensure their success after launch.

Molecular Responsibility

API Characterization Services: Does Your Molecule Need Tutoring?

Part II of a Six-Part Series

By: Derek G. Hennecke, MBA

What's keeping you up at night? Well, let's make a list. It could be the need to secure funding. That's always good for some tossing and turning. Your burn rate, pipeline productivity, and the need to protect intellectual property in a cut-throat market - these things definitely have the potential to affect your nocturnal heart rate. And then there's the basic need to contain costs because, hey, this is a recession.

It doesn't take extra-sensory perception to understand that when your head hits the pillow these days, the number one fear in your closet of anxieties is that your molecule will fail. When the economy was soaring, you might have been able to imagine life after a molecular failure. But in today's market, every molecule you back becomes like your own child. You've got one shot to do it right, with a limited budget. So you ask yourself, where can I cut corners? How can I reduce time to market? Can I get there faster, better, cheaper? And, what am I comfortable not knowing about my molecule's behavior?

Here's where you probably expect me to tell you to spare no expense. After all, I have something to sell you, right? Wrong. Well okay, right on that last point, but wrong on the first one.

The analogy of molecules being like your own child? It's actually not far off. The type and kind of investment to help a child reach his or her full potential, is dependent on the unique circumstances of each child.

So it is with molecules. There is no formula. You need to put the molecule itself at the forefront of all your decisions. At Xcelience, we call this molecular responsibility. It's putting the needs of the molecule ahead of all other considerations - politics, personalities, or other. Ultimately, if you raise that molecule well, everyone will be happy.

There are those who believe that the majority of downstream problems can be avoided with better up-front compound knowledge. These companies invest early and up-front in API characterization services because they have quantified the risk of solid-form issues, such as polymorphic forms sneaking in on you to impact stability, or have the data to show that selecting the appropriate salt with the optimum physical properties will significantly reduce time to market.

They have the data, they have their risk model, and they have built investing in early compound knowledge into their product development strategy and budget. But with discretionary spending nearly evaporated, even these firms may be heavily scrutinizing R&D expenditures earmarked as essential spend. The fact is, some API characterization services are required and some are not.

So how do you decide? Let's start with what is required. ICH Guideline Q6A requires a polymorphic study for each new API according to a three-step decision tree that includes detection of solid phases, characterization to determine whether differences in physical

properties affect drug product performance, bioavailability or stability, and if relevant, the development of quantitative methods and specifications for drug substance and even drug product. Beyond that, it's up to you and your molecule.

Here's the argument for early investment in compound knowledge. Think of API characterization services as a hedge against the downside of your investment. You're increasing your chance of a positive return. Considering how much you've already invested, you simply can't afford not to do it.

The best product approach to API characterization underscores the value of early investment in services prior to manufacturing the first GMP batch as a means to improve the probability for compound success, reduce time to market, avoid costly regulatory or development delays, and to build a sound intellectual property position. In this scenario, undesirable solid forms are identified and eliminated early on using sensitive methodology, and the optimal salt or free base is selected to progress through scale-up and toxicology studies.

Most people understand the importance of setting chemical specifications and addressing chemical stability, but many fail to understand the importance of assessing physical stability. Selecting the optimum salt or free base before the GMP batch has the potential to facilitate subsequent drug development. Even a minimal investment in API characterization or solution stability can provide basic knowledge about the impact of heat, light, or other environmental effects that helps minimize serious downstream problems.

Put a different way, failing to select the optimum salt may result in a host of formulation development and manufacturing obstacles and delays, or the need to re-do toxicology studies. Specifically, solubility issues may impact API recovery. Particle size and shape issues may impact manufacturability (flow, compression, batch uniformity) or result in costly bridging studies to ensure that clinical trial results are relevant to the commercial production batch. Ultimately, selection of an unstable solid form can have a detrimental impact at every stage of the API life cycle, from manufacturing of active powder to manufacturing of the final form, drug product stability, and storage.

Intellectual property is also an important consideration. Salt forms with advantageous physical properties are patentable as new chemical entities, and comprehensive pre-product launch salt screens are required to identify and patent all forms of a high-potential drug. Knowledge of the possible existence of multiple salt forms may help you strengthen your patent by including other forms in your application.

We've worked with some clients who absolutely believe in the value of investing in early API characterization services, and we will tailor our full screen, mini screen, or a la carte preformulation services to meet their specific product needs and goals. For a recent project, we designed a set of customized accelerated stability conditions so that, within a very short period of time, our client had data that allowed them to select between two different solid forms to identify the lead candidate with the highest probability of success. This minimal up-front investment will potentially save numerous days lost to issues that could have arisen in downstream process or manufacturing phases by selecting the sub-optimal candidate.

If you have the cash, going this route is pretty much a no-brainer. Who wouldn't give their child the best possible start in life if money wasn't a factor? Unfortunately, for most of us, money is a factor. So what amount of compound knowledge is sufficient to move forward? The answer to this question is subjective. It's a risk-return scenario. If your molecule is good and stable and reasonably predictable, we're not going to advise you to set up a whole bunch of potentially costly API characterization tests.

Some companies will jump right into a formulation project with a standard prescription of solutions. If you suspect this is happening to you, be very, very wary. One of our first questions is always, what do you know about your API? Is it well-behaved? What are the strengths? Weaknesses? Unknowns?

A good contract research organization will work to understand the product development goals that you have for your molecule, and the physical and chemical properties of the molecule itself, put this in the context of your budget, and go from there.

It is, as I said, a risk-reward ratio. There comes a point where your expenditures are no longer justified by increasing your spend on API characterization.

Sometimes, however, the law of probabilities says that you will encounter problems despite the best laid plans. For clients who come to us at the clinical supplies manufacturing stage, you need to know that we'll be there and take appropriate corrective action when your child acts up. If we encounter unexpected stability or precipitation issues resulting from an unstable form or excipient interaction, you can be confident we have the expertise to address and solve the problem immediately. That's where we really leverage the advantage of having API characterization, formulation development, and manufacturing capabilities all on one site.

I can't promise you your molecule will behave or that you won't have any more sleepless nights worrying about your molecule. But I can tell you that by working together with your budget and your priorities, and putting your molecule's needs as top priority in every decision we make, that you can go to bed secure in the knowledge that you are doing everything in your power to help your molecule achieve it's full potential. ◆

BIOGRAPHY

Derek G. Hennecke, MBA
President & CEO
Xcelience

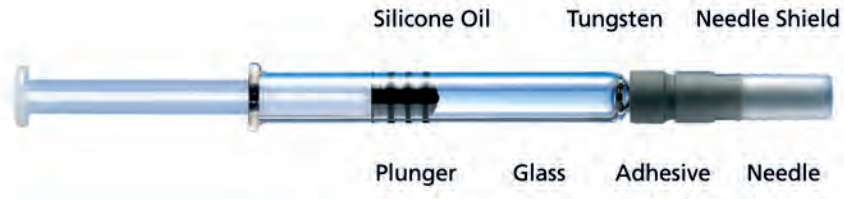
Mr. Derek G. Hennecke is a founding member of Xcelience. From 2004 to 2006, he served as Vice President and General Manager, Pharmaceutics and Biopharmaceuticals of MDS Pharma Sciences, Inc. In this capacity, he was responsible for the business and operations of MDS' CRO formulation development, including capsule development, tablet formulation, modified-release tablets, suspensions, solutions, suppositories, creams, ointments, and gels. Prior to joining MDS, Mr. Hennecke held various drug development management positions for DSM in Canada, Egypt, The Netherlands, and Mexico. In these roles, he built the operations or businesses to introduce various drug products for Europe and the US. Mr. Hennecke has also worked for Roche's research activities in Germany and Canada. He earned his BSc from the University of Alberta (Canada) and his MBA at the Erasmus University in Rotterdam, (The Netherlands).

Drug Delivery of Sensitive Biopharmaceuticals With Prefilled Syringes

By: Arno Fries, PhD

Recombinant proteins, monoclonal antibodies, and other biopharmaceuticals offer medication for life-threatening diseases. However, these products consist of sensitive molecules. Among the causes for chemical and physical instability are leachables in container closure systems.[1-5] Interactions of leached contaminants with therapeutic proteins can result in aggregation, particulate formation, and loss of native protein tertiary structures.[6,7] Even small fractions of aggregated proteins might reduce biological activity and enhance immunogenicity.[8] For these reasons, strategies to prevent aggregation pathways and monitor aggregate levels in biopharmaceutical formulations are important elements of product development.[9]

FIGURE 1



Product Contact Materials in Syringe Systems

BIOMOLECULES RAISE THE BAR

Strength, efficacy, and safety of active molecules are closely related to their chemical and physical properties. Most biopharmaceuticals are more sensitive toward product contact materials from container closure systems than small molecules. The difference can be attributed to several reasons.[3,10] Biomolecules contain, due to their large size, a high number of functional groups that are prone to react with other compounds. This opens a wide range of pathways for undesirable reactions with leachables. In addition, the stability of biopharmaceutical products hinges on the three-dimensional orientation of the molecules (eg, native folding of proteins). Biopharmaceuticals are primarily administered as injectables, and liquid formulations increase the risk posed by leachables. Because these products often contain the active molecule in low concentrations, trace amounts of contaminants might interact with the whole quantity.

PREFILLED SYRINGES

Both for the ultimate end-users and biopharmaceutical companies, prefilled syringes offer advantages over traditional container systems.[11-15] Medical staff and patients prefer ready-to-use injection solutions in syringes because they are convenient and prevent medication errors. The industry is utilizing these benefits with life cycle strategies to gain competitive advantages and increase market shares.[16,17] When molecules are expensive to manufacture, prefilled syringes increase revenues and earnings as they reduce product overfill compared to vials. Due to these benefits, the use of prefilled syringes grows at double-digit rates. The trend is predicted to continue over the coming years.[18,19] However, for stability reasons, a number of biotherapeutics is commercialized in vials as lyophilized formulations. This means the advantages of ready-to-use injection solutions in prefilled syringes are not leveraged.

THE PROCESS IS THE PRODUCT

Container closure compatibility is a regulatory requirement to protect the potency, efficacy, and safety of therapeutics. In glass-based syringe systems, a range of materials gets in immediate contact with active ingredients: silicone oil, tungsten, closure, plunger, glass, and (for staked needle syringes) adhesive and needle (Figure 1). The fact that closures are considered product contact materials is reflected by change control procedures in the biopharmaceutical industry. When the rubber formulation of an established needle shield is modified by the supplier, 93.3% of the companies run complete stability studies.[20]

An evolving trend among biopharmaceutical companies is to enter closer partnerships with syringe suppliers and to scrutinize all aspects of their processes. The paradigm from biopharmaceutical

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manufacturing, "the process is the product," is being transferred to the production of prefilled syringes. The rationale behind this shift in attention is that all substances used during glass cutting, forming, printing, needle staking, washing, siliconization, assembly, packaging, and sterilization are potential contact materials with sensitive biomolecules. Biopharmaceutical companies want to catalog these materials and understand how syringe suppliers control their processes.

The following outlines recent advances in the field of prefilled syringes. Strategies to mitigate stability risks for sensitive biopharmaceuticals are discussed. Special focus is placed on alkalinity, tungsten, and silicone oil as sources of incompatibilities.

pH RANGE

When sensitive products are applied in glass syringes, the pH value of the formulation needs to be considered.[10] Elevated pH might trigger oxidation and hydrolysis of biopharmaceuticals.

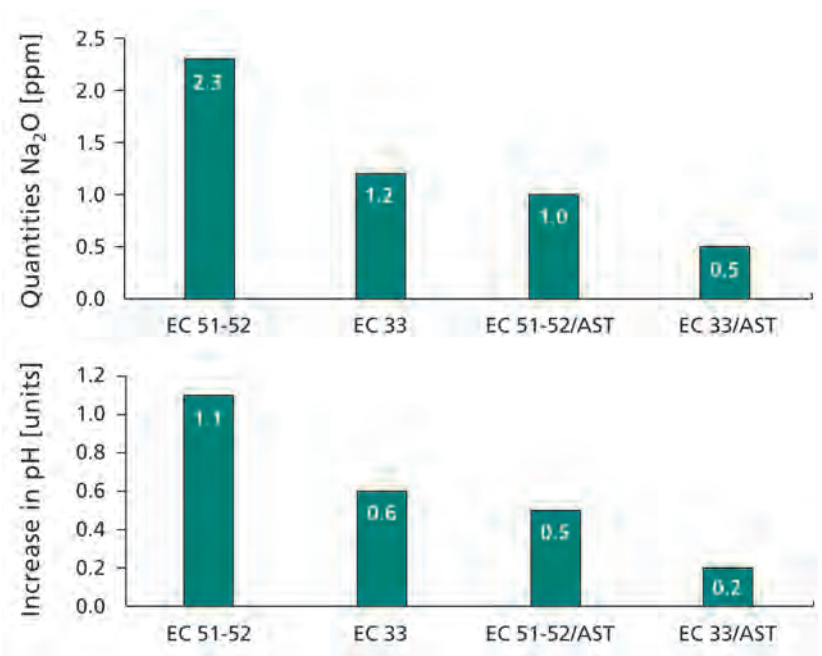
For the production of syringe barrels, glass tubing from Type I borosilicate glass according to USP, EP, and JP is used. Standard glass tubing has an extension coefficient of 51-52 and consists of 70% to 80% SiO_2, 15% B_2O_3/Al_2O_3, and up to 7% Na_2O. The role of sodium is to lower the forming temperatures of glass to 1,000°C to 1,200°C, a prerequisite for industrial converting processes. Glass is a well-characterized material, and Type I borosilicate has excellent hydrolytic resistance.[21] However, the material is being heated during the syringe manufacturing cycle, and at temperatures above 800°C, sodium cations are migrating from inside the glass barrel to the surface. Each single syringe-forming step increases the quantity of sodium oxide on the glass surface by 15% to 30%.[22] When an aqueous formulation is filled and stored in a syringe, sodium cations are being leached from the glass surface into solution. This causes in unbuffered solutions an increase in pH.

How can alkali ion leachables in glass syringes be reduced? The principal strategies are use of glass material with lower sodium content, treatment of the glass surface, and a combination of both. Figure 2 compares analytical results with 1-ml long Luer cone syringes manufactured with these methods.

Syringe barrels from Type I borosilicate glass with extension coefficient 51-52 (EC 51-52) contain on average 2.3 ppm residual sodium oxide on the interior surface. Quantitative analysis is achieved by flame atom emission spectrometry according to ISO 4802-2.[23] When the barrels are manufactured from Type I borosilicate glass of extension coefficient 33 (EC 33), analysis shows a significantly reduced sodium oxide level of 1.2 ppm. This result is in line with data according to EP testing by equivalence titration with 0.01 M hydrochloric acid (EC 33: 0.46 ml HCl, EC 51-52: 0.90 ml HCl) and pH measurement with pH meter (EC 33: pH 6.1, EC 51-52: pH 6.6, aqua bi-dest.: pH 5.5).[24] Syringes from EC 33 glass increase the pH value of aqueous solutions by 0.6 units, whereas EC 51-52 glass barrels increase the pH by 1.1 units.[25] These data reflect that EC 33 glass tubing contains lower quantities of sodium oxide (4%) than EC 51-52 glass.

Syringe barrels produced from EC 51-52 glass and treated with ammonium sulfate (AST) contain on average 1.0 ppm sodium oxide in accordance to ISO 4802-2 testing. EP titration (AST: 0.44 ml HCl, untreated barrels: 0.90 ml HCl) and pH measurement (AST: pH 6.0, untreated barrels: pH 6.6) confirm this result. The increase in pH of surface-treated barrels is 0.5 units, which is 0.6 units lower than in untreated barrels. For ammonium sulfate treatment, dosing pumps are used to spray an aqueous solution of the agent onto the inner surface of syringe barrels. During the annealing step of the syringe manufacturing process, residual sodium oxide is converted under heat into the much better water-soluble sodium sulfate as follows: $Na_2O + (NH_4)_2SO_4 \rightarrow Na_2SO_4 + 2\ NH_3 + H_2O$. Removal of sodium sulfate is achieved downstream during washing of the syringe barrels and reduces significantly the amount of alkali ions on the glass surface.

FIGURE 2



Alkalinity & pH Shift in Glass Syringes

Quantitative analysis according to ISO 4802-2 shows that syringes manufactured from EC 33 glass and treated with ammonium sulfate contain merely 0.5 ppm residual sodium oxide on the interior surface. This is 78% lower than in untreated syringes from EC 51-52 glass. The pH of aqueous solutions in barrels from EC 33 tubing that are ammonium sulfate treated increases by 0.2 units, a decrease of 82% compared to standard syringes. The combination of both methods (EC 33 glass and AST) effects the strongest reduction of alkali leachables. This provides an efficient strategy to control alkalinity and pH-related interactions between sensitive biopharmaceuticals and glass-based prefilled syringes.

TUNGSTEN LEACHABLES

Transition metals are known as a cause for instability of sensitive products.[1] Tungsten can undergo interactions with protein therapeutics, leading to oxidation, aggregation, and degradation.[26-30]

In manufacturing processes of glass syringes, tungsten metal is commonly used due to its heat resistance. Pins from this material are keeping the bore open while the cone is being mechanically shaped with forming wheels (Figure 3).

Tungsten is well characterized and stands out among all metals with the highest melting point (3,422°C), the highest tensile strength at elevated temperatures, and the lowest vapor pressure.[31] Even though tungsten is very wear-resistant, the metal is prone to oxidation under the conditions of syringe forming with temperatures up to 1,250°C. On the surface of tungsten pins, tungsten (IV) oxide (WO_2) can be formed at temperatures under 400°C and tungsten (VI) oxide (WO_3) between 500°C and 800°C. In aqueous solution, tungsten (VI) oxide produces a mixture of soluble mono, oligo, and polytungstates, which are stabilized at low pH.[32,33] These large anions are highly charged species. They can interact with bipolar protein molecules through electrostatic attraction and induce formation of colloidal solutions and aggregates.[32,33] Tungsten compounds can also react with hydrocarbons to organometallic complexes and with molecules containing donor atoms to chelate complexes under formation of O-W-O, O-W-S, O-W-N, S-W-N, and S-W-S bonds. The metal and its compounds are also known as heterogeneous and homogeneous catalysts that convert high quantities of substrates through non-stoichiometric reactions.[34] Other metal leachables occasionally found in drug products (eg, Fe^{3+}, Ni^{2+}, and Mn^{n+} from stainless steel tanks used in manufacturing equipment) are known for similar interactions with active molecules.[1]

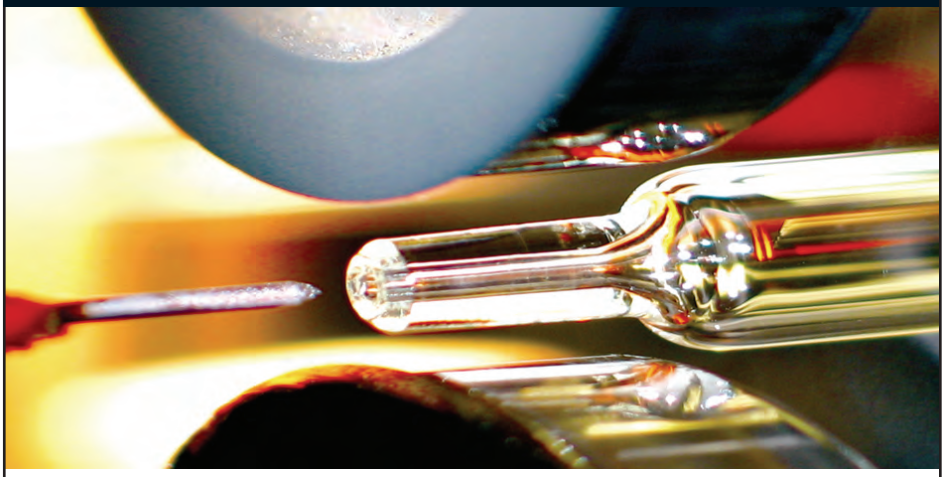
Prefilled syringes formed with tungsten pins contain trace amounts of tungsten compounds in the cone section, which is part of the product contact surface. Syringe filling processes with plunger placement under vacuum intensify the contact between active molecules and tungsten because air bubbles in the cone of the syringe are pulled out.[33]

Proprietary methods for the extraction of tungsten from syringe barrels and the subsequent quantitative physicochemical analysis have been developed. Extractable tungsten concentrations are typically below 500 ppb and can be lower than 100 ppb, depending on manufacturing cycle and washing process. Staked needle syringes contain the lowest amount of extractable tungsten as most of the bore is covered by the needle.

Incorporation of tungsten in syringe barrels can be further reduced by controlling the abrasion of tungsten pins or through substitution of tungsten with other materials. Wear of forming pins can be lowered by horizontal barrel-forming technology. This manufacturing process is using lower temperatures compared to vertical-forming techniques. Other methods are directed at controlling the physical properties of the forming pins. As a substitute for tungsten, alloys from group 9-10 transition metals can be employed. This approach allows tungsten-free syringe forming. However, intake of material from substitute pins into syringe barrels cannot be ruled out. Some biopharmaceutical companies prefer the use of tungsten pins because potential effects of tungsten on their products are better understood than for most other transition metals. Forming pins from non-metallic materials and alternative techniques of syringe forming are at an experimental stage.

To evaluate product stability of biopharmaceutical formulations, spiking studies in early phase development with material extracted from used tungsten (metal) pins are recommended. Subsequent stability studies in prefilled syringes verify the preliminary data and specify accepted tungsten (metal) levels. Advanced manufacturing methods for prefilled syringes together with targeted

FIGURE 3



Cone Forming With Tungsten Pins

stability studies ensure that interactions of highly sensitive biomolecules with tungsten are prevented.

SILICONE LUBRICANTS

Even though silicone oil is inert toward most drug products, interactions with sensitive biopharmaceuticals have been observed. Such incompatibilities include aggregation, deformation, and inactivation of native protein structures.[7,27]

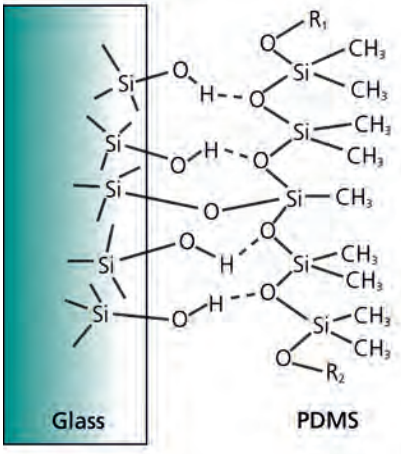
Prefilled syringes are containers and drug delivery systems at the same time. Functionality of these systems (viable activation and gliding forces of the plunger) is accomplished by siliconization. Silicone oils are viscous, inert materials with excellent characteristics as hydrophobic lubricants.[35,36] They consist of a mixture of polydimethylsiloxane (PDMS) molecules with Si-O chains, which vary in length and number of OH groups. This molecular structure determines how silicone oil layers are adsorbed onto glass surfaces and the distribution, thickness, composition, and uniformity of the layers. In established manufacturing processes on the lines of syringe suppliers, biopharmaceutical companies, and CMOs, syringes are oily siliconized by spraying 0.4- to 1.0-mg silicone oil (eg, Dow Corning 360, Medical Fluid) into the barrels.

Advanced siliconization technology has been developed to lower the level of free (non-bound) silicone oil in prefilled syringes. The baked siliconization method uses emulsions of silicone oil (eg, Dow Corning 365, 35% Dimethicone NF Emulsion, diluted in HPW) sprayed into syringe barrels followed by heat treatment in a tunnel. Proprietary techniques and downstream washing processes vary depending on syringe supplier. Critical quality attributes of the siliconization process are controlled through the settings of siliconization pump and nozzle, the volume flow of silicone spray and air, the concentration of the silicone oil emulsion and tunnel temperature, speed, and length. This technology alters the nature of the lubricant in the following way.[37,38] Heat-induced polymerization reactions reduce fractions of low molecular weight from the silicone oil. Removal of water enables the lubricant to spread out evenly over the glass surface and creates a thin, uniform film. Mono-layers of the lubricant are affixed to the glass surface. The interactions between polydimethylsiloxane and molecules from the glass surface range from van der Waals forces to covalent Si-O bonds. This means thermal fixation processes convert silicone oil into Si(R)O coating as illustrated in Figure 4.[38] The thickness of silicone oil layers on the glass surface can be measured by reflectometry. A comparative study using cartridges as glass containers found for oily siliconization a layer thickness with a mean of 232.67 nm and for baked siliconization of 76.83 nm.[39]

Parenteral biopharmaceutical products vary widely in nature. The sensitivity of the active substance, the viscosity of the formulation, the drug delivery system, and its mode of operation (eg, prefilled syringes either manually or driven by autoinjector device) determine the principal requirements. Silicone coatings of prefilled syringes can be customized to meet specific needs. Variation of process parameters adapts the characteristics of the siliconization. Best results are obtained when syringe manufacturer (supplier) and biopharmaceutical company (end user) partner and work along the following project steps:

1. End user: Specification of accepted silicone oil levels and system functionality
2. Supplier: Development of baked siliconization process for the specified attributes
3. Supplier: Manufacturing of customized baked silicone syringes in sample quantities
4. End user: QC testing of the samples, filled-syringe stability studies, and evaluation
5. Supplier: Scale-up, process validation, and industrial manufacturing of the syringes

FIGURE 4



Model of Silicone Coating

Fundamental understanding of the design space of baked siliconization allows the syringe manufacturer to derive relevant process parameters from the specified quality attributes of the syringes. A range of syringe samples are produced through custom-engineered processes. Quality inspection and initial stability studies with the set of samples determine which silicone coating is ideal for purpose.

A case study has demonstrated how customization of baked silicone coatings facilitates stability of sensitive molecules in prefilled syringes (eg, vaccine candidate in biopharmaceutical development). The study has deepened the insight into the relationship between siliconization parameters and critical quality attributes.[40] The amount of extractable silicone oil could be reduced below the detection limit (0.03 mg) of ICP-AES according to EN ISO 11885.

With low levels of lubricant quantity, the specified syringe functionality was fulfilled (plunger gliding forces in the range of 5 to 10 N).

Close partnerships between biopharmaceutical companies and syringe suppliers are instrumental in controlling the impact of product contact materials on sensitive biotherapeutics. Principal requirements regarding drug delivery systems are ideally defined and specified in an early phase of biopharmaceutical development. Manufacturing processes and quality attributes of prefilled syringes can be custom-engineered according to these needs.

SUMMARY

In today's biopharmaceutical market, products are exposed to fierce competition. The role of drug delivery strategies to differentiate products is growing. A number of biopharmaceuticals has already been commercialized in the prefilled syringe platform. However, syringe systems are sources of potential incompatibilities with sensitive molecules. The prefilled syringe industry has therefore engineered manufacturing processes that mitigate stability risks from alkali ions, tungsten, and silicone lubricants. Advanced methods for surface treatment to control pH, tungsten-reduced forming techniques, and baked siliconization processes to immobilize silicone oil have been developed. Syringe manufacturers have established expertise in material science and process technology to understand biopharmaceutical requirements. Evolving needs of highly sensitive pipeline products can be met with customized drug delivery systems. Current technology allows biopharmaceutical companies to exploit the benefits of prefilled syringes and realize the full potential of their products. ◆

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BIOGRAPHY

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Intelligent Sustained-Release Using a Selective Charged Barrier Membrane

By: Emma A. Durand

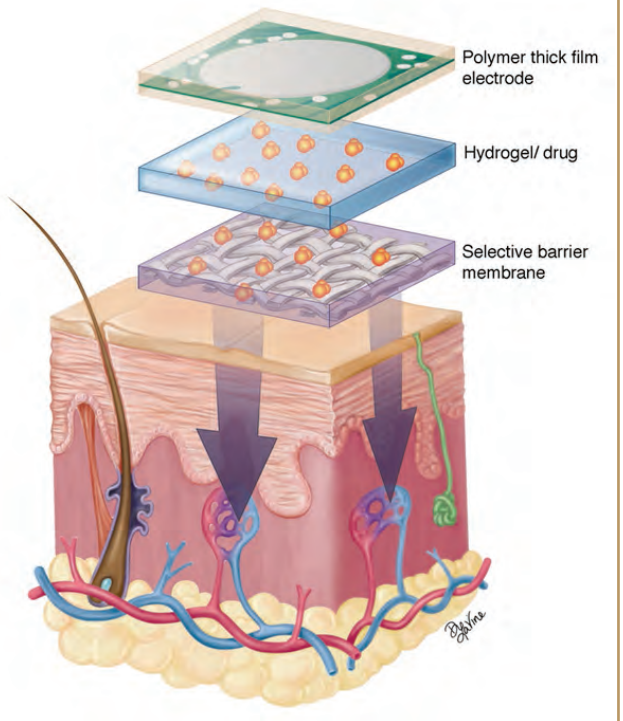
A new approach to enhancing the transport of drugs across the stratum corneum uses a proprietary selective barrier membrane to prevent the inadvertent transport of drugs by diffusion, even at elevated skin temperatures.

INTRODUCTION

With the commercial market for transdermal patches now approaching nearly three decades of practical and regulatory precedent, much has been learned and applied from the experience of earlier generation, small molecule "passive" products. Newer, active transdermal drug delivery approaches are on the near-term horizon, promising much more patient- and physician-friendly, as well as more reliable and effective methods of drug administration. The Isis Biopolymer team has combined its experience in advanced polymer development, medical devices and system design to develop the intelligent Isis Patch, currently in preclinical trials. Multiple tests on 75-kg pigs have been completed, and human testing will commence in Q3 2009 at two sites.

As passive and active patches grow in usage, their limitations are now becoming well understood, with patients, healthcare workers and pharmaceutical providers encountering problematic issues ranging from troubles with skin adherence and irritation to lack of physician control. Adding to slowed adoption have been difficulties with under- and over-dosing, as well as problems with portability of power supply and overall cost effectiveness. The Isis Biopolymer approach to transdermal drug delivery uses an intelligent iontophoretic patch and biosensing technology to address many of these shortcomings. Using proprietary, polymer thick film conductive inks, adhesives and dielectrics, along with advanced Radio Frequency Identification Bluetooth LE and battery technology, the Isis approach allows for a more practical application of the transdermal patch in clinical settings. Making the dosing system programmable as well as compact, wireless, portable and user-friendly has allowed for the patch to be more intelligent, as well as more suitable for ambulatory use. Breakthroughs have been leveraged by the company in both pliable polyester substrate and hydrogels, using technologies not available or applicable to prior-generation patches. This approach will support lower cost development and production and enable delivery of up to three drugs simultaneously, as well as a more diverse spectrum of drugs than is currently available.

FIGURE 1



The Isis Patch combines polymer thick film electrodes with hydrogel-based drug delivery through a selective barrier membrane.

ADDRESSING MODULATED RELEASE

Achieving physician and patient usability together with low cost manufacturing have proven to be challenging. Yet, the major barrier to transdermal delivery of drugs continues to be the skin itself. Permeating the skin's outer layers and enhancing the transport of drugs across the stratum corneum has been the focus of much research and many prior approaches to transdermal products, both active and passive. Significant problems have arisen due to a lack of methodology for ensuring true sustained release, that is, the ability to modulate how much and/or when a drug is released and to control release consistently, over an extended period. This deficiency in intelligence must be addressed by next-generation transdermal drug delivery products for a number of important reasons, including the following:

1. Potentially serious hazards can result from longer than recommended duration of application;
2. Application of more than the recommended number of patches can lead to overdose;
3. Smaller patients can be equally susceptible to overdose; and
4. Elevated body temperature can affect transport.

The following outlines a new approach to overcoming the skin's anatomy and barrier properties, in order to broaden the number and types of drugs deliverable via active transdermal patches and to provide physicians with increased control and dosing compliance.

TRANSDERMAL ADVANTAGE

For a wide range of reasons, delivering medicine to the general circulation through the skin is a desirable alternative to oral delivery. Many patients forget to take their medicine, while even faithfully compliant patients tire of swallowing pills, especially for those taking multiple medications. Another advantage is minimizing side effects; bypassing the gastrointestinal tract prevents GI irritation and avoids partial first-pass inactivation by the liver. Further, steady or modulated delivery and absorption of a drug over many hours or even days is usually preferable to the blood level spikes and troughs typically produced by oral dosage forms.

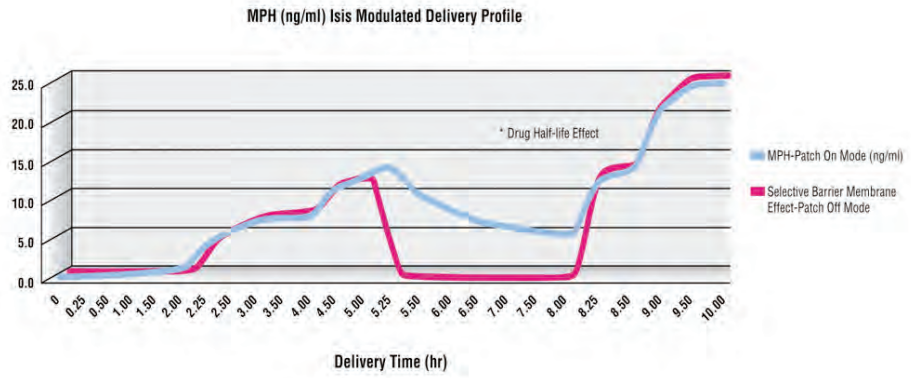
FIGURE 2

Dr. Joseph Amaral, MD, a Director at Isis Biopolymer, tests drug efficacy using the Isis Patch on live pig skin.

These are clearly among the many advantages of today's transdermal products; however, there continues to be a major drawback to transdermal delivery. Inadvertent delivery caused by changes in body temperature and metabolic rates are problematic, even more so with certain classes of drugs, such as analgesics. The estrogen-progestin patch and the fentanyl patch, which can last for 72 hours, offer real benefits to patients. Yet, while the transdermal approach is highly desirable, there remains the obstacle of the skin itself. Just as the function of the GI tract is to render material suitable for absorption once ingested, the skin's function is to keep substances out of the body. The barrier to transdermal delivery is, of course, the stratum corneum, the top layer of the epidermis. This is the skin's homeostatic and protective barrier, consisting of keratinized, flattened remnants of once-active epidermal cells. By design of nature, it is hydroscopic but impermeable to water, as well as flexible and tough. The thickness of the stratum corneum is about 10 microns on the back and abdomen, thicker on the palms and soles, and can be as thick as 600 microns. Many drugs that are suitable today for transdermal delivery, including clonidine, estradiol, fentanyl and nicotine, represent potent, low molecular weight molecules that are highly active. To increase the range of drugs available for transdermal drug delivery, a number of chemical and physical enhancement techniques have been developed with the goal of transporting drugs across the skin barrier without irritation. The controlled delivery afforded by iontophoresis involves the application of a small electrical current to maintain a constant current, thus, enabling drug transport. The amount of compound delivered is more or less directly proportional to the quantity of charge involved. In theory, this should give an improved onset time and also a more rapid offset time, so that once the current is switched off, drug transport should stop.

For this article, the issues of drug concentration and the impact of iontophoresis on pH will not be reviewed, as these subjects have been well documented in the literature. The focus here is on the issue of inadvertent drug delivery. This issue can be quite problematic for many drugs, including fentanyl and other analgesics. Iontophoresis

FIGURE 3



Isis Modulated Delivery Profile

clearly has vital applications in pain management. Appropriate modulation of the delivery profile means that iontophoresis can provide almost instant relief in response to acute pain episodes. This is important, for example, in applications such as post-operative pain and chronic pain as experienced by cancer patients. Because the input of the drug is current-controlled, kinetics allow non-invasive administration on demand in a manner similar to conventional, patient-controlled anesthesia, but without needles. In addition, maintenance doses, which take into account such parameters as sleep and diet, can be achieved and customized with variable modulated delivery. Finally, in addition to providing systemic pain relief, iontophoresis can be utilized for local pain relief or local anesthesia, such as for minor surgical procedures.

CURRENT TERMINATION

The major problem that has surfaced with iontophoretic devices dispensing analgesics occurs when drug permeation across the skin continues after termination of current. Iontophoresis, as is known, uses a weak electrical current to stimulate drug-carrying ions to pass through the intact skin, propelling high concentrations of charged medications by repulsive electromotive force.

In many devices, iontophoretic delivery of analgesics is more than able to match IV input kinetics. This is particularly important where the analgesic demonstrates an extensive first-pass effect or has a short half-life and must be given 3 to 4 times per day.

SELECTIVE BARRIER MEMBRANE

In a typical drug delivery membrane, the drug is contained in a reservoir, surrounded by a membrane. The release of the drug is constant, as long as a consistent concentration of the drug is maintained within the device. But a constant concentration can only be maintained if the reservoir contains a saturated solution and sufficient excess of solid drug. Such systems are only used for low or moderate delivery of drugs.

Isis Biopolymer has developed an intelligent, selective barrier membrane that allows compounds to be transported or blocked from transport. While the appropriate current density is transporting the drug, the Isis selective barrier membrane can be switched to either facilitate or prevent transport. This capability is controlled entirely by the system's microprocessor, without the need for professional (or any type of user) interaction. Similarly, as part of the manufacturing process, openings in the membrane which initiate or prevent drug transport are calibrated to individual drugs. Finally, the density of the current determines the rate of transport.

The Isis Patch utilizes the physics of electrophoresis and dielectrophoresis; these terms imply the interplay between electrical phenomena and motion. Because polymer dispersions contain substantial amounts of liquid, it is possible to formulate a field-sensitive, drug dispersion. Responding to an applied field in the membrane, the drug dispersion properties, such as viscosity and other physical properties, may be controlled. The response time to those field changes can approach the order of milliseconds. The control field in the membrane is able to increase resistance to flow, thus, allowing cessation of drug transport. In the Isis selective barrier membrane, the rate of transport depends upon the current density and the variable permeability of the membrane to the drug.

LIFESPAN/ISIS BIOPOLYMER TRIAL

Isis recently completed trials of four drug therapies at Providence, RI-based Lifespan research facilities. Tested drugs included methylphenidate, cefazolin and ibuprofen L-dopa, each based on the use of live pig skin. Extensive ex vivo research using pig skin has demonstrated the ability of a variety of molecules to be absorbed into the skin through the stratum corneum. The purpose of this trial was to evaluate the transdermal delivery of different drugs using the Isis Patch technology in an in vivo animal model by examining serum concentrations achieved for these drugs. The study evaluated molecules with potential widespread human clinical applications that have molecular weights less than 500 Daltons.

Extensive literature review for testing transdermal delivery systems revels that the pig is a widely accepted model and one favored by researchers because of the similar absorption characteristics of porcine to human skin. Six Yorkshire pigs weighing 30 to 50 kilograms were utilized for the study. The animals were allowed to acclimate for five days at the testing facility, fasted overnight and anesthetized in a sterile operating room. The animals' body hair in the abdominal region was removed and the area prepped in a sterile fashion. The animals were maintained under anesthesia for the duration of the trial.

Four Isis Patches were placed on the abdominal area containing each of the drugs. To eliminate location bias, the exact location of the patches varied in location on each of the six animals. The hydrogel/drug electrode size of all patches was held constant at 5 cm^2

and allowed for 600 mg to be loaded into the active electrode site. Each patch was loaded with 150 mg of the specific medication, which equates to a 25% loading of the drug in the hydrogel material.

The Isis Patches were programmed with a modulated delivery profile. The patches were not turned on for the first two hours to document the effectiveness of the selective barrier membrane. The patches were turned on for three hours, turned off for three hours, and turned on again for two hours. Three animals had Isis Patches programmed at half maximum voltage, and the other three had patches programmed at full voltage. A baseline blood sample was taken and continuous blood sampling performed throughout the modulated drug delivery process. The 10-ml blood samples were allowed to clot, spun and the serum was separated for testing purposes. All serum samples were initially frozen in liquid nitrogen and then placed at -80°C for storage.

Figure 3 demonstrates the effect of the selective barrier membrane over time. The restrictive effect on the medication when the current is reversed in the barrier membrane is clearly seen. The Isis Patch's selective barrier membrane allows for a modulated delivery profile; thus, rapid uptake and a zero-modularity mode were achieved.

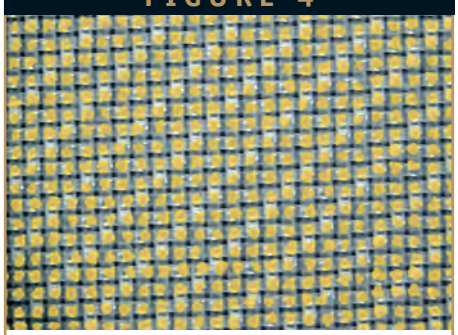
Isis also tested the passive delivery of a compound from a gel formulation with the iontophoretic delivery of the compound contained in a hydrogel. Varying application times were used, including 30, 60 and 125 minutes, after which the skin was tape-stripped and the compound subsequently extracted from the tapes. The target dosage of the instant compound was 15.5 mg delivered resulting in a blood serum assay of 156 mg/ml.

Notably, on areas of skin contacted by the patches in a passive mode (current off), compound levels were undetectable. Also of importance is this feature's applicability to lidocaine patches for local anesthesia. As recent reports confirm, there are potentially serious hazards in using skin-numbing patch products for relieving pain from medical procedures. These topical anesthetics work by blocking pain sensation in the skin. Some of the medication in a topical anesthetic (or anesthetic contained in a patch reservoir) can pass through the skin into the bloodstream. If skin temperature increases, more anesthetic can be transported. As a result, the amount of anesthetic medication that reaches the bloodstream is unpredictable and may be high enough to cause life-threatening effects, such as irregular heartbeat or breathing difficulties. The Isis Biopolymer selective barrier membrane prevents such inadvertent or unpredictable delivery, even at elevated skin temperatures.

CONCLUSION

Transdermal administration of drugs has assumed an important place in drug therapy, with many of the shortcomings of previous generations of products now being addressed by more portable, user friendly applications. The issue of inadvertent delivery caused by changes in body temperature or metabolic rates can be addressed by selective barrier membranes, applying principles of facilitated diffusion. Incorporating such functionality into the microprocessor-controlled patch ensures that compounds are transported or blocked from transport, thereby ensuring controllable, predictable and accurate dosing. By preventing inadvertent delivery of current classes of transdermally delivered drugs, Isis has paved the way for improved dosing compliance of new and existing drugs for transdermal delivery.

FIGURE 4



This dyed compound shows the effect of an electrical field on a compound within the grid of the selective barrier membrane. This facilitates complete cessation of drug delivery.

BIOGRAPHY

Ms. Emma A. Durand is President & Chief Technology Officer at Isis Biopolymer, Inc., founded in 2007 to develop a major advance in intelligent non-invasive drug delivery called the Isis Patch. Ms. Durand holds over 40 US and international patents, covering diverse areas of mechanical, electrical, and chemical engineering, virtually all of which been employed in the development of successful commercial products. Prior to founding Isis Biopolymer, she was Executive Vice President and Chief Technology Officer of American Biophysics Corp.; a Co-founder and Chief Technology Officer of EvaluTech, LLC; and a Founder of Sublimation Systems, Inc., Key-Tech Inc.; and Poly-Flex Circuit Inc. Ms. Durand attended the Massachusetts Institute of Technology, majoring in Mechanical Engineering.

Development & Characterization of Inhaled Formulations for Systemic Drug Delivery

By: M.W. Samaha, PhD; H.A. El-Maradny, PhD; D.M. Ragab, PhD; and F.M. El-Khawas, PhD

ABSTRACT

The drying of powder aerosols has traditionally followed the spray-drying method. Spray-dried powders were prepared of bovine serum albumin (BSA) with GRAS (generally recognized as safe) excipients for inhalation viz Tween 20, sodium chloride, and beta-cyclodextrin. The spray-dried formulations were then analyzed for aerodynamic behavior, surface morphology, and physical state. The Aerolizer® (Novartis Pharmaceuticals) and Handihaler® (Boehringer Ingelheim Pharma) were used as the inhalation devices, and the in vitro deposition was calculated using a twin-stage impinger at two different flow rates (30 and 60 L/min). Primary powders with different polydispersity, but comparable physical and mass median aerodynamic diameter (MMAD), were obtained. Particle sizing in the impinger and by laser diffraction indicated that aerosols exited an Aerolizer or Handihaler inhalation device as particle aggregates rather than isolated particles. An aggregation index was computed for the different formulations studied. The aggregation index values obtained for spray-dried powders of BSA with the different excipients used in this study indicated a variation in aggregate sizes as a result of changing the type and concentration of excipients as well as the operating conditions, ie, inhaler device and air flow. The effects of the inhaler device and air flow on the aerosolization performance were investigated. The class and the concentration of excipients were optimized by considering two inhalation indices, the emitted dose (ED) and respirable fraction (RF). Among all the combinations tested, the BSA/0.9% w/v sodium chloride formulation was particularly optimum and exhibited an ED value of 74% of the nominal dose (emitted from the Handihaler device using 60 L/min air flow) and an RF value as high as 53.29%. Whereas, 0.5% w/v beta-cyclodextrin formulation with BSA showed an ED of 75.46% of the nominal dose and an RF value of 46.32%. According to the aggregation index results obtained, one can conclude that the differences in RFs rather resulted from differenced in powder cohesiveness with the type of excipients aerosolized under the same operating conditions.

INTRODUCTION

To improve powder aerosol technologies, scientists and manufacturers have acknowledged the importance of understanding the determinants affecting powder deposition. The effects of particle surface characteristics, air flow rate, inhalation devices, and excipients on aerosol generation are some of the fundamental areas that have been under continuous investigation.[1-5]

In some spray-dried powders, clusters of aggregated particles were observed and may cause an increase in the fraction of particles deposited at the oropharynx. The tendency of proteins and peptides to accumulate on the surface of spray-dried powders as clusters was described in various studies.[6] During atomization, the air/liquid interface of the spray solution greatly and suddenly expands.[7] This is a distinct interface in which proteins or peptides tend to adsorb each other. However, Maa et al found that adding Tween 20 to the spray-dried solution reduced surface aggregation of recombinant human growth hormone.[8] In another study using BSA, Alder et al reported similar results in which increasing concentrations of Tween 80 reduced the surface accumulation of BSA in a concentration-dependent manner.[6]

Electrolytes are also beneficial in spray-drying of proteins, preferably strong electrolytes. In preliminary investigations, it has been reported that the incorporation of electrolytes into liquid formulation containing protein to adjust the ionic strength of the solution is effective in protecting the protein during spray-drying. It is postulated that due to an increased concentration of electrolytes in solution, the ions tend to concentrate on the droplet surface during spray-drying, thereby protecting or shielding the active protein in the droplet core during the spray-drying process.[9] Thus, these salts can be employed to not only minimize protein aggregation, but also

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increase the aerosol performance of the resulting spray-dried compositions.[10]

Cyclodextrins (CDs) are cyclic oligosaccharides with a hydrophobic central cavity. Drugs may form monovalently bonded complexes with CDs by inclusion into the hydrophobic cavity. CDs have been investigated as drug delivery vehicles to the lungs.[11]

The objective of this work was to determine the effects of formulation excipients and physical characteristics of inhalation drug particles on their aerosolization properties in order to optimize their RFs. This will determine which formulations could be the most appropriate for pulmonary protein delivery.

Dry powders were prepared with BSA alone or with different concentrations of Tween 20, sodium chloride or beta-cyclodextrin. Aerodynamic behavior was estimated in vitro using an impinger and by particle sizing at the exit of an Aerolizer or a Handihaler at different flow rates.

MATERIALS

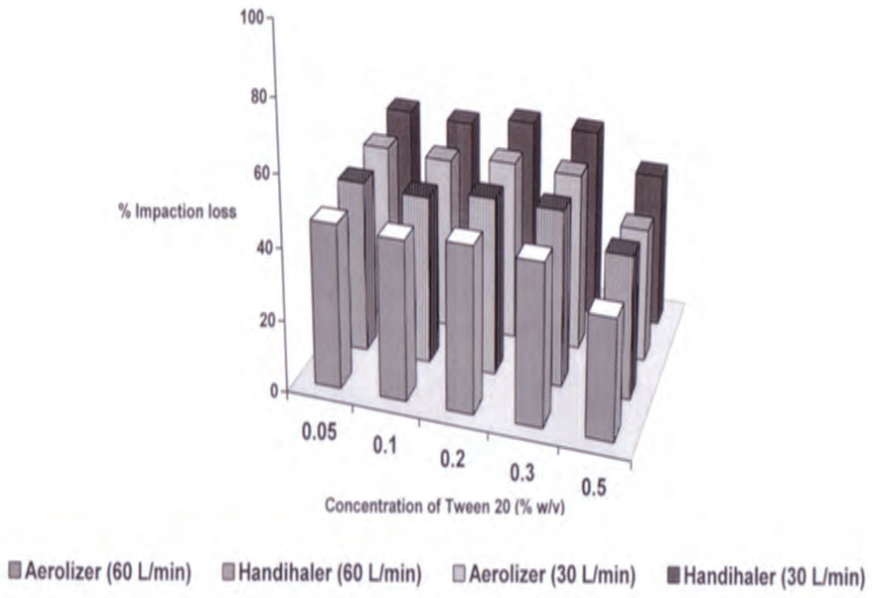
The following materials were used: bovine serum albumin (BSA), 95% albumin (Sigma-Aldrich); Tween 20 (Aldrich Chemicals Co. Ltd.); sodium chloride (ADWIC, El-Nasr Pharmaceutical Co.); beta-cyclodextrin (Sigma-Aldrich); sodium hydroxide (ADWIC, El-Nasr Pharmaceutical Co.); hard gelatin capsules (Novartis Pharmaceuticals).

FORMULATIONS OF THE DRY POWDERS

Dry powder of BSA was made by spray-drying.[12] BSA was dissolved in distilled water. Next, the pH was adjusted to 7 by addition of a few droplets of NaOH 0.01N. The concentration of BSA chosen was 0.1% w/v. Solution was pumped into the drying chamber of the spray-dryer (Lab Plant Ltd.).

The spray-dryer operates on the principle of a nozzle spraying in a parallel flow (the sprayed product and the drying air flow are in the same direction). The adjustable parameters

FIGURE 1



The effect of inhaler device and flow rate on the percentage impaction loss of spray-dried bovine serum albumin powders containing different concentrations of Tween 20.

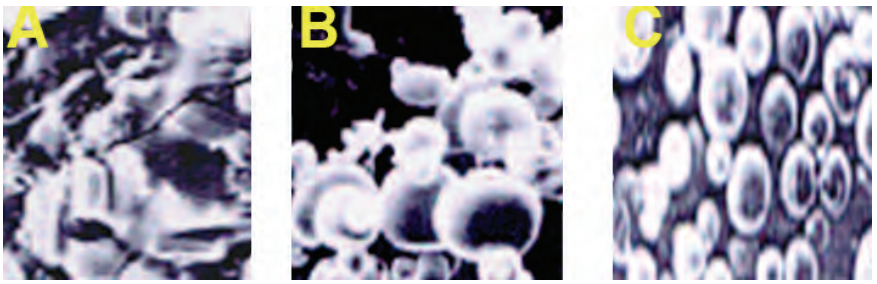
TABLE 1

Aerodynamic Diameter (µm)	Tap Density	Span Index	D50 (µm)	Concentration of Excipient % w/v	Type of Excipient
6.87	0.50	1.51	9.72	**0.05**	Tween 20
3.93	0.48	2.18	5.67	**0.1**	
3.46	0.39	2.96	5.54	**0.2**	
3.11	0.35	1.99	5.25	**0.3**	
3.74	0.40	2.54	5.91	**0.5**	
6.42	0.30	1.54	11.72	**0.1**	Sodium Chloride
2.54	0.18	1.00	5.93	**0.5**	
0.89	0.14	1.95	2.39	**0.9**	
1.26	0.17	1.57	3.02	**1.3**	
4.07	0.25	1.61	8.13	**0.1**	Beta-cyclodextrin
3.31	0.19	2.14	7.59	**0.3**	
0.97	0.16	3.38	2.42	**0.5**	
1.37	0.18	1.92	3.20	**0.9**	

Study of the effect of excipient type and concentration on the particle size, density, and aerodynamic diameter of spray-dried particles.

include inlet and outlet temperature, solution pump flow rate, and the aspirator partial vacuum. In the present experiment, the inlet air temperature was established at 150°C, the pump flow rate was 10 mL/min, the aspirator was set to 40 m^3/hr, and the atomizing air was 700 L/hr. The outlet temperature depended on the inlet temperature, the pump, and aspirator flow rates, and was 75°C. The solution was pumped into the feeding system of the spray-dryer. The resultant powder was blown through the cyclone separator and collected in a container. Exhaust air was extracted out of the cyclone by a vacuum pump and filtered by a fiber filter. The powder was collected and analyzed.

FIGURE 2



SEM micrographs of spray-dried BSA powders containing 0.3% w/v Tween 20 (a), 0.5% w/v beta-cyclodextrin (b), and 0.9% w/v sodium chloride.

TABLE 2

Handihaler		Aerolizer		Concentration of Excipient % w/v	Type of Excipient
Aggregation Index		Aggregation Index			
Flow Rate 60 L/min	Flow Rate 30 L/min	Flow Rate 60 L/min	Flow Rate 30 L/min		
1.14	1.29	1.24	1.33	**0.05**	**Tween 20**
1.95	2.23	1.98	2.26	**0.1**	
2.17	2.48	2.21	2.53	**0.2**	
2.37	2.71	2.37	2.76	**0.3**	
2.00	2.35	2.02	2.38	**0.5**	
1.17	1.34	0.88	1.20	**0.1**	**Sodium Chloride**
2.49	3.00	1.36	2.33	**0.5**	
3.92	6.01	2.68	5.48	**0.9**	
4.18	5.56	2.07	3.56	**1.3**	
1.73	1.79	1.72	1.80	**0.1**	**Beta-cyclodextrin**
1.98	1.99	1.92	2.09	**0.3**	
5.35	4.65	5.21	4.89	**0.5**	
4.93	5.05	4.83	4.91	**0.9**	

Study of the effect of excipient type and concentration on the aggregation behavior of spray-dried particles using the Aerolizer® and Handihaler® as inhalation devices.

STUDY OF THE EFFECT OF DIFFERENT EXCIPIENTS ON BSA AEROSOLIZATION PROPERTIES

Different concentrations of Tween 20 (0.05%, 0.1%, 0.2%, 0.3%, and 0.5% w/v), sodium chloride (0.1%, 0.5%, 0.9%, and 1.3% w/v), and beta-cyclodextrin (0.1%, 0.3%, 0.5%, and 0.9% w/v) were prepared separately in 0.1% w/v BSA solution. Each solution was pumped separately into the drying chamber of the spray-dryer under the same aforementioned conditions. All spray-dried powders were collected separately and analyzed.

PARTICLE SIZE, DENSITY & SURFACE MORPHOLOGY

Visualization of particle size and morphology was achieved using a conventional scanning electron microscope (SEM) (Jeol JSM-5300).[4] The particle size distribution of the primary powders was measured in suspensions using a Cilas laser diffractometer (Cilas L-100, Quantachrom). Isopropyl alcohol was used as a dispersion medium, and the dispersion was vortexed for 1 minute before sizing. The polydispersity of the powders was expressed by the Span index in the following equation:

$$Span\ Index = D_{(v,90)} - D_{(v,10)} / D_{(v,50)}$$

Where, $D_{(v,90)}$, $D_{(v,10)}$, and $D_{(v,50)}$ are the equivalent volume diameters at 90%, 10%, and 50% cumulative volume, respectively. The particle size of the primary powders was described by the volume median diameter (VMD).[5]

The powder density (ρ) was evaluated by tap density measurements.[13] Experiments were performed in duplicate and were highly reproducible. The theoretical aerodynamic diameter of individual particles, D_{aer},was calculated based on the following equation:

$$D_{aer} = (\rho/\rho_1)^{0.5} * D$$

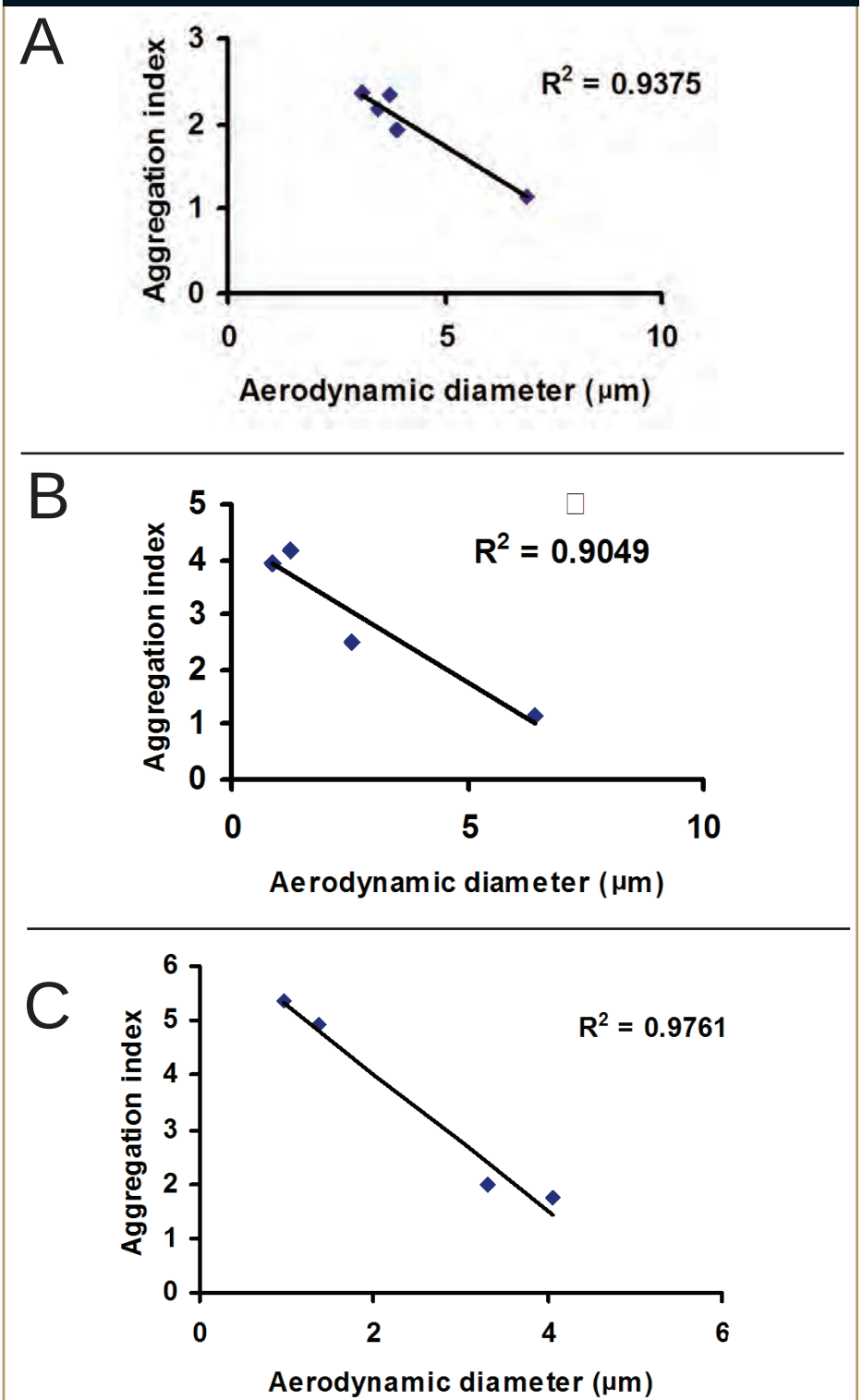
Where (ρ) is the powder density, (ρ1) is the density of water (equal to 1 g/cm^3), and (D) is the volume median diameter of particles.[4]

IN VITRO AEROSOL DEPOSITION

The dispersion behavior (the breaking up of agglomerates to regenerate the primary particles) of each powder was assessed using a twin-stage liquid impinger (TSLI) with a glass throat (USP apparatus 2). The powder was aerosolized using Aerolizer and Handihaler dry powder inhaler devices (DPID) and then dispersed at two different flow rates (30 and 60 L/min). An inhaler was attached to the inlet of the TSLI, and the impinger was fixed on the testing stand. The flow rate was maintained by a vacuum pump. The deposition pattern in TSLI was fractioned into the amount of drug deposited on the capsule and device, throat, first stage, and second stage of the impinger. Samples were then collected from each compartment of the impinger. The amount of drug at each compartment was then determined by spectrophotometric analysis (Perkin Elmer). The fine particle fraction (FPF) or equivalently the RF is the percentage of the total dose at stage 2, corresponding to particles less than 6.4 microns. The emitted dose (ED), which is the percentage of the total powder mass exiting the capsule, was also determined and calculated via the following equation:

ED = Total Powder Mass – Amount of Drug Collected at the Capsule & Device (C, D)

FIGURE 3



Correlations between the aggregation index and aerodynamic diameter of spray-dried powders prepared using Tween 20 (a), sodium chloride (b), and beta-cyclodextrin (c).

The cumulative mass of powder less than the stated size of each stage of the liquid impinger was calculated and plotted on a log paper as percent of total mass recovered in the impinger against the effective cut-off diameter. The experimental mass median aerodynamic diameter (MMAD) of the particles is defined from this graph as the particle size at which the line crosses the 50% mark, and the geometric standard deviation (GSD) was calculated via the following equation:

$$GSD = (X/Y)^{0.5}$$

Where X and Y are the particle sizes at which the line crosses the 84% mark and the 16% mark, respectively.[14]

RESULTS & DISCUSSION

The particle size distribution (D50), span index, and aerodynamic diameter of the different formulations of BSA prepared with different concentrations of Tween 20, beta-cyclodextrin, and sodium chloride are presented in Table 1. The polydispersity was expressed by the span index, which ranged from 1.00 to 3.38. A small span index indicates a narrow size distribution. Polydispersity of the primary powder affected the impaction loss, which is defined as the mass fraction of particles collected in the throat and stage 1 of the impinger (Figure 1). In comparison with the smaller span index powders, the impaction loss for larger span index powders was much higher and flow dependent, as impaction loss is proportional to the air flow and square of particle or agglomerate size.[15]

Particle density is an important parameter in aerosol physics. Spray-dried powders are often approximately spherical and hollow. A hollow interior imparts a low tap density at 0.3% w/v Tween 20, 0.9% w/v sodium chloride and 0.5% w/v beta-cyclodextrin, which will be increased by a more narrow size distribution. In addition, smaller particles are usually more dense, hence the bulk density of small-size powders will be higher.[16] Of primary interest is its use in the calculation of particles' aerodynamic diameters. The aerodynamic diameter is the diameter of unit density sphere that has the same settling velocity as the particle in question. The aerodynamic diameter varies with particle density and geometric diameter. It increases via increasing the tap density. Increasing the concentration from 0.1% w/v to 0.5% w/v for the used excipients approximately decreased the Daer by one-, three-, and four-fold for Tween 20, sodium chloride, and beta-cyclodextrin. Therefore, low density particles are being explored as a means of improving the delivery of inhaled therapeutics.[17]

The particles produced for BSA measured in the presence of different excipient concentrations were small and porous with primary geometric particle diameters between 2.39 and 11.72 microns and powder densities of < 0.6 g/cm^3. Calculated primary aerodynamic diameters ranged between 0.89 and 6.87 microns.

Porous particles have recently attracted attention for pulmonary deposition. SEM micrographs of spray-dried BSA powders prepared with different excipients are shown in Figure 2. Formulations containing beta-cyclodextrin and sodium chloride showed smooth, spherical, and less-aggregated particles. In the case of Tween 20, the particles are highly crumpled with folded structures. The particles are engineered to be less than unit mass density by virtue of a porous structure with trapped air volume within the particle. Because these particles have a mass density significantly lower than

TABLE 3

Handihaler 30 L/min		Aerolizer 30 L/min		Concentration of Excipient % w/v	Type of Excipient
Capsule & Device Retention	Respirable Fraction (stage 2)	Capsule & Device Retention	Respirable Fraction (stage 2)		
40.38	7.72	45.99	4.72	**0.05**	**Tween 20**
40.04	8.96	44.64	6.96	**0.1**	
34.56	11.72	40.99	8.72	**0.2**	
33.02	13.50	39.82	10.53	**0.3**	
48.49	7.97	57.46	5.30	**0.5**	
38.58	9.51	64.35	11.04	**0.1**	**Sodium chloride**
38.26	22.09	56.21	24.16	**0.5**	
35.58	38.73	54.07	29.06	**0.9**	
48.54	22.47	65.87	22.55	**1.3**	
50.16	21.70	69.86	12.04	**0.1**	**Beta-cyclodextrin**
47.85	26.15	71.56	12.49	**0.3**	
46.47	35.28	70.09	24.40	**0.5**	
48.56	25.38	68.26	15.72	**0.9**	

Study of the effect of excipient type and concentration on the aerosolization behavior of spray-dried particles using the Aerolizer® and Handihaler® as inhalation devices at 30 L/min.

unity, particles with an aerodynamic diameter in the respirable size range can be achieved despite having a geometric particle size greater than 10 microns.[17]

Inhaled aerosols are typically described by log-normal size distributions that are defined by a mass median diameter (MMAD) and geometric standard deviation (GSD). Although the data obtained revealed aerodynamic diameters of individual particles below 7 microns, the MMADs measured in the impinger operated at 30 and 60 L/min were larger, probably due to the formation of particle aggregates. In addition, dispersion of powders in the impinger was variable, indicating polydispersity. It has been reported that if the GSD is greater than 1.2, powder aerosols are polydisperse.[15] Different polydispersities would have affected the contact areas and hence cohesion between particles.[18]

To further confirm the concept of aerodynamic particle size, an aggregation index was proposed and obtained by dividing the MMAD by the D_{aer}. Table 2 demonstrated the calculated aggregation index values for the two dry powder inhaler devices at 30 and 60 L/min. Results obtained for the aggregation indices showed change in aggregate size with an increase in air flow rate. The aggregate size was lowered upon increasing the air flow rate from 30 to 60 L/min. Figure 3 demonstrates the correlation between the D_{aer} and aggregation index. A linear relationship with a good correlation coefficient (R = 0.94) was found. The aggregation index was increased upon decreasing the D_{aer}. For example, spray-dried powder of BSA containing 0.9% w/v sodium chloride, having the least D_{aer}, showed the highest aggregation index value (6.01). These results agreed with Curtis et al.[19] They studied the interaction between lysozyme, as a model protein, and chloride ions. They found that at high salt concentration (0.9% w/v), tryptophan residues are buried in a non-polar environment, and the quenching is consistent with the energy transfer between the tryptophan moieties, which leads to protein aggregation.

For further investigation of aerosolization performance, the powder's respirable RF and ED were determined using TSLI at a flow rate of 30 and 60 L/min (Tables 3 & 4). This study demonstrated that the dispersion behavior of BSA powders depends on an interplay between the primary particle size, air flow, and the inhaler dispersion efficiency, which increased the fine particles in the aerosol cloud. For large particles, the dependence of dispersion on air flow and inhaler was weaker. The amount of fine particles in the aerosols thus depends on exactly what inhaler, air flow, and powder were used. The percentage of drug particles emitted from the Handihaler was greater than that emitted from the Aerolizer device. Increasing the flow rate from 30 to 60 L/min significantly increased the ED. An optimum ED value was obtained at 0.3% w/v Tween 20, 0.9% w/v sodium chloride, and 0.5% w/v beta-cyclodextrin.

The point that needs to be considered next is the regional deposition of the emitted dose. The RFs defined for this purpose are also listed in this table. The RF obtained increased by about two-fold upon increasing the flow rate from 30 to 60 L/min. On the other hand, the effect of inhalation device on RF was prominent. An increment in RF resulted when using the Handihaler device. The highest RF values (28.68%, 53.29%, and 46.32%) were obtained with 0.3% Tween 20, 0.9% sodium chloride and 0.5% beta-cyclodextrin at a 60 L/min flow rate using the Handihaler, respectively.

The flow dependence of RF in the Aerolizer and Handihaler can be attributed to the powder cohesiveness and the inadequate dispersion efficiency of the inhaler. The

TABLE 4

Handihaler 60 L/min		Aerolizer 60 L/min		Concentration of Excipient % w/v	Type of Excipient
Capsule & Device Retention	Respirable Fraction (stage 2)	Capsule & Device Retention	Respirable Fraction (stage 2)		
30.39	21.69	37.35	16.96	0.05	Tween 20
29.83	23.37	35.02	20.59	0.1	
23.95	26.73	30.86	23.05	0.2	
22.30	28.68	29.15	25.99	0.3	
37.59	22.67	48.58	17.98	0.5	
28.76	24.08	54.53	25.61	0.1	Sodium Chloride
28.45	36.66	46.39	38.73	0.5	
25.78	53.29	44.26	43.63	0.9	
38.72	37.04	56.06	37.12	1.3	
28.22	32.75	47.94	23.08	0.1	Beta-Cyclodextrin
25.92	37.19	45.63	27.53	0.3	
24.54	46.32	48.16	36.99	0.5	
26.61	36.43	46.33	26.76	0.9	

Study of the effect of excipient type and concentration on the aerosolization behavior of spray-dried particles using the Aerolizer® and Handihaler® as inhalation devices at 60 L/min.

powder in the Aerolizer is dispersed simply by the air flowing through a grid in the mouthpiece whereas in the Handihaler, the powder is emptied and dispersed from a small hole at each end of the capsule spinning at 1200 rpm, and is further dispersed through the mouthpiece by the air entrained from the two air inlets of the inhaler. The Handihaler is apparently more efficient as more complete dispersion of the powders is achieved at the same air flows.

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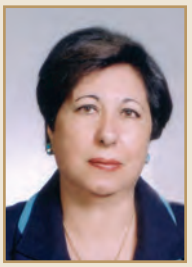
BIOGRAPHIES

Prof. Dr. Magda Samaha earned her PhD from the University of Wisconsin, Madison in Pharmaceutics with Professor Dr. Gordon Amidon as her advisor. Dr. Samaha has had a major role in developing correlations of solubility parameters of pharmaceutical solids with other physical quantities, for instance, the advancing and receding contact angles of polymers; the surface free energy for a number of drugs; the CMC of polyoxyethylated ionic surfactants. She is currently the Head of Industrial Pharmacy Department at the College of Pharmacy, University of Alexandria in Egypt. She has participated in several joint research articles relating to the optimization of drug delivery from dry powder inhalers using different drying techniques.



Prof. Dr. Ferial El-Khawas earned her PhD in 1965 from the Faculty of Pharmacy, University of Alexandria, Egypt, under the supervision of Prof. Tawashi. Since then, she has actively participated in both teaching and research in the field of Industrial Pharmacy both in Egypt and abroad. She has supervised a number of Master and Doctor theses and has published a number of research papers in various local and international journals. Her research field included topics on powder technology, drug stability, product formulation and optimization as well as recent non-conventional dosage forms. Prof. El-Khawas has also occupied various administrative positions during her academic career, such as Head of the Department of Industrial Pharmacy and Vice Dean of the Faculty of Pharmacy, University of Alexandria.

Dr. Hoda El-Maradny earned her PhD from the Faculty of Pharmacy, University of Alexandria, Egypt, under the supervision of Prof. El-Khawas and Prof. Samaha. Her PhD thesis is titled Evaluation of Fluidization Technique in the Processing of Pharmaceutical Solid Dosage Forms. Her research topics are related to sustained-release dosage forms, pulsatile-release tablets, and powder technology for inhalable dry powder formulation.

Dr. Doaa Mohamed Ragab is an Assistant Lecturer of Industrial Pharmacy, Faculty of Pharmacy, Alexandria University, Egypt. She has recently earned her MS under supervision of Prof. El-Khawas, Prof. Samaha, and Dr. El-Maradny. Her thesis is related to the development and characterization of inhaled formulations for systemic drug delivery. Her research interests include topics related to drying technology, ie, spray-drying, freeze-drying, spray-freeze drying, and supercritical fluid technology for preparation of hollow porous particles.

Rethinking Biopharmaceuticals With Albumin Fusion Technology

By: Dave Mead, PhD, and Ruth McDermott, PhD, MBA

INTRODUCTION

Biologics are becoming an increasingly dominant presence in the therapeutics market. In recent years, biologics have revolutionized the approach to the treatment of many diseases, including ones that previously had no effective therapeutic options. Many treatments that were once considered to be inadequate or flawed have now been developed further through microbial expression to increase effectiveness and reduce costs. Novozymes Biopharma, a world leader in yeast-based protein expression, has more than 20 years of experience providing expert processing solutions for biologics.

However, the increased usage of these new techniques within biological therapeutics has also thrown up a great number of challenges and issues. There are a number of factors that add constraints to the field of biologics, in particular, issues such as low *in vivo* stability and lack of efficacy, due to poor half-life and bioavailability. These issues can result in high peaks or low levels of the drug in the patient, resulting in unwanted side effects and/or limit the therapeutic benefit. Developing protein therapeutics is challenged by delivery and complex manufacturing. Novozymes Biopharma's albufuse® and associated technology is one tool that has been designed to manage these difficulties.

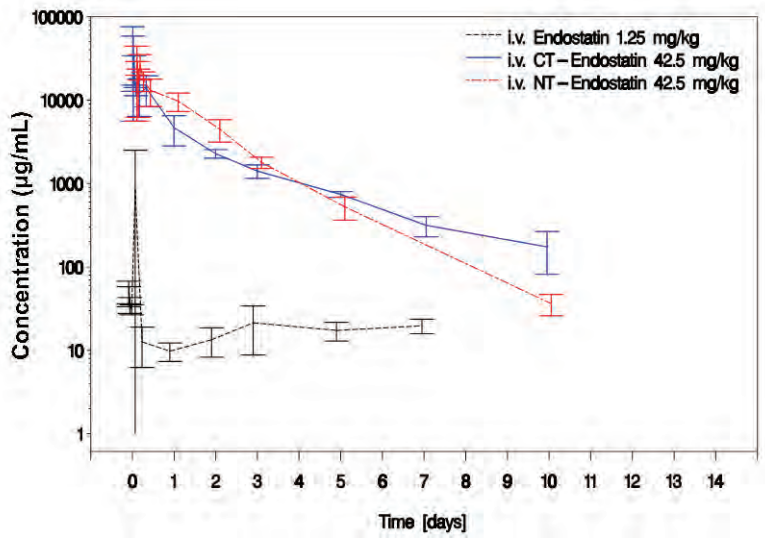
ALBUMIN FUSION TECHNOLOGY

albufuse is an albumin fusion technology that offers the ability to make completely new therapeutics that were previously out of reach. The fusion technology produces albumin joined to a therapeutic protein or peptide, defined at the genetic level. Albumin, present in high volumes in the bloodstream, is the natural choice for drug delivery as it has no endogenous activity, a naturally long half-life of 20 days, and is an effective carrier for transporting many molecules around the body. albufuse has been shown to increase a protein's half-life from "minutes to hours" and "hours to days."

albufuse offers a single-step expression solution alternative to lengthy and costly post-production chemical processing required of other methods for extending circulatory half-life, and offers the potential for a more consistent and natural alternative for effective protein drug half-life extension. The low production costs achieved through high expression levels in Novozymes Biopharma's *Saccharomyces cerevisiae* protein expression system further emphasises the breadth and significance of the potential advantages albufuse technology offers for future biopharmaceutical product enhancement and development.

The albufuse concept is suitable for a great many peptides and proteins. The heart-shaped albumin molecule has

FIGURE 1



Endostatin Circulatory Half-Life (IV)

several points, particularly at either of the C- or N- termini, where proteins and peptides can be placed. It is even possible to fuse two different proteins together with albumin in the same recombinant molecule to give two different functions (bivalent) at the same time. This flexibility means that the concept can also be used to make novel products, such as bifunctional proteins, as well as improving existing products.

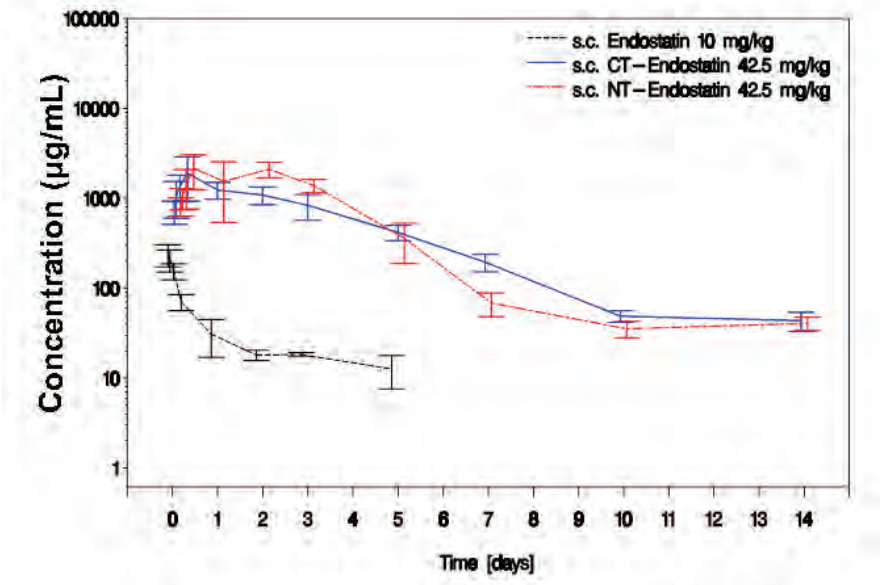
Albumin fusions create new opportunities for the development of novel drugs and treatments, as well as creating value by providing effective solutions to the pharmaceutical industry. Significant cost savings can also be made because of the ease of manufacture of the protein, and there are no additional post manufacture purification steps required by other technologies, such as PEGylation.

HALF-LIFE EXTENSION BENEFITS

The increased *in vivo* half-life of the therapeutic protein fused to the albumin is the major key clinical advantage of albufuse. An increased half-life significantly reduces the frequency of administration of the therapeutic protein, which can reduce the overall dosage. As some biopharmaceuticals have to be administered by a nurse at home or at a clinic, the number of visits can be significantly reduced, resulting in better compliance and ease of use. Additionally, there is improved stability and shelf-life of the proteins.

A significantly reduced dose means that treatment is more cost-effective, an increasingly important consideration due to the growing focus on healthcare costs and accessibility to medicine. The risk of possible side effects is also reduced as a lower dose means that the toxicity level of the protein within the patient may not be reached. Instead, the drug dose remains within the therapeutic range, increasing the patient's response to the drug. It has been demonstrated that albufuse-based molecules can lead to more favorable tissue distribution within the body, reducing the risk of localized retention at the site of administration.

FIGURE 2

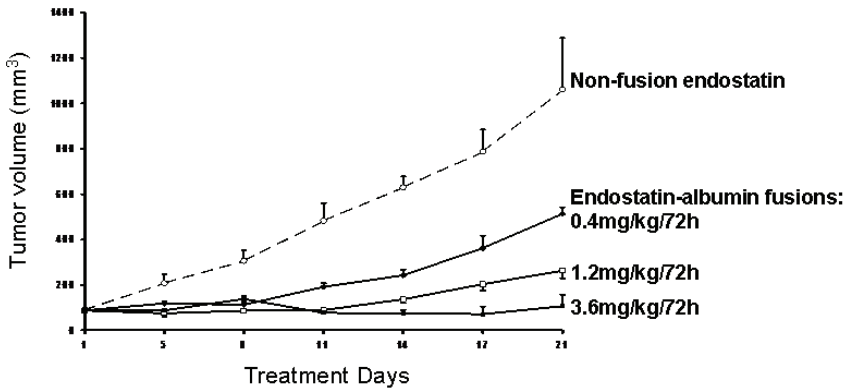


Endostatin Circulatory Half-Life (SC)

PROTEIN EXPRESSION SYSTEMS

The albufuse technology can be utilized in a wide variety of protein expression systems. However, Novozymes Biopharma's proprietary yeast expression platform has been developed to be particularly effective in producing

FIGURE 3



Endostatin Fusion Activity Studies in In Vivo Tumor Models (SC)

TABLE 1

Route of Administration	Half-Life (h)		Ratio of albufuse Improvement
	Non-Fusion	Albumin Fusion	
i.v.	2	24-50	12-25x
s.c.	5	28-56	6-12x

Elimination (T1/2) of endostatin albumin fusions in an *in vivo* model.

albufuse molecules. Based on a proprietary 2-micron plasmid construct, the system allows the expression of an extensive range of proteins, representing many classes of biotherapeutics. These include protease inhibitors, enzymes, transport proteins, cytokines, anti-angiogenic polypeptides, anti-inflammatory polypeptides, and growth hormones. The advantages of using this protein expression system includes the ability to generate intact proteins with low cost of goods, due to large-scale manufacturing with low purification costs, in a system that is free of animal-derived components. The latter is of rising importance as the regulatory authorities begin to implement strict guidelines around the use of animal-based products and ingredients in pharmaceutical processes and products. The Novozymes Biopharma yeast expression system has another key advantage in that is provides a highly consistent and reliable supply of the therapeutic protein of interest, a major concern for companies as they develop their products through clinical trials and to market.

Novozymes Biopharma has used its yeast expression system to develop a portfolio of protein products for the Biopharma industry. These include animal-free ingredients for use in upstream processing, such as recombinant human albumin, transferrin (marketed in conjunction with Millipore Corporation under the joint CellPrime™ brand) and Recombumin® for use in the formulation of final products.

HEPATITIS C VIRAL INFECTION - CASE STUDY

Interferon is used to treat people suffering from chronic hepatitis C viral infections. However, with a normal half-life of 5 hours, interferon is soon lost from the body. One way to make it last longer is to use PEGylation, whereby a chemical is bolted on to the interferon. This extends the half-life to 35 hours. However, by fusing interferon to human albumin, the administration is increased to once every 2 weeks. Human Genome Sciences Inc.[1] has developed Albuferon® using albufuse under license and in collaboration with Novartis. Albuferon requires half the number of injections compared with PEGylated interferons, and Phase II results demonstrated that Albuferon offers at least comparable efficacy, comparable safety, and the potential for less impairment of health-related quality of life. One Phase III trial has already been successfully completed, meeting all of its primary endpoints, and a second Phase III trial is approaching its final stages. The product is expected to be launched on the market in 2010.

Albuferon is just one of the drugs under development featuring albufuse technology. Other companies, such as Dyax Corp., are also using Novozymes Biopharma's albufuse and yeast expression technology under license. Dyax utilizes its proprietary drug discovery technology to identify antibody, small protein, and peptide compounds for clinical development. Dyax has been granted a non-exclusive research and development license for use of Novozymes Biopharmas' technology to develop albumin fusions of Kunitz domain proteins and antibody fragments for therapeutic and diagnostic applications.

CSL Behring LLC has also employed this technology in the development of their future protein biotherapeutics based on plasma proteins.[2] The proof-of-principle study showed for the first time that it was possible to fuse the coagulant Factor VIIa genetically to human albumin and thereby meeting an unmet need in haematology by significantly improving pharmacokinetic parameters.

ALBUFUSE IN CANCER THERAPY TREATMENT

Novozymes Biopharma has demonstrated the applicability of its expression technology and albufuse with a wide range of therapeutic proteins, including endostatin. Endostatin is a negative regulator of angiogenesis, the development of new blood capillaries, and as such is a proven anti-tumour therapy. Rather than acting on the tumor directly, this compound works by affecting the blood vessels that feed the tumor. As a therapy, anti-angiogenic drugs would be expected to require administration over a long period of time, initiated during the active angiogeneic phase of tumor

development, and then years beyond to prevent any new tumor growth. Therefore, a drug that has an extended presence in the patient with retained activity is desirable.

Novozymes Biopharma generated versions of fusion molecules that combined recombinant human endostatin and albumin at either the N- or C-terminal ends. Novozymes Biopharmas' yeast expression system produced high levels of each version, with simple purification steps resulting in high-quality products.

The bioavailability of both versions of the albumin fusion endostatins were compared in *in vivo* models, using both intravenous (IV) and subcutaneous (SC) administration (Figures 1 & 2).

The results indicate that the availability in serum was markedly higher for albumin fusion endostatin compared to the non-fused molecule. In addition, after SC administration, the peak concentrations were greater than 8-fold higher for the albumin-fused substances. Also, the elimination half-lives were enhanced by 12-fold (C-terminal) and 6-fold (N-terminal) over the classic endostatin.

In vivo tumor models demonstrated the therapeutic efficacy of the endostatin-albumin fusions in a dose-dependant manner. Figure 3 shows that the fused versions of the endostatin were similar to classic endostatin in reducing tumor growth, thus demonstrating that the activity of the protein is retained following fusion to albumin.

LATEST APPLICATION

The latest key application for albufuse technology is in the increasingly important area of antibody fragment expression. The numerous clinical, diagnostic, and consumer applications of antibody-based therapeutics are limited by the high costs of process development and commercial-scale manufacture. Novozymes Biopharmas' scientists have focused on achieving high-level expression of scFv albumin fusions of > 5g/L. A reliable production process that offers quick scale up will help facilitate a more rapid transition of antibody molecules to market. These issues can be addressed by using Novozymes Biopharmas' yeast expression platform, and in combination with albufuse, has been shown to significantly enhance the *in vivo* residence time of the fragment. Novozymes Biopharma has demonstrated this by producing a range of scFv-albumin protein fusions (N-terminal, C-terminal, and bivalent) and comparing to non-fused recombinant scFv and to recombinant human albumin (rHA). After intravenous and subcutaneous application in animal models, all three scFv-albumin fusions showed significantly increased bioavailability of the active scFv when compared to the non-fused molecule. The pharmacokinetics of all three fusions was comparable to that of rHA. Data modeling simulation indicated that improved dosing regimes for fused versus unfused molecules could be achieved, extending from every 6 hours to every 3 days.

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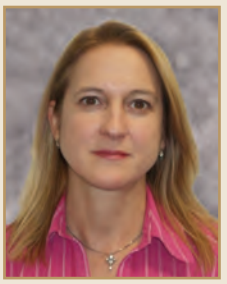
BIOGRAPHIES

Dr. Dave Mead is Director, Business Development at Novozymes Biopharma UK Limited, based in Nottingham (UK). He earned his BS in Microbiology from the University of Kent, followed by his PhD from UMIST (Manchester, UK) in Plasmid-host Interactions in yeast. He initially worked as a Research Scientist in GSK's Biotechnology Group. Dr. Mead has held a number of roles within Novozymes BioPharma Limited, including Fermentation Manager with responsibility for the development of commercial and scaleable fermentation processes integrated with molecular biology and downstream purification, including technology transfer, both internally and externally. He was also responsible for setting up and managing the Technical Support function for Recombumin® manufacturing before taking responsibility for the company's intellectual property and business development. He has negotiated a number of key technology and product licenses.



Dr. Ruth McDermott is Business Development Manager at Novozymes Biopharma UK Limited, based in Nottingham (UK). Prior to joining Novozymes, she led the Biomedical Team at the University of Liverpool's Business Gateway, responsible for knowledge and technology transfer and interactions with bio/pharma industries. After earning her PhD in Cellular Biochemistry, Dr. McDermott spent several years as a Research Scientist in academia and also at Cobra Therapeutics Limited. After studying for her MBA, she moved into a career as Business Development Manager and held various roles involving managing technology commercialization and business innovation utilizing novel biotechnology sourced from University of Manchester and across the North West region. More recently, she headed up the Biotech business unit at the University of Manchester Incubator Company (UMIC), managing and running the biotech incubation activities.

PARTICLE SIZE DISTRIBUTION

Light Microscopic Determination of Particle Size Distribution in an Aqueous Gel

By: Philo Morse, MS, and Andrew Loxley, PhD

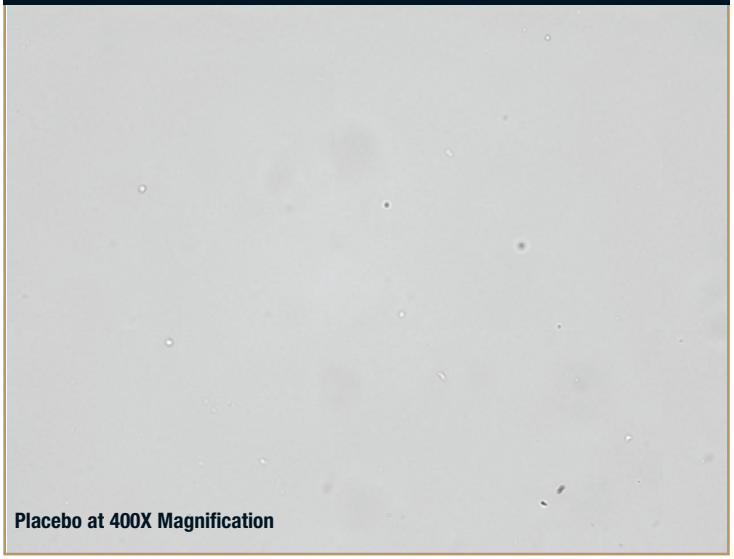
INTRODUCTION

The need for particle size control in the manufacture of pharmaceuticals is becoming increasingly apparent as the pharmaceutical industry attempts to capitalize on some APIs with less-than-ideal solubility profiles. Also, significant advances in drug delivery have been made in which a finely divided API, with the concomitant increase in specific surface area, has resulted in increased bioavailability. Precise particle size control technologies have also assisted in the development of drug delivery platforms for the delivery of a medicament to the lung. As these trends have occurred, the need for highly reproducible particle size assessment techniques has grown significantly in the past decade. The interest in particle size measurements will remain high, particularly in view of FDA trends toward recommending more thorough descriptions of particle size distributions in submissions in which the emphasis of a drug product claim is based in a tightly controlled particle size.

COMPARISON OF METHODS TO MEASURE PARTICLE SIZE DISTRIBUTION

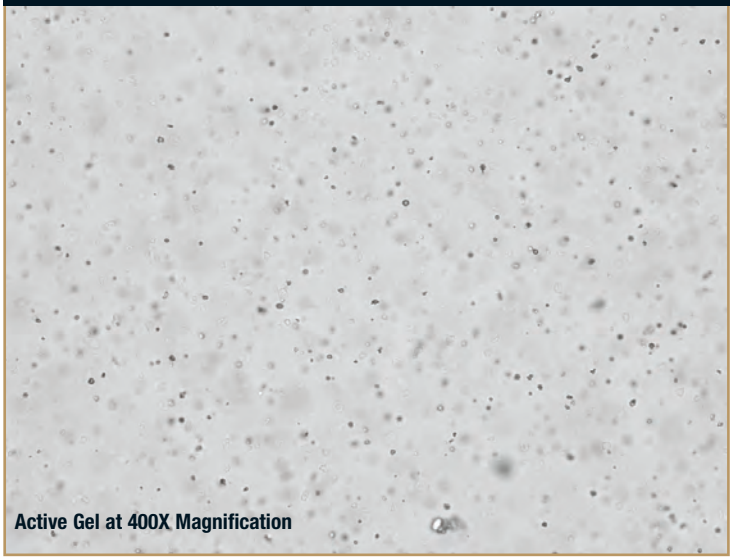
Particle sizing of dispersion can be accomplished using laser scattering or diffraction techniques or by disc centrifuge techniques if high resolution of the size distribution is required. Laser scattering requires very low particle concentrations, usually requiring significant sample dilution. The particles in the sample must be below 1 micrometer in size and free to undergo Brownian motion. For laser diffraction methods, dilution is again often required to optimize the intensity of diffracted light at the detectors, though dilution requirements are not as stringent as for scattering techniques. These methods give weight-average particle size, and although these can be

FIGURE 1



Placebo at 400X Magnification

FIGURE 2



Active Gel at 400X Magnification

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mathematically converted to number-weighted distributions, the conversions can produce misleading artifacts.

Disc centrifuge methods rely on the ability of the particles to move through the sample under the influence of a centripetal force generated in a spinning disc containing the sample; so the sample viscosity must be low enough that the force overcomes viscous resistance to particle movement in the field. While some drug product formulations can be diluted without significant change to the particle size distribution (allowing appropriate sample concentrations and viscosities for the aforementioned methods) for the development of highly viscous gel-based products, whose API particle size distribution may be affected by significant sample dilution, standard methods may not be not appropriate. As a pharmaceutical contract research organization (CRO), Particle Sciences routinely develops such viscous systems for clients (especially for topical products), and to enable useful particle sizing of such products, has developed two methods to determine the particle size distribution of suspended API in a viscous aqueous gel that involve a minimum of sample preparation and can analyze samples with broad particle size distributions.

The methods are based on laser diffraction using a specifically designed cell for viscous paste analysis, and image analysis of optical photomicrographs using image analysis software to identify particles and numerically bin them according to shape and size.

TABLE 1

Sample	Magnification	# Objects	d10	d50	d90
Placebo Alone	400X	106	0.73	1.4	3.2
Placebo Spiked w/ 1.9 µm Latex Beads	400X	23031	2.5	3.5	4.4
Placebo Spiked w/ 5.3 µm Latex Beads	400X	4090	2.8	6.1	6.9
Placebo Spiked w/ 20.9 µm Latex Beads	400X	482	1.8	22.1	26.1
Placebo Spiked w/ 43.3 µm Latex Beads	100X	622	16.2	45.2	63.9
Active Gel	400X	7197	2.2	4	7.1

Spiked Placebo Gel Linearity Results

TABLE 2

Added Particle Size (µm)	Determined Size (d50 in µm)	% Deviation
1.90	3.5	84.2
5.34	6.1	14.2
20.9	22.1	5.7
43.3	45.2	4.4

Accuracy of Method

TABLE 3

Added Particle Size (µm)	Determined Size (d50 in µm)	% RSD (n=4)
1.90	3.5	1.6
5.34	6.1	2.7
20.9	22.1	2.6
43.3	45.2	0.3

Precision of Method

TABLE 4

Sample	Magnification	No. Objects	d50
1 mil Thickness (25 µm)	400X	10806	2.2
2 mil Thickness (50 µm)	400X	10282	2.2
5 mil Thickness (125 µm)	400X	10513	2.2

Gel Thickness Study

The method of particle size distribution determination by optical microscopy and image analysis is a technology-intensive method requiring the capacity to automatically acquire and analyze a large number of photomicrographs. Particle Sciences uses a powerful optical microscope fitted with a dedicated digital camera and automated stage and focusing movement, controlled by software that also handles the analysis of the images collected. This enables automatic collection of the large number of image objects required for statistically relevant analysis, which includes measurement of length, width, area, circle diameter, roughness, etc.

With careful selection of objectives and camera, the technique also has a broad dynamic range in which the upper limit is several millimeters at low magnification, and the lower limit that is close to 1 micrometer, which is correlated to the resolution inherent in the use of white light illumination. A significant advantage of microscopy over laser diffraction is verifiable and calibrated accuracy, as calibration of the instrument may be carried out with the use of NIST traceable stage micrometers and verified by the use of the monodisperse latex microspheres. This is opposed to that available for laser diffraction, which is based on first principles, and the measurement may only be

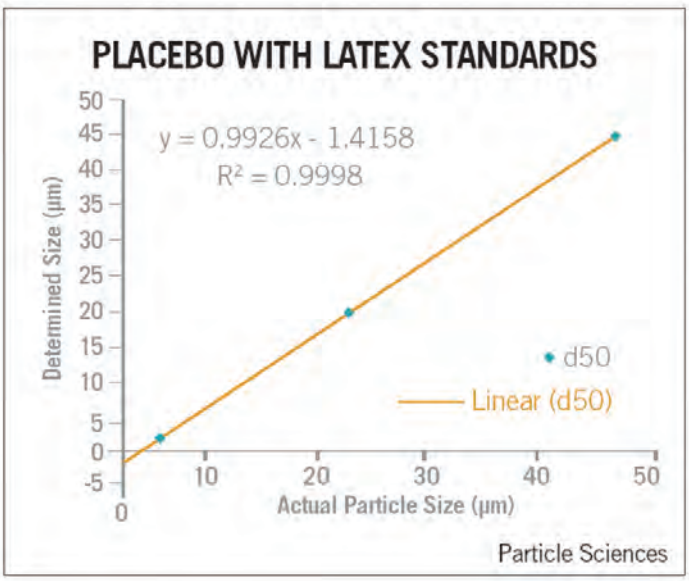
verified with the use of monodisperse latex microspheres but no corrections or "calibrations" may be performed to modify the instrument result if an inaccurate result is observed. Optical microscopy, however, suffers in the need for a very large number of observations. ISO 13322-1 contains a guide for the number of particles required at a 95% confidence based on the width of the particle size distribution. The shortcoming in this of course is the analyst has no knowledge of this fact a priori, and the range of distribution widths described by ISO 13322-1 are too few to describe many real-world particle size applications even though the largest of the distributions requires an extraordinarily high number of observations.

Sample preparation in the case of microscopy is very simple, requiring only the sandwiching of ~100 microliters of sample between a slide and a cover slip with gentle pressure to achieve a sample thickness of ~25 micrometers.

Particle size standards are assorted monodisperse polystyrene latex standards ranging from 1.0 micrometers to 43.6 micrometers, and commercially available polydisperse glass microbead standards of 1 to 10 micrometer, 3 to 30 micrometer, and 10 to 100 micrometer size ranges.

The method described herein was developed for the analysis of a gel based on hydroxyethyl cellulose (HEC) and containing 0.05% (w/w) micronized API. The placebo was prepared in the same fashion as the active, but without API. The monodisperse standards were prepared at approximately 0.001% (w/w) by adding approximately 1 microliter of 1% (w/w) dispersions of latex microspheres to 10 g of placebo, mixed thoroughly by hand, centrifuged at 150 g for 30 minutes to remove entrained air bubbles. Polydisperse standards were prepared at 0.005% (w/w) by the addition of 0.1 g standard beads to 20 g of placebo gel, mixed thoroughly by hand, and centrifuged at 150 g.

FIGURE 3



Placebo With Latex Standards

CHALLENGES TO VALIDATION OF PHYSICAL CHARACTERIZATION METHODS

If particle size is to be a quality control criteria for a given product or claims of product stability are to be made based on a specific particle size, the method of particle size distribution determination will have to be validated. The US FDA cGMP section 211.165(e) requests methods to be validated. The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented. Such validation and documentation may be accomplished in accordance with section 211.194(a). These requirements include a statement of each method used in testing the sample to meet proper standards of accuracy and reliability, as applied to the tested product[1].

Laser methods are incapable at this time of API specificity. An optical system is currently available that incorporates near infrared spectroscopy as a detection method (SyNIRgi, Malvern Instruments, Ltd.). This system should be able to discern between API and excipients or impurities. However, for this discussion, all particles will be included in the microscopic and laser-sizing techniques regardless of the identity of the particle.

Often ignored in particle sizing method validation are the parameters of detection limit and quantitation limit of which only the detection limit may be addressed by reference to the instrument manufacturers claims. Range and linearity can be examined in the same way as in all other techniques in which placebo or vehicle is spiked with standard material, and measurement is carried out in the intended fashion. In the case of automated image analysis techniques, the lower bound of the range will be defined by the area inscribed by a minimum number of pixels that are capable of carrying any size/shape information.

In this case, the lower limit was defined in the image analysis routine as a 5 x 5 pixel square or a diameter of approximately 1 micrometer. Accuracy and precision can be assessed by the proximity of the experimental values to those published for the standard material, and the coefficient of variation calculated from repeated measurements of the spiked sample, respectively. Intermediate precision or analyst-to-analyst variation can be seen by

the examination of multiple preparations of the material by multiple analysts and calculation of the resulting RSD between analysts and the RSD of all samples pooled. Resolution of the method, defined as the ability of a technique to differentiate between discrete monodisperse particle sizes, can be addressed in the linearity/range examinations. If the definition is based on an instrumental ability to resolve monodisperse particle sizes that are mixed, the assessment becomes more difficult.

PRELIMINARY VALIDATION OF A MICROSCOPY TECHNIQUE

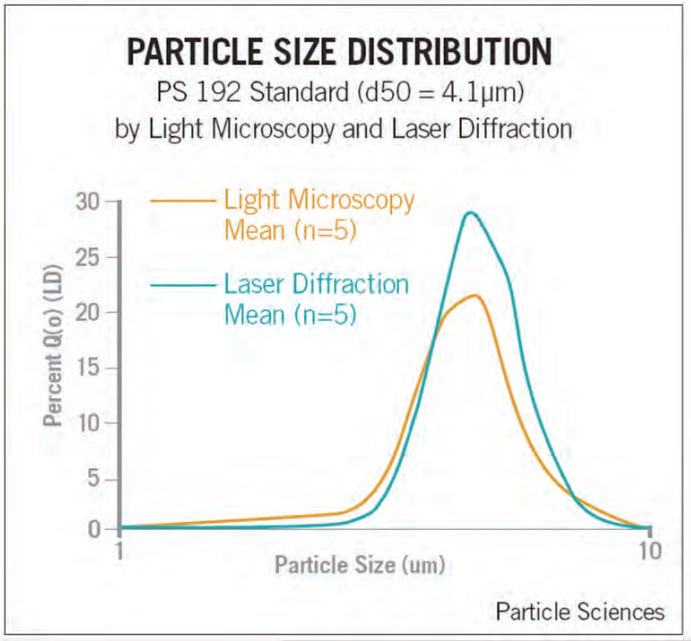
The determination of particle size by microscopy requires the use of defined routines that rigorously control the collection of photomicrographs and the binary processing of the image results. Figures 1 and 2 are example photomicrographs of the placebo and active HEC gels, respectively, at 400X magnification.

Confirmation of the counting/image analysis technique for particle sizing was accomplished by mixing placebo gel with latex beads of known size, performing the proposed sample preparation, and analyzing the slide via the counting/acquisition routine. The results of spiked placebo gel determinations agree very well with expected values, as shown in Figure 3.

For measuring the largest particles (43 micrometers), the result was generated by the use of the 100X microscope objective to allow more particles per field to be captured. If required, the method could be modified so that all results will be generated using the lower magnification. This would be contingent on the linear range required of the final method.

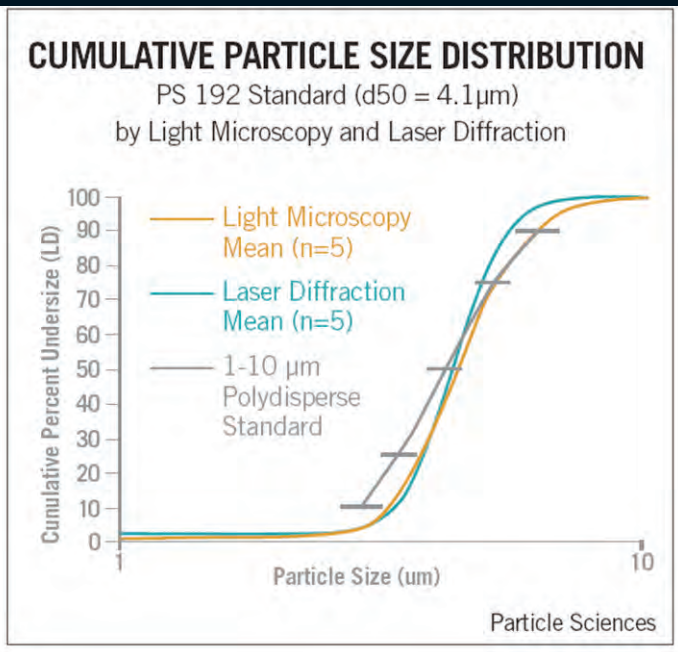
The accuracy and precision results of the method are collated in Tables 2 & 3, respectively. Acceptable precision is demonstrated with a maximum RSD of 2.7% for four determinations performed on the 5.34 micrometer latex beads spiked into the placebo. A minimum RSD of 0.3% is demonstrated for the four determinations of the 43.3 micrometer beads spiked into the placebo. The accuracy of the method shows significant deviations. A deviation of 84.2% was found for placebo gels spiked with 1.9 micrometer latex beads. The larger spiked particle diameter results were more accurate with minimum deviation of 4.4% demonstrated for 43.3 micrometer latex beads spiked into the placebo, and a maximum deviation of 5.7% demonstrated for 20.9 micrometer beads spiked into the placebo. The absolute error of ~1 micrometer is quite small, to be expected, and not considered an issue for the tracking of change in particle size, for

FIGURE 4



Particle Size Distribution

FIGURE 5



Cumulative Particle Size Distribution

which this method was developed, nor for relating particle size to other system analysis, such as in vitro release testing (IVRT).

A further indication of method "robustness" was investigated in which an active gel was assessed using the counting routine, and the gel thickness was varied. This was accomplished by using spacer tapes of 1, 2, or 5 mil in thickness to separate the cover slip from the slide to create a gap for the sample. The results in Table 4 indicate that the sample thickness had little effect on the determined median (d50) particle size of the active gel.

CORRELATION OF LASER DIFFRACTION METHOD WITH LIGHT MICROSCOPY

Ideally, the ultimate verification of any analytical techniques involved in particle size analysis would be the exact agreement with another technique. To this end, the two techniques discussed here were used to examine samples of a polydisperse particle size standard suspended in water. Presented in Figure 4 are overlaid microscopic particle size distribution and laser diffraction particle size distribution of the 1 to 10 micrometer polydisperse standards (PS192). The laser diffraction data are the average of 5 distribution measurements. The distribution results from each method agree well with the 95% confidence intervals provided with the certified standard values (Figure 5). The results of similar determinations performed with the HEC gel showed an upward shift (~2 micrometers) in the particle size distribution on estimation by microscopy.

We have shown that optical microscopy can be used to monitor the particle size of API in an aqueous gel. The method is able to be validated, robust, and reliable as can be seen by the establishment of linearity, precision, and accuracy, with minimal sample preparation. In addition, because only very small volumes of gel are required, microscopy presents no challenge when only small volumes of sample are available.

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BIOGRAPHIES

Mr. Philo Morse joined Particle Sciences in early 2008. With several years experience in the development of testing methods for inhaled pharmaceutical dosage forms, he has accepted the responsibility of managing Particle Sciences' Physiochemical Characterization Laboratory. Mr. Morse has over 15 years of experience in academic research and development, pharmaceutical industry research and development, and quality control laboratories. He earned his MS in Chemistry from SUNY College of Environmental Science and Forestry in Syracuse, NY.

Dr. Andrew Loxley is Director of New Technologies at Particles Sciences Inc., a contract research organization in Bethlehem, PA, specializing in pharmaceutical formulation development. He leads a variety of projects, many based on novel and proprietary nanotechnologies, in fields from HIV vaccine and microbicide development to gene-silencing siRNA delivery. Prior to joining Particles Sciences, he led the development efforts in next-generation lithium ion batteries at A123 Systems Inc, electrophoretic displays at EINK Corp., and latex-based adhesives at Synthomer Ltd. British-born, he earned his BSc in Chemistry from the Univeristy of Sussex and his PhD in Physical Chemistry focusing on Microencapsulation from the University of Bristol.

POWDER CHARACTERIZATION

Dynamic Powder Characterization for DPI Formulations

By: Robert Price, PhD, and Tim Freeman

INTRODUCTION

Formulating pharmaceutical blends for dry powder inhalers (DPI) is challenging, even for an industry with well-established powder processing skills. For a DPI, the active pharmaceutical ingredient (API) is usually a fine cohesive powder, which is then blended with a coarser carrier excipient to improve flow properties. During inhalation, the API is stripped from the surface of the carrier and delivered to the lungs, leaving the excipient to be ingested. With a passive DPI, the motive force for this aerosolization/elutriation process is provided by the patient, with inhalation activating the device.

The inclusion of excipient fines in the blend has been shown to improve drug delivery, a finding that has been explained by a number of hypotheses. In this discussion, we consider the way powders behave in DPIs and examine the dynamic and bulk powder properties that help to explain the mechanisms that dominate performance. Experimental studies illustrate the impact of blending on the in situ formation of fines and the effect this has on powder properties and aerosolization characteristics.

UNDERSTANDING DPIs

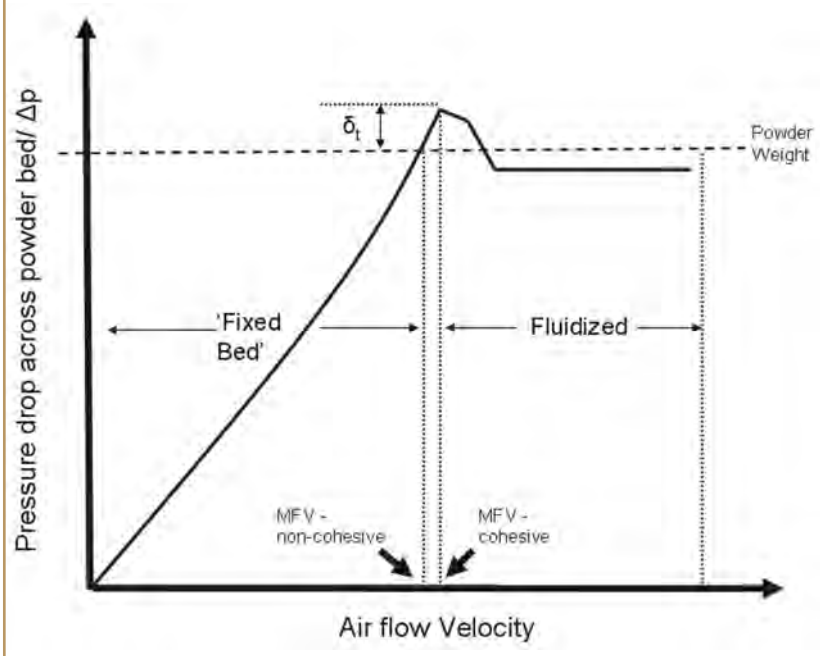
Before actuation, a DPI dose is confined as a small plug or bed of powder within the device. Inhalation draws air through the bed at a rapidly accelerating velocity, causing it to aerosolize, producing a powder stream that is carried into the body on the incoming breath. During delivery, API is stripped from the carrier, allowing its deposition in the lungs, while the larger carrier particles remain in the throat and are ingested.

The fluidization characteristics of the formulation are important, influencing discharge of the dose from the device and elutriation of the API. Failure to achieve satisfactory fluidization may result in incomplete discharge of the dose. Furthermore, if the energy or force applied to particles during activation is insufficient to overcome the attractive forces between API and carrier, the drug will remain attached to the excipient, preventing its deposition in the lung. Establishing the required fluidization characteristics is therefore an important part of product development.

Detailed examination of the fluidization process gives a more in depth understanding of the factors that influence behavior. The pressure drop induced by flow through a packed bed is directly proportional to the velocity of the flowing fluid, as described by Carman.[1] This relationship holds until the bed begins to fluidize (Figure 1). If there are no interactive forces between particles, then fluidization starts when the pressure drop across the bed is equal to the weight of the particles; this is the point of incipient fluidization. When the upward force induced by the flowing air exceeds the gravitational pull, particles begin to escape from the bed. The air velocity at which this occurs is referred to as the minimum fluidization velocity (MFV).

In reality, there are always forces of attraction between particles, thus the

FIGURE 1



Correlation Between Pressure Drop & Air Velocity for a Powder Bed

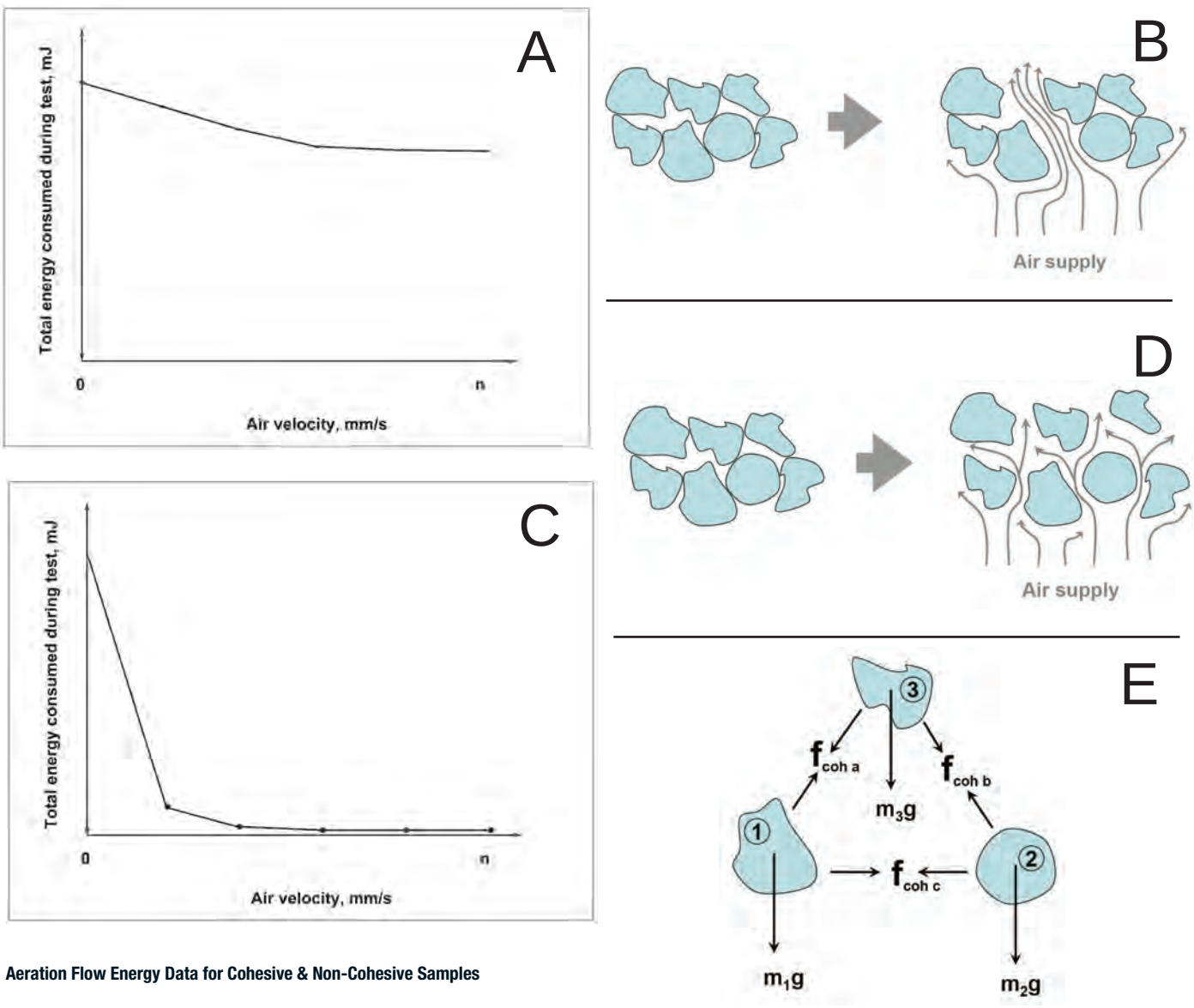
pressure drop rises above this point ahead of fluidization, before decreasing relatively sharply as the bed begins to disperse. The pressure drop/air velocity required to induce fluidization is immediately obvious from a plot of the two parameters (Figure 1). When inter-particle forces are strong (ie, the bed has high tensile strength), high pressure drops will develop before fluidization of the bed.

Pressure drop and differential velocity (between the moving air and the static bed) are at their greatest just before the bed yields and starts to fluidize; it is at this point the DPI dose is subject to the greatest aerodynamic drag. The magnitude of this force impacts aerosolization behaviour, so there is a direct link between the tensile strength of the bed and DPI performance. Tensile strength is in turn influenced by packing/consolidation within the bed as well as the magnitude of inter-particle forces.

A vital part of the delivery process is the stripping of API from carrier. De-aggregation and elutriation are caused by the aerodynamic drag applied to the particles and/or by particle-particle or particle-device collisions. Energetic, turbulent flow promotes this process, and many devices include components designed to increase the Reynolds number.[2] Tortuous flow paths through the device, impactor grids, and other methods of increasing airflow resistance are all regularly employed. As noted, however, the inclusion of fines also enhances this delivery process.

The active site theory suggests that fine excipient particles bind to high-energy sites on the carrier, blocking them from the API, which subsequently attaches to sites of lower energy from which it is more easily

FIGURE 2



Aeration Flow Energy Data for Cohesive & Non-Cohesive Samples

dislodged.[3] Experimental studies to confirm this theory have produced somewhat contradictory results.[2] An alternative explanation, the agglomerate theory, suggests that blending in the presence of fines forms mixed drug-fine excipient agglomerates that bind relatively loosely to the carrier and are easily detached.[4] A less well-explored route to understanding the effect of fines is to investigate their impact on bulk properties and fluidization behavior, which as the preceding discussion has highlighted, underpins DPI performance.

UNDERSTANDING THE NATURE OF POWDERS

Powders can exhibit an extremely wide range of behaviors as their use in DPIs demonstrates. During activation of a DPI, aeration transforms a small stationary bed into a fluid cloud of powder that is easily inhaled by the patient. This sensitivity of powders to air content is widely recognized, but there are many other variables that influence a powder's behavior, and indeed, which affect its sensitivity to air. Primary variables, such as particle shape, size, and distribution, and surface texture are important, but other external parameters have an impact, humidity being a prime example. This complexity makes multi-faceted powder characterization much more informative than single-number approaches that examine just one aspect of performance.

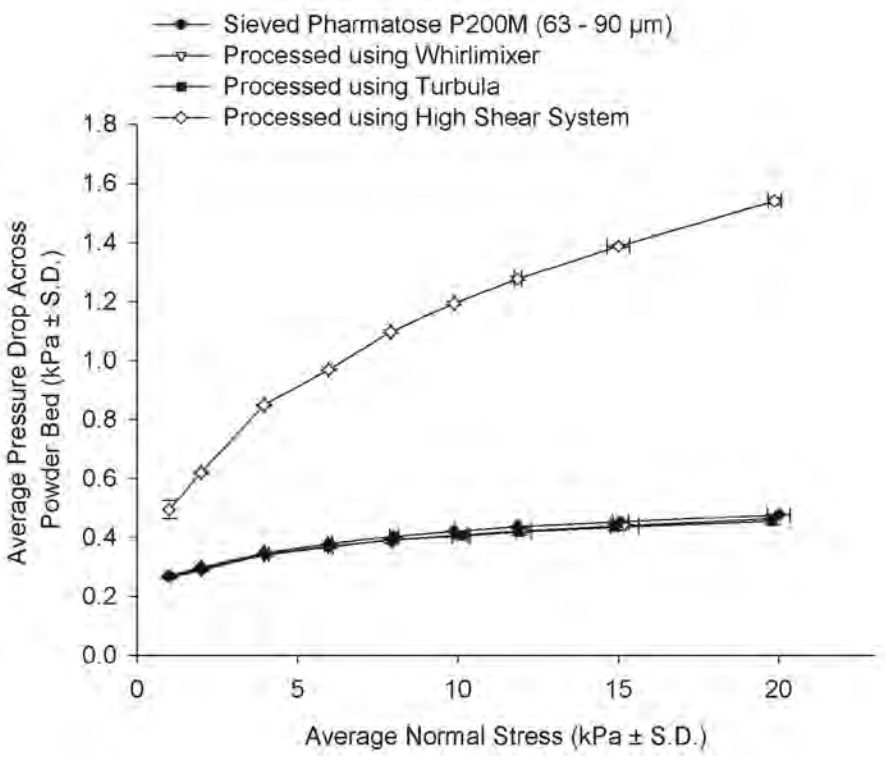
One of the simplest and most commonly used classifications for powders is cohesivity. A "sticky" powder that flows poorly and tends to clump is considered to be cohesive, while one with free-flowing particles is non-cohesive. However, classification is not clear-cut because powders exist across a spectrum of cohesivity. Nor is it particularly useful if it is not accompanied by an understanding of the impact of cohesivity on the process. A cohesive powder has stronger particle-particle interactions than a non-cohesive material, and this has consequences for bulk, shear, and dynamic properties, which can all be used to quantify this characteristic. For DPI applications, the key focus is flowability and fluidization behavior, so properties that describe cohesivity in these terms are especially valuable.

The degree of cohesivity exhibited by a powder is determined by the relative strength of inter-particle and gravitational forces, more cohesive materials having inter-particle forces significantly in excess of those induced by gravity (Figure 2). In general, it is fine powders, particularly those with a mean particle diameter of less than 30 microns, that are cohesive, although particle shape and surface roughness are also influential. Such powders have a tendency to pack in relatively open structures, while non-cohesive materials pack closely, with a much lower free volume.

In terms of bulk properties, this open packing is evidenced by relatively low bulk density and high compressibility. Cohesive powders hold air easily, but compression squeezes it out, markedly increasing bulk density. Another defining characteristic is low permeability, where relatively small void spaces coupled with strong interparticle forces make it difficult for air to flow between particles in the bed. Permeability is of direct relevance when considering fluidization behavior, as this relies on the separation and suspension of particles in an upward air flow. When particle interactions are strong, the bed resists fluidization, with air tending to channel through the bed rather than fluidizing it uniformly.

With powder rheometers, which uniquely enable the characterization of materials in an aerated state, fluidization behavior can be studied directly. Measuring flow energy as a

FIGURE 3



Permeability Data for a Range of Lactose Samples

function of air flow through the sample quantifies the response of a powder to a fluidizing flow. With a non-cohesive powder, flow energy decreases rapidly with increasing velocity, typically to a very low level, as the air flows easily between the particles lubricating their movement. The flow energy of a cohesive powder on the other hand may show little response to increasing air velocity, the sample resisting the flow of air, which ultimately tends to channel through the bed rather than uniformly fluidizing it. Little reduction in flow energy is observed.

This ability of powder rheometry to measure parameters that directly reflect fluidization behavior makes it a valuable tool for DPI formulation as the following experimental study demonstrates.

INVESTIGATING THE IMPACT OF BLENDING ON FINES & DPI PERFORMANCE

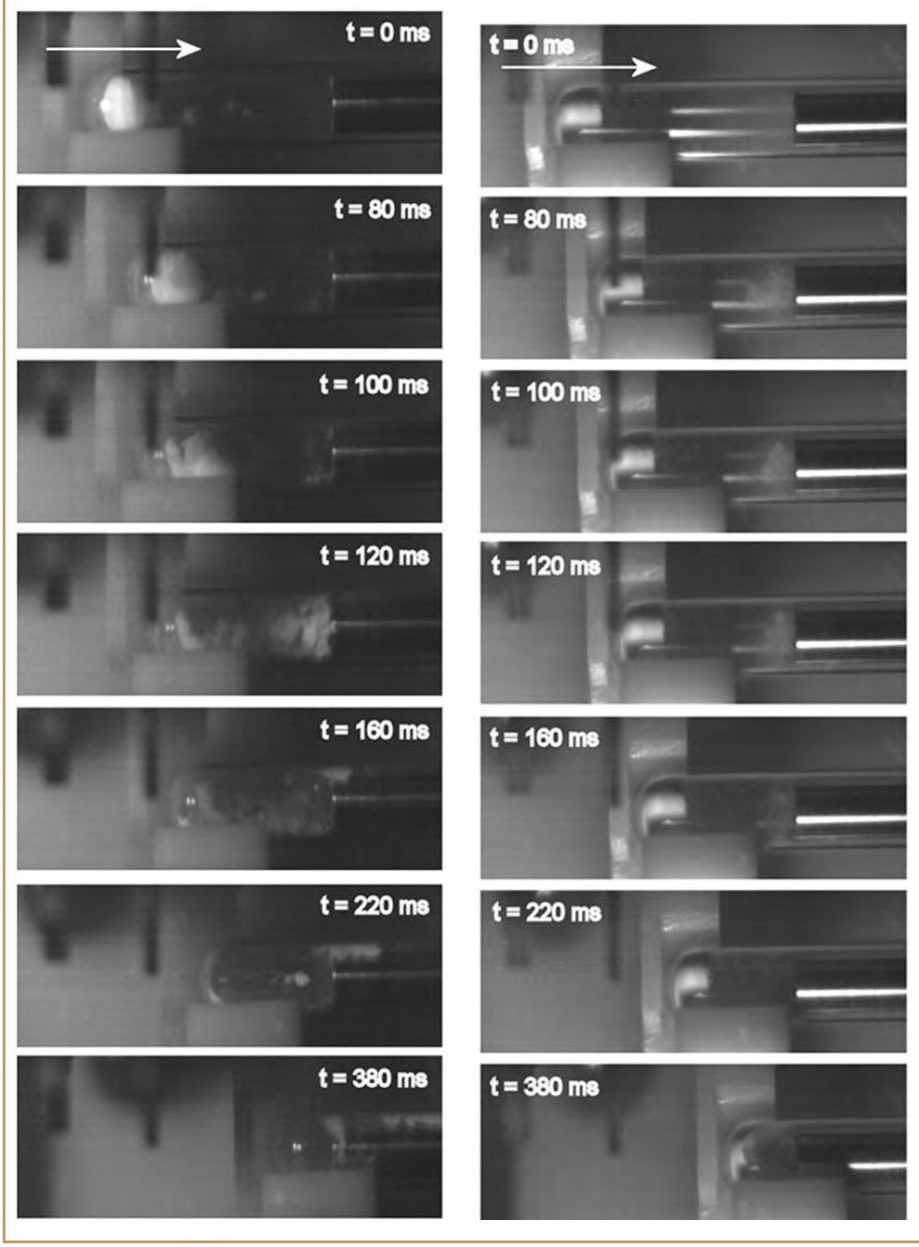
Samples of lactose were produced by blending material in the 63- to 90-micron fraction (sieve analysis) in three different units - a whirlimixer, a turbula, and a high-shear mixer. Binary samples containing a known quantity of Budesonide were also produced in order to assess the impact of blending on drug delivery. The flow properties of the lactose samples were measured using an FT4 Powder Rheometer from Freeman Technology (Welland, UK).

The bulk densities of the whirlimixer and turbula samples were 0.67 ± 0.02 g/cm^3 and 0.66 ± 0.05 g/cm^3, respectively, but that of the high-shear mixer sample was much lower at - 0.47 ± 0.01 gm/cm^3. To investigate permeability, the pressure drop induced by an air velocity of 2 mm/s was measured under varying applied stresses in the range 1 to 20 kPa (Figure 3). The resulting data confirm that there is little difference between the sieved, whirlimixer, and turbula samples, which are all highly permeable. In contrast, the high-shear mixer sample has much lower permeability. These two results suggest that the powder processed in the high-shear mixer is more cohesive than the other samples, a finding endorsed by its relatively high compressibility (data not shown).

Particle size analysis reveals that while the whirlimixer and turbula have little impact on size and distribution, the high-shear mixer decreases median particle size, generating a significant amount of intrinsic fine lactose material. This increase in fines makes the powder much more cohesive, suggesting that there will be a corresponding change in fluidization behavior and DPI performance.

FIGURE 4A & 4B

High-Speed Images of the Fluidization Behavior of Lactose Samples Produced Under Different Blending Conditions



Fluidization of the lactose samples was visualized using a high-speed camera and purpose-built rig: two distinctly different dispersion mechanisms were observed. With the high-shear mixer sample, the bed fractures at a certain air velocity, the powder lifting as a plug (Figure 4A). Eventually, this plug yields to give a dense cloud of particles and agglomerates. Within the cloud, flow is chaotic, promoting particle-particle and particle-wall collisions. The bed fractures toward its base but not specifically at the support interface. In sharp contrast (Figure 4B), fluidization of the other samples proceeds by a process of erosion, small pockets of particles being gradually entrained from the surface of the sample once a specific velocity is exceeded.

In vitro aerosol deposition testing of the lactose/budesonide blends was carried out to assess the impact of blending on drug delivery. The blend processed in the high-shear mixer gave the best drug delivery performance, confirming its superior properties for DPI applications. Both emitted dose (the total amount of powder released during actuation) and fine particle dose (the amount of material lying in the size range suitable for delivery to the lung) were significantly higher than for the other samples.

This study suggests that fines affect the performance of a DPI formulation by changing its response to air. Including fines makes the formulation more cohesive, thereby increasing resistance to air flow, and ultimately, the intensity of the aerosolization/elutriation process. These conditions promote delivery of the dose and removal of API from the carrier, increasing fine particle fraction. While this finding does not discount mechanisms proposed previously to explain why fines improve the effectiveness of delivery, it does provide formulators with an alternative strategy for enhancing DPI performance.

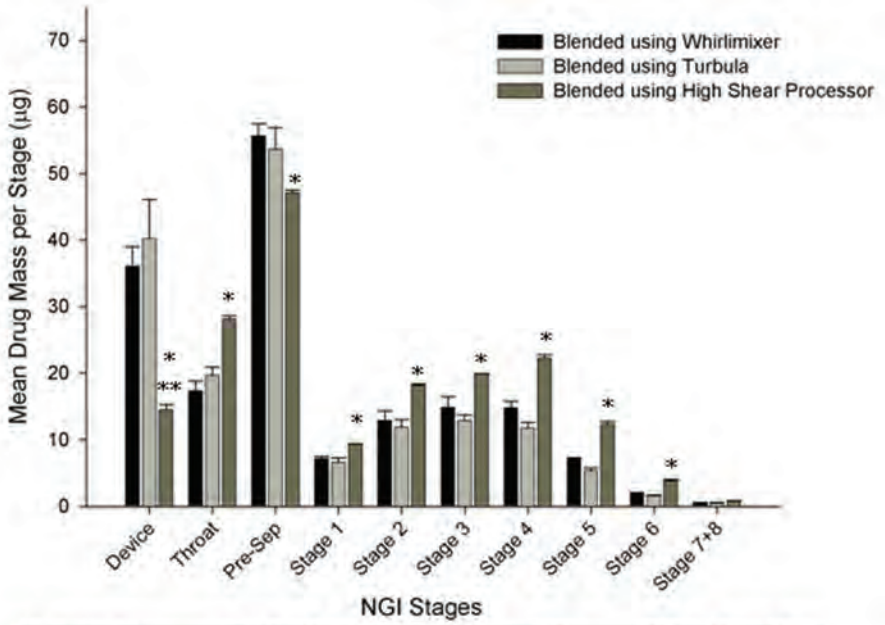
In a complementary study, the aerated flow energy of samples containing different concentrations of fines was studied using the FT4 Powder Rheometer from Freeman Technology. Figure 6 shows the correlation between fine particle dose and aerated flow energy (the energy required to induce flow in an aerated sample). As fines content increases, from 0 through to 10%, there is a corresponding increase in flow energy. The bed becomes more cohesive, and air cannot permeate between the particles to lubricate flow. This effect transforms fluidization behavior, increasing fine particle dose, which correlates directly with flow energy.

CONCLUSION

Developing successful DPI formulations that deliver drugs to the lungs is challenging. The mechanisms governing the aerosolization/elutriation process, which strips API from the carriers used to improved flow performance, are complex and not yet fully understood, although several studies show that the inclusion of excipient fines encourages this process.

The work described here suggests that fines impact the bulk and dynamic properties of a formulation, influencing fluidization behavior, which in turn, affects DPI efficiency. Fines promote cohesivity, decreasing permeability and giving the powder bed greater tensile strength. Once the DPI is activated, this increased resistance to air flow induces a significant pressure drop

FIGURE 5



Formulation	MMAD ± GSD (µm)	ED (µg ± SD)	FPF_{ED} (% ± SD)
Whirlimixer	3.4 ± 2.1	132.2 (± 7.6)	31.5 (± 1.1)
Turbula	3.5 ± 2.2	123.8 (± 6.7)	27.7 (± 0.8)**
High Shear	3.2 ± 2.1	161.9 (± 1.6)**	39.2 (± 0.4)***

Emitted Dose & Fine Particle Fraction Data for Samples Produced Using Different Blending Conditions

over the powder plug. The formulation is subjected to greater aerodynamic drag forces, and this increases the intensity of the dispersion process. Visual imaging indicates that fluidization can be transformed from a gradual process with steady powder erosion to a more dramatic event involving bed fracture and high-energy rupture of the powder plug.

Powder rheometers, which are unique in enabling the measurement of aerated powders, are proving to be a valuable tool for DPI development, which requires optimization of the response of a formulation to air. Because there is a direct correlation between the dynamic property of aerated flow energy and fine particle dose, they provide highly relevant data. The best systems also measure bulk and shear properties that give complementary insight into powder behavior. This encourages a knowledge-based approach to DPI development as advocated by Quality by Design.

ACKNOWLEDGEMENT

Figures 1, 2, 3, 4, 5, and 6 are reproduced from reference No. 2 with kind permission of Springer Science and Business Media.

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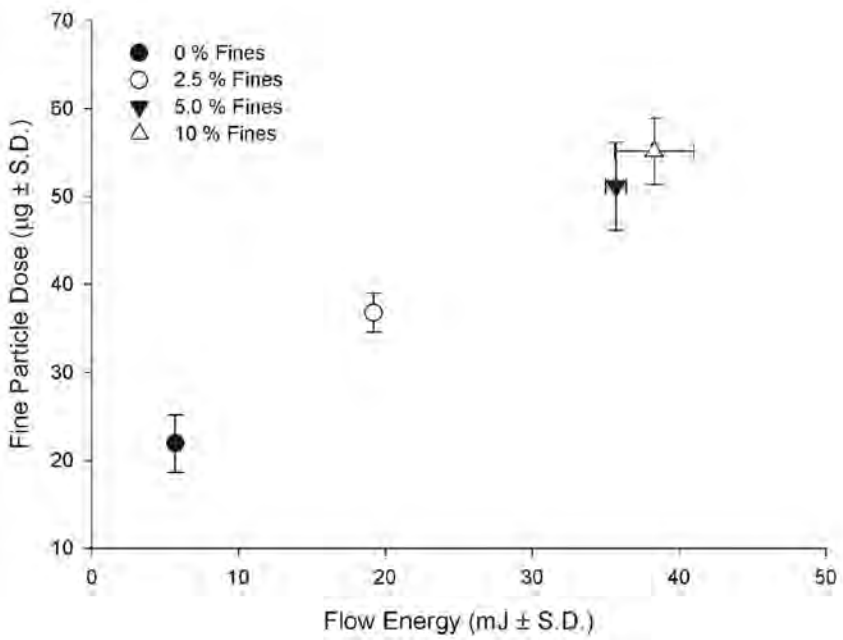
FIGURE 6



Relationship Between Fine Particle Dose & Aerated Flow Energy (FT4, Freeman Technology) for Samples Containing Different Levels of Fines

BIOGRAPHIES

Dr. Robert Price is a Reader in Pharmaceutical Technology in the Department of Pharmacy and Pharmacology at the University of Bath in the UK, where he leads the pharmaceutical technology research group. His main research interests are pharmaceutical surface science and particle engineering. A key area of work is focussed on investigating the physicochemical properties that govern inter-particulate adhesion, issues relating to the surface stability of processed particles, and the general areas of particle technology and crystal growth. He has extensive contact with large pharmaceutical organizations as well as close involvement with small innovator pharmaceutical companies.

Tim Freeman has a degree in Mechatronics from the University of Sussex in the UK and has worked for Freeman Technology since the mid 1990s. Since Freeman's launch of the FT4 Powder Rheometer, he has been responsible for application and method development and works closely with customers in the pharmaceutical and powder-processing industries. Mr. Freeman is currently Director of Operations for Freeman Technology.

BIODEGRADABLE MICRORSPHERES

A New Process Producing Biodegradable Microspheres of Peptide Drugs: Suspension - Encapsulation

By: Cherng-ju Kim, PhD

ABSTRACT

A method is herein reported of preparing drug-containing biodegradable microspheres by dissolving a drug and biodegradable polymer (PLA, PLGA) in an organic solvent(s) to form a drug-polymer-solvent phase and then mixing the drug-polymer-solvent phase with an aqueous suspension containing an in situ-formed inorganic gel (eg, hydroxyapatite) to form a dispersion composed of drug-polymer-solvent droplets dispersed in an aqueous suspension. Evaporating the organic solvent(s) from the dispersion while stirring converts the drug-polymer-solvent droplets to drug-containing solid microspheres. The step of recovering the drug-containing microspheres from the dispersion includes adding acid to the dispersion to dissolve the inorganic gel and centrifuging/filtering them. Encapsulation efficiency of low molecular weight drugs (eg, verapamil HCl) increased from 65% to 99% as pH of the suspending medium increased between pH 7 and pH 11, respectively. However, encapsulation efficiency of a peptide drug (eg, leuprolide acetate) of about 95% was achieved for pH ranging from 7 to 10. Drug-release profile from leuprolide acetate microspheres of about 10% loading showed a sigmoidal pattern of a slight initial burst (ie, < 5% release) and minimal release (time-lag) for 4 days followed by a nearly constant release up to 80% release for 20 days and then tailing for 7 days. As drug loading increased higher than 10%, the initial burst release was larger. It has been demonstrated that drug-containing microspheres were successfully produced by the suspension-encapsulation process with the volume ratio of organic phase (100 mL) to aqueous phase (400 mL) in which the organic phase consisted of 25% PLGA polymer concentration in 24/76 %v/v methanol/dichloromethane and 10% drug loading.

INTRODUCTION

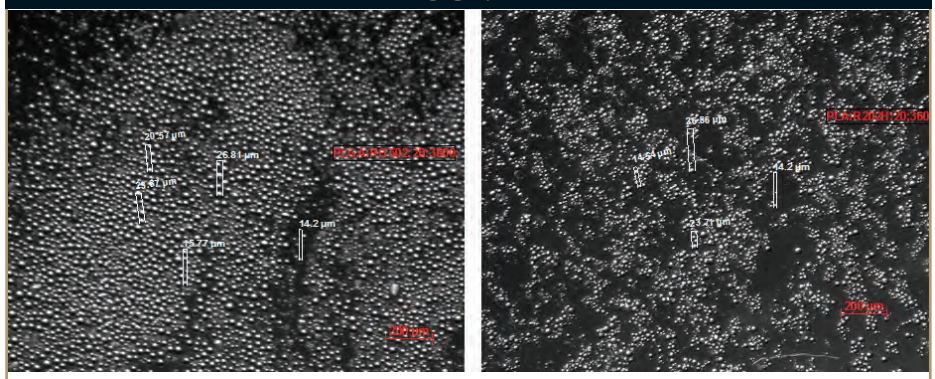
Biologically active drugs, such as peptides and proteins, need to be administered by injectable polymeric controlled-release delivery systems because these drugs are not stable in the gastrointestinal tract due to proteolysis.[1-3] Injectable polymeric controlled-release delivery systems reduce the number of inconvenient, daily subcutaneous injection doses, provide a stable level of the drug in the body over a longer time, and improve patient compliance. One type of controlled-release drug formulations that has been used is biodegradable microspheres containing drug trapped inside the microspheres. The most commonly used biodegradable polymeric microspheres are made of polylactic acid (PLA) and a copolymer of lactic acid and glycolic acid (PLGA) that exhibit their biocompatibility along with regulatory approval. As the polymer biodegrades in the body by a homogenous (bulk) degradation process, the drug is released. Microspheres ranging preferably from 10 to 30 microns can be injected with a standard hypodermic needle, instead of surgically implanted. Such products are LUPRON Depot® and Sandostatin LAR®, which are biodegradable microspheres containing leutinizing hormone-releasing hormone (leuprolide or LHRH) and somatostatin (octreotide) analogues, respectively.

The widely used method to prepare biodegradable microspheres is the solvent evaporation method.[4-6] In this method, a drug-containing organic polymer solution is emulsified typically into an aqueous dispersion medium. The methods can be further classified into water-in-oil-in-water (W/O/W) and oil-in-water (O/W) emulsion methods. In a W/O/W double emulsion, an aqueous drug solution is prepared and mixed with a solution of the polymer in a water-immiscible, volatile organic

solvent by using a homogenizer to form a W/O emulsion. The W/O drug-polymer emulsion is then emulsified with a large amount of an aqueous phase containing an emulsifying agent to form a W/O/W emulsion. The organic solvent evaporates during stirring, resulting in the drug-polymer droplets in the W/O/W emulsion to solidify into microspheres. In an O/W method, drug and polymer are dissolved in an organic solvent or a mixture of organic solvents, such as dichloromethane or a methanol/dichloromethane mixture, respectively. The drug-polymer-organic solvent solution is dispersed in an aqueous phase containing an emulsifying agent to form small drug-polymer-solvent droplets in the aqueous phase. Then the rest of the process follows the same as the W/O/W emulsion method.

A widely used emulsifying agent in the solvent evaporation method is polyvinyl alcohol (PVA) (80% hydrolysis, cold-water soluble). PVA is intrinsically a polymer composed of lypophilic vinyl acetate (20%) and hydrophilic vinyl alcohol (80%) and thus able to emulsify oil in water. This solvent evaporation method of producing drug-containing biodegradable microspheres has some disadvantages. PVA can adhere to the microspheres and contaminate them. One may not observe this problem when the volume ratio of organic to aqueous phases is as low as 3 mL O/400 mL W, which is a common laboratory practice. When the process is scaled up, one needs a larger volume ratio (eg, 100 mL O/400 mL W) that can prepare 250-g microspheres with 5-L reactor volume. As a result, one may observe in this case that a small portion of microspheres is very fine (submicron size) and thus haze and cloud supernatant is obtained after centrifugation (20 min @ 1500 rpm) due to the emulsifying capability of PVA. In addition, PVA adheres on the surface of microspheres. The adhesion can be visualized by the resulting, unclear drug-polymer solution when an attempt is made to dissolve the dried, drug-containing biodegradable microspheres in the same

FIGURE 1



Photographs of drug-containing biodegradable microspheres produced with in situ-formed hydroxyapatite: Left for PLGA and Right for PLA.

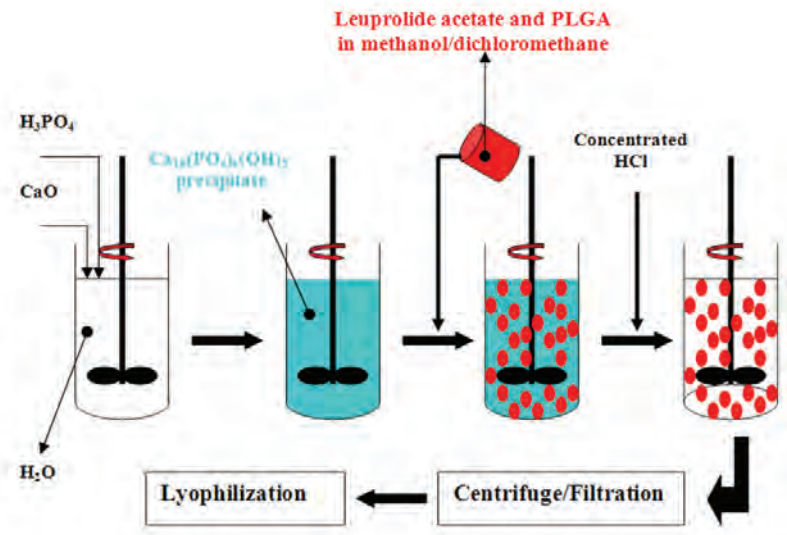
TABLE 1

Drug	Polymer	Polymer Conc. (%)	Loading (%)	pH	Encapsulation Efficiency (%)
Verapamil HCl	R202H[a]	20	10	9.0	67.6
		28.5	10	9.0	76.2
		33.6	10	9.0	76.3
		28.5	10	10.0	75.8
		28.5	10	8.5	72.0
		28.5	10	7.7	65.0
	R203H[a]	25	10	9.0	75.0
		25	10	11.0	99.2
Nicardipine HCl		25	10	9.0	94.3
Leuprolide Acetate	RG502H[b]	25	10	10.0	100.0
		25	10	9.0	96.2
		25	10	8.0	93.7
		25	10	7.0	96.3
		25	16.5	10.0	92.0
	RG503H[b]	21.4	10	10.0	93.0

a: polylactic acid
b: poly(lactic acid-co-glycolic acid)

Encapsulation efficiency of various drugs.

SCHEME 1



Suspension–encapsulation process to produce biodegradable microspheres containing peptide drugs.

solvent(s). New methods of producing biodegradable drug-containing microspheres are needed.

NEW PROCESS: SUSPENSION - ENCAPSULATION

A new process producing drug-containing biodegradable microspheres has been developed in our lab based on a suspension-encapsulation technique.[7] Peptide drug (LHRH) and biodegradable polymer (eg, PLGA, PLA, etc) are dissolved in a mixture of methanol and dichloromethane. The drug/polymer solution (3 mL) is dispersed into an aqueous suspension medium (400 mL) consisting of in situ-formed, gelatinous inorganic gel such as hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$] prepared via the following equations:[7-9]

Equation 1.

$$10Ca(OH)_2 + 6H_3PO_4 = \mathbf{Ca_{10}(PO_4)_6(OH)_2}\ (\text{precipitate}) + 18H_2O$$

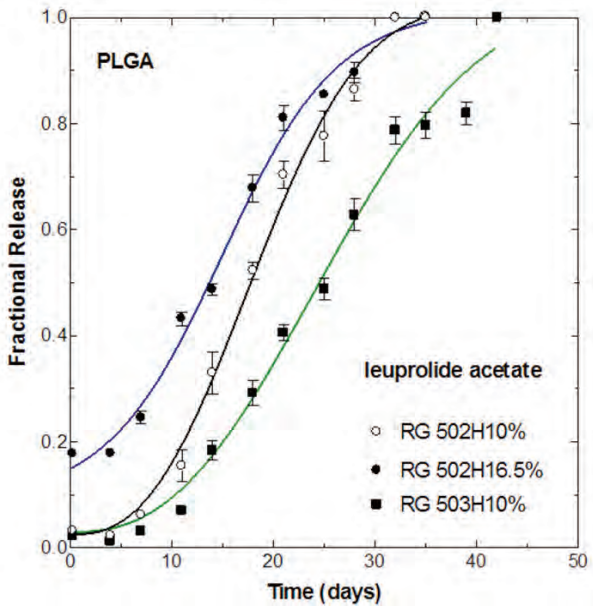
Equation 2.

$$10CaO + 6H_3PO_4 = \mathbf{Ca_{10}(PO_4)_6(OH)_2}\ (\text{precipitate}) + 8H_2O$$

Equation 3.

$$CaCl_2 + 2NaOH = Ca(OH)_2 + 2NaCl +$$
$$10Ca(OH)_2 + 6H_3PO_4 = \mathbf{Ca_{10}(PO_4)_6(OH)_2}\ (\text{precipitate}) + 18H_2O$$

FIGURE 2



Release of leuprolide acetate from PLGA RG502H and RG503H microspheres.

First, the dispersion is homogenized by a high-shear mixer at 5,000 rpm or higher for a predetermined time period. The solvents are removed by stirring at 600 rpm at 25°C for 30 min, and then the temperature is raised to 40°C for 1 hour or longer followed by cooling the suspension to 25°C. Then, concentrated HCl is added to the suspension to dissolve the suspending medium by the following equation: $\mathbf{Ca_{10}(PO_4)_6(OH)_2} + 20HCl = 10CaCl_2 + 6H_3PO_4 + 2H_2O$. The solidified microspheres are next recovered by centrifugation and/or filtration. Clear supernatant is obtained by centrifugation (20 min @1500 rpm). This new process is simple to operate, as described previously. The schematic process using in situ-formed hydroxyapatite to produce biodegradable microspheres is shown in Scheme 1.

PROCESS DEVELOPMENT & ENCAPSULATION EFFICIENCY

Unlike polyvinyl alcohol used for common W/O/W and O/W emulsion-evaporation processes, in situ-formed, gelatinous inorganic gel used in this study does not have any emulsifying ability and acts as a suspending agent. The hydroxyapatite gel appears to coat around the drug-polymer-solvent droplets, which become more viscous as the solvent(s) evaporates, as a protective layer to maintain small, consistent droplet sizes and prevent the droplets from coalescing during stirring and evaporating. The organic solvent evaporates, just as with a standard O/W emulsion method using an organic emulsifier (eg, polyvinyl alcohol), leaving behind solidified polymer microspheres with entrapped bioactive drugs. The reason the process is called suspension-encapsulation (or evaporation) rather than emulsion-evaporation is that organic phase droplets become solid microspheres dispersed in an aqueous medium after the process is over, and there are no emulsifying agents used but a suspending agent. This is coming from the analogy that in polymer science and engineering, the processes of organic phase monomer droplets polymerized in an aqueous medium in the presence of suspending and emulsifying agents are called suspension polymerization and emulsion polymerization, respectively.[10] Emulsion polymerization produces very small particles (sub-microns), whereas suspension polymerization makes larger particle sizes.

When a new process is being developed especially for encapsulation of highly water-soluble and expensive peptide drugs, the encapsulation efficiency of the drugs is a very important parameter due to the cost of the drugs. Thus, common, inexpensive drugs as model drugs were utilized for developing and optimizing the suspension-encapsulation process. In this study, verapamil HCl has been chosen as a test drug for developing the suspension-encapsulation process. Due to the use of in situ-formed inorganic gel prepared with acid and base, the

pH of the suspension was chosen as a variable. Table 1 shows the effect of pH on the encapsulation efficiency. As pH increased from 7 to 11, the encapsulation efficiency increased from 65% to 99%. However, a decrease in a recovery yield of microspheres due to the fast hydrolysis of biodegradable polymers was observed. It seems that around pH 9 good encapsulation efficiency is provided. Low drug solubility in water (eg, nicardipine HCl) resulted in higher encapsulation efficiency. However, encapsulation efficiency of leuprolide acetate of about 95% was obtained at pH 7 to 10 of the suspending medium. Unlike verapamil HCl that becomes a less water-soluble free base at pH close to and greater than its pKa, leuprolide acetate precipitates due to the insolubility of the drug in dichloromethane when methanol leaches out to the aqueous medium.

Because no polyvinyl alcohol or other emulsifiers needed to be used, the microspheres were prepared by this process such that they were not contaminated with any adherents (eg, PVA). This method used inexpensive materials and was easily scaled up. The solidified microspheres were recovered simply by dissolving the hydroxyapatite with acid, and then recovering microspheres by centrifugation and/or filtration from the clear aqueous supernatant solution. Agglomerated particles were obtained when preformed hydroxyapatite rather than in situ-formed one was employed to make biodegradable microspheres.

DRUG RELEASE

Figure 1 shows photographs of PLGA RG502H and PLA R202H microspheres ranging of 10 to 30 microns suitable for subcutaneous injection prepared with the suspending medium of in situ-formed hydroxyapatite. Different microsphere sizes can be obtained by varying the stirring rate of high-shear mixer, the concentration of polymers in the solvents, etc. For a given operating condition, RG 502H provided larger particle sizes than R202H because the viscosity of the former was heavier than the latter. Biodegradable microspheres were shiny, and no debris was attached on the surface of the microspheres.

Release kinetics of leuprolide acetate in 0.1M PBS is shown in Figure 2. PLGA RG502H (Boehringer Ingelheim, Germany) microspheres are suitable for a 1-month depot formulation. As observed in other investigator's articles, the release of leuprolide acetate from PLGA microspheres shows a typical tri-phase.[11,12] Initial burst peptide release was observed due to the fast dissolution of peptide located at the microsphere surface followed by a time lag of 4 to 5 days. The microspheres then hydrated significantly and eroded due to the breakdown of the polymer chain (bulk erosion process).[13] Middle portion of peptide release after the time lag exhibited a near constant and continuous release. The initial burst release was dependent on drug loading.

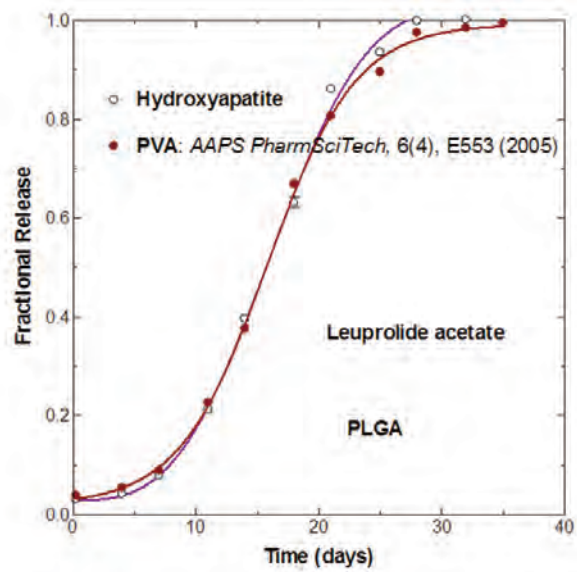
Figure 3 demonstrates that this process, employing in situ-formed hydroxyapatite as a suspending medium, has the capability of matching the release profile of leuprolide acetate from commonly used polyvinyl alcohol as a dispersion medium.[12]

One can encapsulate LHRH drugs as well as other drugs with this process. For example, one is able to encapsulate goserelin acetate treating prostate cancer (Zoladex), octreotide acetate (somatostatin analogue) treating acromegaly and tumor (Sandostatin LAR Depot, monthly), and risperidone treating schizophrenia (Risperdal Consta, biweekly).

SCALE-UP & FUTURE DEVELOPMENT

The suspension-encapsulation process has been developed herein with 3 ml of drug-polymer solution with 20 w/v% to 25 w/v% polymer content in 400 mL of suspension medium. In order to manufacture commercial quantity of biodegradable microspheres of peptide drugs, this process must be scaled up. If one increases the total volume while maintaining the same volume ratio of organic phase to suspension medium, the huge reactor size is required. For example, about a 150-L reactor size is needed to obtain 250 g of drug containing biodegradable microspheres. This requires large centrifugation/filtration equipment to handle 150-L volume and a longer processing time. Thus, one should increase the volume ratio of organic phase to aqueous phase. In our laboratory, we successfully produced about 25 g of biodegradable microspheres containing about 10% bioactive drug by 100-mL methanol/dichloromethane (24/76 v/v%) and PLGA in organic phase and 400-mL suspension medium. However, when the

FIGURE 3



Comparative releases of leuprolide acetate from PLGA microspheres.

attempt was made to produce the same microspheres with 0.5% polyvinyl alcohol, cloudy supernatant after centrifugation (20 min @ 1500 rpm) was obtained because a small portion of very fine (sub-micron) microspheres was produced due to the emulsifying capability of polyvinyl alcohol. When the dried, biodegradable microspheres were dissolved again in the same solvents, a cloudy drug-polymer solution was obtained because PVA, adhered on the solid microspheres, that was difficult to remove simply by washing after filtration. This phenomenon was not observed with in situ-formed hydroxyapatite. A pilot (or full) scale encapsulation process producing 250 g to 500 g of biodegradable microspheres is under construction, and the results will be reported in due course. In addition, a process preparing biodegradable microspheres of protein drugs is under development.

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BIOGRAPHY

Dr. Cherng-ju Kim is Professor of Pharmaceutical Sciences, UAMS College of Pharmacy, Little Rock, AR. He earned his BEng in Chemical Engineering from Korea University in Seoul, Korea, his MEng in Environmental Engineering from Manhattan College in Riverside, NY, and his PhD in Chemical Engineering (Polymer Reaction Engineering) from McMaster University in Hamilton, Ontario, Canada. After working in industry for several years, he became a Research Associate in the Faculty of Pharmacy at the University of Toronto and subsequently joined the School of Pharmacy at Temple University in Philadelphia in 1992 as an Assistant Professor. He was promoted to Associate Professor with tenure and Director of Graduate Studies at that institution in 1998 and served in those roles until 2002 when he moved to Loma Linda University School of Pharmacy as Chair of Pharmaceutical Sciences. His primary research interests include the development of polymeric materials for controlled release drug delivery systems and the modulation of drug release kinetics. As the author of *Controlled Release Dosage Form Design and Advanced Pharmaceutics: Physicochemical Principles*, he published more than 60 papers and 6 patents in this field. His innovative controlled release technology at Temple University eventually led to fruitful results and reached a major licensing agreement with a pharmaceutical company (the largest licensing agreement in Temple University technology transfer history at that time). At UAMS, he has reached another licensing agreement with a foreign pharmaceutical company. He can be reached at ckim@uams.edu or (909) 725-3082.

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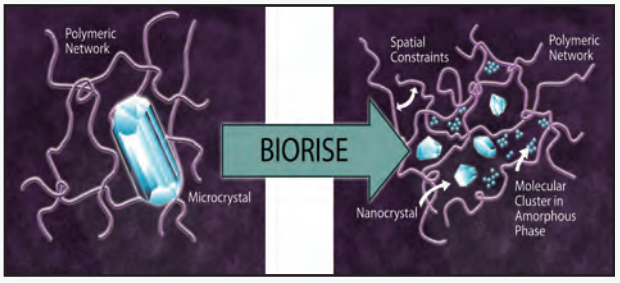

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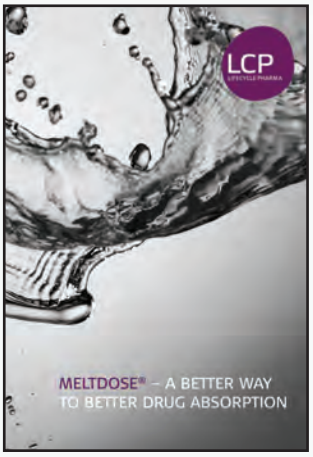
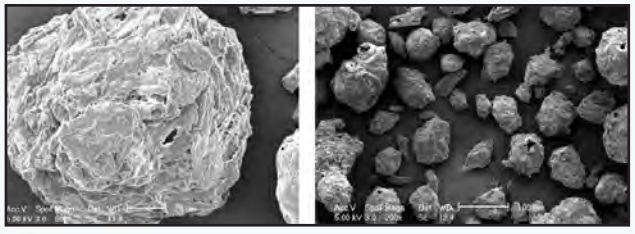


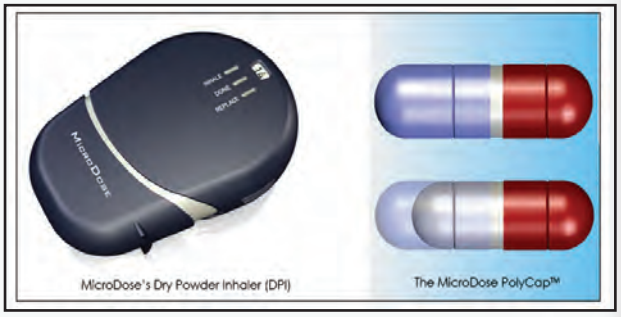
LCP is an emerging specialty pharmaceutical company focused on certain cardiovascular indications and organ transplantation. It currently has one product on the market, seven clinical development programs covering five product candidates, and three product candidates in preclinical development. Its first commercialized product, LCP-FenoChol, has received FDA approval for sale in the US under the brand name Fenoglide™ and is marketed in the US by Sciele Pharma. Fenoglide and its other development compounds are based upon its unique drug delivery technologies. The proprietary MeltDose® platform enhances the absorption of poorly soluble drugs. Applying MeltDose technology creates new versions of existing drugs with improved oral bioavailability, improving efficacy, allowing for lower dose, and in some cases, reducing food effect and/or potential side effects. For more information, visit LCP at **www.meltdose.com.**

Performance Excipients



Mallinckrodt Baker recently launched PanExcea™ MHC300G performance excipient, a homogeneous particle that serves as a filler, binder, and disintegrant for immediate-release applications. Manufactured using novel particle engineering technology, the granular spherical excipient provides multifunctional performance capabilities that enable efficient and cost-effective drug development and manufacturing. PanExcea MHC300G lowers the total cost of ownership for the drug formulator by facilitating direct compression of even the most difficult APIs. It offers extensive API compatibility and variable API load capability to increase formulation flexibility. PanExcea MHC300G, which can be used as a building block or as a complete excipient, provides formulation development flexibilities and efficiencies, and enables implementation of Quality by Design (QbD) initiatives. For more information, contact Mallinckrodt Baker at (800) 943-4747 or visit **www.MallBaker.com/PanExcea.**

Next-Generation Products



MicroDose Technologies is pioneering the creation of next-generation products utilizing its proprietary technologies. MicroDose's Dry Powder Inhaler (DPI) and PolyCap™ combination oral dose capsule system promise to dramatically improve efficacy and compliance. MicroDose's next-generation DPI is a state-of-the-art electronic inhaler providing superior delivery for both small and large molecules to the lungs. It provides a platform technology that is low cost, reusable, and environmentally friendly, which can support a full pipeline of products. MicroDose's PolyCap System is a proprietary approach that enables the rapid development of FDC therapies in a single dose, but separated by a physical barrier. Utilizing the proven strengths of capsules and the advantages of a barrier system, it allows for more rapid development timelines and lower regulatory requirements. For more information, contact MicroDose Technologies, Inc. at (732) 355-2100 or visit **www.microdose-tech.com.**

Technology *Showcase*

Specialist Medical Therapies

PH&T is a pharmaceutical company engaged in research, development, and production of generic drugs for specialist therapies and innovative medical devices sold internationally through licensees and distributors. PH&T has developed and patented Turbospin®, a medium-resistance, single-dose, multi-use DPI, available for size 2 or size 3 capsules. Turbospin has been designed as a portable pen-shaped device, which is user friendly and discreet to use for high patient compliance. The use of Turbospin for pulmonary drug delivery represents an optimal solution for inhalation product development by virtue of its propellant-free nature, single-breath emptying, and wide range of payloads. For more information, visit PH&T at **www.phtpharma.com.**

Passive Safety Device

In response to the continued concern over unprotected needle exposures and the mandated Safety and Prevention regulations, Rexam has developed a fully passive safety device for prefilled syringes: the Safe'n'Sound. The Safe'n'Sound provides healthcare industries and patients with full protection from needlesticks to avoid any contamination. Compared to a standard syringe, the Safe'n'Sound system guarantees passive protection as the syringe retracts automatically in the system after the injection without any action by the user. Compact, light, and transparent, the Safe'n'Sound has only three components (a sleeve, a body, and a spring). For more information, contact Rexam at (847) 541-9700 or visit **www.rexam.com/pharma.**

Subcutaneous Delivery

The OmniPod Drug Delivery System has made subcutaneous delivery a viable route of administration. The system has two components: The Drug Delivery Manager (DDM) and Pod. The Pod is a small, lightweight device that adheres to the body, can deliver 2 ml of liquid medication, and be programmed to infuse the drug in nearly any delivery profile. Drug is delivered via a soft cannula that is automatically inserted into the body in a fraction of a second. Insertion is virtually pain free, the user never sees a needle, and the sharp is safely contained in the Pod after use. The DDM is a handheld wireless controller allowing control of the drug delivery profile for optimized outcomes. For more information, contact SubQ Solutions, Inc. (a subsidiary of Insulet Corporation) at (781) 457-4723, jgaribotto@SubQSolutions.com, or visit **www.insulet.com.**

Contract Service Provider

PharmaForm doesn't just provide its clients with creative solutions; it creates successful partnerships. As a pharmaceutical contract service provider, it offers a wide range of formulation, drug product development, manufacturing, analytical testing and stability services, patent litigation support services, and product platform licensing opportunities. Its formulation scientists have core expertise and experience in improving solubility of poorly soluble compounds. One such available technique to clients is Evaporative Precipitation into Aqueous Solutions (EPAS), a process that causes the formation of nano-sized particles that can help enhance bioavailability of a poorly soluble compound. PharmaForm's state-of-the-art facility is registered with the FDA and the DEA and is cGMP/GLP Compliant. For more information, contact PharmaForm at (512) 834-0449 or visit **www.pharmaform.com.**

Executive Summary

Richard Boehner
President
Symyx High Productivity Research

Symyx Technologies: Turning R&D Into ROI

Symyx Technologies enables companies in life sciences, chemicals and energy, and consumer and industrial products to transform their scientific R&D and achieve breakthroughs in productivity and return on investment. The California-based company's scientific information management enables scientists to design, execute, analyze, and report experimental results faster, easier, and less expensively. Its microscale, parallel experimentation enables a single scientist to rapidly explore a broad experimental space and develop comprehensive data sets and directional information in days. Symyx contract research delivers these advantages on an outsourced project basis and enables companies to increase R&D productivity, agility, and flexibility. *Specialty Pharma* magazine recently caught up with Richard Boehner, President of Symyx High Productivity Research, to discuss the latest trends in R&D within the life sciences industry (including the increase in outsourcing) and to get a first-hand account of what his company is doing to help R&D organizations in life sciences better respond to the rapid changes taking place in the industry.

Q: ***R&D within the life sciences industry is undergoing significant changes. From your perspective, what is happening and why?***

A: Patent protection is expiring for many blockbuster drugs at a time when R&D costs have risen to unsustainable levels and R&D performance continues to disappoint. Add to this a global economic downturn, and pharmaceutical companies are looking for ways to reduce the costs and improve the effectiveness of their of drug discovery and development operations. As a result, pharmaceutical and biotechnology companies are accelerating the pace of R&D outsourcing. However, many companies are focusing primarily, or even exclusively, on the cost-savings component of outsourcing and overlooking other important criteria.

Q: ***Is there something wrong with focusing on savings, and what are the other criteria companies should consider?***

A: It's not that lowering the cost of R&D isn't important, but the history of other industries show that the benefit of outsourcing simply to lower cost is transitory. The key to companies achieving long-term sustainable benefits through outsourcing is for them to increase productivity as well as reduce costs. It's also important that a company's outsourcing strategy incorporate IP protection and risk mitigation. Failure to take these factors into account can quickly wipe out any savings through the loss of trade secrets, regulatory fines, and the cost of litigation.

Q: ***What is Symyx doing to help companies meet these challenges?***

A: Symyx was founded on its proprietary high-throughput experimentation and advanced informatics technology for chemical and energy companies. Over time, we began applying that technology to the pharmaceutical industry in a variety of applications.

Symyx High Productivity Research uses the specialized tools and software we've developed so that a single scientist can execute microscale, parallel experiments that yield hundreds of results in days, rather than the weeks or months required by a team of scientists using traditional laboratory methods. Our microscale capability requires less expensive, early stage experimental material (usually milligrams as opposed to grams), and our advanced informatics provide directional information that our clients can use to pursue the most promising R&D paths.

We have a 14-year history of enabling our customers to achieve extraordinary breakthroughs in R&D productivity, including up to 90% lower cost per experiment, 10 to 25 times more experiments per year, and up to 90% less-expensive, early stage material required for experiments. We also have a solid reputation for protecting a customer's IP and providing regulatory traceability.

Finally, companies can access the advantages of Symyx scientific information management and microscale, parallel experimentation by purchasing our software and hardware products, contracting our research services, or both. This provides companies unsurpassed options for optimizing their R&D productivity, flexibility, agility, and cost effectiveness.

Q: ***Symyx built its reputation on chemical-based R&D, but you've recently added biological capabilities. How have you done this, and what does it mean for your customers?***

A: In August 2008, Symyx acquired Integrity Biosolution, LLC, also known as IntegrityBio. They had built a strong contract offering in formulation research and analytical services, providing high-quality, cost-effective formulation and stability solutions for large-molecule biopharmaceuticals along with GMP fill/finish services for Phase I and II clinical trial volumes. Symyx is applying its unique microscale, parallel experimentation and advanced informatics technology for large molecule research to deliver new, higher levels of research productivity and directional information to biopharmaceutical clients. Now, life science companies can work with Symyx to meet their biological- and chemical-based contract research needs.

Q: ***How does your offering compare with other CROs?***

A: Symyx High Productivity Research incorporates our proprietary microscale, parallel experimentation and advanced informatics technology to enable a single scientist to execute more experiments in less time and to deliver directional information, not just data, to our clients. This allows our clients to make better decisions faster, as well as save money. This is what differentiates Symyx from the typical CRO, and why we offer a sustainable, longer-term competitive advantage.

Q: ***What type of companies are using your contract research services, and what services are you specifically providing?***

A: We're working with a number of larger pharmaceutical companies, including Bristol-Myers Squibb. We are also working with smaller biopharmaceutical companies on a range of contract projects, including solubility studies, polymorph screening, salt selection, co-crystallization, API stability in liquid and solid formulations, excipient compatibility, organic synthesis, and process optimization.

Q: ***What major changes do you see on the R&D horizon in the life sciences industry?***

A: Larger pharmaceutical companies are undergoing a seismic shift in their R&D operating structures, and within the next few years, they will more closely resemble smaller biotechnology companies in their operations. They will spend less overall on R&D and only 20% to 40% of what they're currently spending on in-house research, IP will become their primary core competency, and they will outsource much of their R&D. To win over the next 5 to 10 years, companies will have to add technology that significantly improves R&D productivity, protects IP, and mitigates risk. Those that outsource only to lower costs will find themselves at a competitive disadvantage and may not survive. ■

SPECIALTY PHARMA
Strategies For Business Development

Biopharmaceutical Contracting

Emerging Trends in Outsourcing Protein & Peptide Manufacturing

By: Cindy H. Dubin, Contributor

Patricia Haller, PhD
Director, GMP Production and Process Development

Firuz Shakoori, MSc
Director of Sales, American Peptide Company, Inc.

Rodney Lax, PhD
Senior Director of Business Development, North America PolyPeptide Laboratories Group
.

The market for contract manufacturing of prescription drugs exceeded $30 billion last year, a 10% increase that is being fuelled by specialist production of biologics and sterile products, according to market research company Kalorama, which estimates that 2008 saw $30.5 billion in contract manufacturing of pharma products, with around $2.7 billion of that in the biopharmaceutical sector. That includes both outright manufacturing of product and secondary manufacturing, creating a finished product out of the APIs provided in bulk. The latter of which is driving current growth.

The growing number of biotechnology-driven protein and peptide drugs, antibiotics, chemotherapeutic agents, and other compounds administered as sterile injectables, with its concomitant technological requirements, has brought about an increase in the demand for contract sterile manufacturing services, according to the report.

Some observers have suggested that one possible consequence of the investment in biologics capacity in recent years could be overcapacity. While there is no evidence yet of overcapacity, insiders say it could happen. What is not expected to happen is the recession affecting contract manufacturing. The March 2, 2009, edition of Pharmafocus reports that, according to Kalorama, "While it's too early in the cycle of this economic downturn to call anything a recession-proof market, the outsourcing of drug manufacturing is an area that could see growth in a downturn."

***Specialty Pharma* recently posed some tough questions about the protein and peptide manufacturing market to some experts, including Patricia Haller, PhD, Director, GMP Manufacturing, American Peptide Company, Inc.; Firuz Shakoori, MSc, Director of Sales, American Peptide Company, Inc.; and Rodney Lax, PhD, Senior Director of Business Development, North America, PolyPeptide Laboratories Group.**

Q: ***A very specialized CMO market has emerged thanks to increased outsourcing by Specialty Pharma companies. How can a CMO set itself apart from its competition in this competitive protein and peptide manufacturing market?***

Dr. Lax: By being "special" and trying to offer better value than the competition. With respect to pharmaceutical peptides, there are in fact less than 10 established GMP manufacturers that offer a full range of GMP services that would take a customer from lead development through to commercial, large-scale manufacture of drug substance. Of those few CMOs, probably half have taken more than a dozen peptide-based drug substances through to approval. So a track record of approvals and regulatory experience is one very important asset that sets a CMO apart from its competitors. Using an experienced company is not just risk mitigation. Such companies will usually have an established Regulatory Affairs department and can draw on their wealth of regulatory and GMP experience in order to advise and support their customers.

Experience and capacity aside, customers will be evaluating three aspects of a CMO's services, namely quality, timing, and cost. These are interlinked; and as the adage goes, you can only have two of these at any one time. Generally, for a drug substance, quality will and should be first priority. Performing clinical trials with a poorly characterized API or with deficient GMP is a recipe for disaster somewhere down the line. So, in terms of setting oneself apart from the competition, a sound GMP system and the application of appropriate analytical development and characterization (the latter is obligatory for longer peptides) are assets. Finally, being flexible within the confines of diligent manufacture and GMP conformance, and giving customers what they want is one key to success.

Dr. Haller: Market research conducted by American Peptide Company (APC) showed that Specialty Pharma companies demand quality peptides from CMOs. In addition, these pharma clients are seeking value-added services and expert consultation for their peptides. To fill these needs, APC launched a customized service platform, Total Peptide Management. This program begins in the planning stages of the production where the clients' peptide, specification requirements, analytical and process qualifications, and project timelines are discussed. The peptide is manufactured under strict adherence to cGMP regulations, and updates are provided on the manufacturing progress. This Total Peptide Management program continues after the peptide is delivered with regulatory support for Chemistry, Manufacturing, and Controls (CMC), Drug Master Files (DMF), and stability studies. This program is designed to help Specialty Pharma companies bring innovative drugs to market faster and in a cost-effective manner.

Q: ***As the CMO market grows, production capacity can create a bottleneck for some manufacturing providers. How can a Specialty Pharma company be sure its project(s) won't get caught in this production jam?***

Dr. Lax: The growing market for peptides can cause capacity issues. Between 2002 and 2007, the market CAGR (continuous annual growth rate) exceeded 10%. Given the time required to acquire large-scale equipment and qualify this, some companies no doubt found that they had more projects on their hands than they could comfortably cope with. The answer is to be found in diligent analysis of a customers' requirements (how much and when) and then careful planning. Our approach is to gain an early overview of requirements for immediate use, during clinical development and after commercialization. This enables us to choose the best manufacturing strategy and to place the project in the appropriate facility. Of course, the customer must be duly diligent and determine whether the CMO actually has the capacity and that it will be available for their project. It is not out of the question for a CMO to quote on multi-10-kg quantities of a peptide without having the equipment to manufacture this or mention that the investment will be needed later. During development, delays may occur unexpectedly if manufacturing issues arise. Typically, scale-up and the longer hold times associated with scale-up result in the need for additional development. Customers should give their CMOs and their own colleagues adequate time to accommodate overcoming such obstacles.

Dr. Haller: Any delay in the launch of a product or the initiation of a clinical trial can cost Specialty Pharma companies millions of dollars in lost revenue. We understand the importance of timelines and are expanding our US-based production facility to meet the demand for peptide APIs. We encourage our clients to perform a thorough vendor selection process. This process may include visiting/auditing the manufacturing facility and meeting the management team. In addition, clear communication of the requirements of the project, including timelines and long-term projections, ensures successful completion of each production batch. Furthermore, proper planning is beneficial for both the Specialty Pharma companies and the CMOs; therefore, initiate discussions with the CMOs preferably 3 to 6 months before production starts. During production, monitor progress with periodic updates on the batch. Lastly, as the drug moves to later stages of clinical development or commercialization, diversify production risks by qualifying secondary suppliers.

Q: ***When it comes to process development of peptides, do you require pay up-front or do you risk payment later?***

Mr. Shakoori: CMOs are under tremendous pressure with respect to timeline expectations from customers. With multiple clinical candidates under simultaneous development in the pipeline, customers are often under enormous scrutiny and pressure from investors and management. On the CMO side, incomplete process development at the early stage often manifests in the form of late delivery, lower yields, and variable product quality. To minimize these dangers, we have assembled a highly experienced, educated team of process chemists and engineers, equipped with the proper equipment and infrastructure. We are therefore able to make the best use of constrained development windows to ensure the implementation of robust, safe, and high-yielding manufacturing processes with only modest investment in the early stage of a project during feasibility studies. Whether a development window is performed "at risk" or with pre-payment is decided on a case-by-case basis in close discussion with the customer.

Dr. Lax: Historically, we do not require up-front payment, unless the routine credit check suggests we should. However, with the lack of funding for smaller companies in question during this recession, we are taking a much harder look at this and will generally require some sort of security for first-time customers.

Q: ***How do you handle issues of tech transfer for large-scale manufacturing?***

Dr. Lax: We avoid the issue by placing the project from day one in a facility (we have six) that will be able to handle the large-scale manufacture.

Mr. Shakoori: Tech transfer for large-scale manufacturing has always been a complex task in chemical manufacturing; the specific purification and regulatory challenges associated with peptide APIs make this even more complex. Although no process can ever be developed to perfection, a careful and focused effort in process development before tech transfer certainly helps minimize the potential for downstream problems. We have several key factors that help minimize tech transfer issues. First, early feasibility studies focused on synthetic and analytical process development help ensure that only scalable, robust, and safe processes are developed. Second, before tech transfer, a team comprising project management, process development, manufacturing, and QA/QC is assembled to review proposed manufacturing parameters to ensure compliance on all fronts, spanning technical, economic, and regulatory. Finally, during manufacturing, process development and QA work in close conjunction with manufacturing on any issues that may arise to ensure timely and acceptable resolution. In all situations, the customer is kept appraised of manufacturing progress, with no surprises upon delivery.

Q: ***What analytical technology do you rely upon to increase efficiency in peptide/protein purification?***

Mr. Shakoori: The purification and isolation of synthetic peptides and proteins places a high premium on supporting analytical techniques. Resolution, cycle time, sensitivity, accuracy, and precision are all critical elements in process analytical technology for peptide manufacturing. The majority of analytical work at our company focuses on reversed-phase high performance liquid chromatography (RP-HPLC), as well as mass spectrometry. In selected situations, infrared (IR) and nuclear magnetic resonance (NMR) spectroscopies are applied for analysis of raw materials, process intermediates, and products. We view each project as a unique entity and do not apply a "canned" approach. Our scientists select mobile and stationary phases, gradients, analysis, and isolation methods optimal for each project. Particularly in this economic environment, the use of appropriate process analytical technology is an absolute imperative to achieve reliable, high product recovery and purity without excessive product cycle times.

Dr. Lax: During pre-GMP development or during the first GMP campaign, we do extensive analytical development to make absolutely certain there are no surprises later. Where appropriate, we use the information gleaned in analytical development to guide our choice of preparative systems in the manufacturing process. Obviously, if we need to tweak these later, discover that we can simplify the process, or need to add an additional purification step, we will do this before we validate the process.

Q: ***CMOs are benefitting from secondary manufacturing activities (not your primary focus), particularly in regard to biotech-derived protein and peptide drugs. How are you expanding your capabilities to handle secondary manufacturing of these products?***

Dr. Lax: In terms of GMP manufacturing, The PolyPeptide Group is exclusively focused on peptides. We do, however, perform custom organic synthesis at our facility in Strasbourg, and some of these products are used in our peptides. We manufacture non-peptidic small molecules/organic moieties in quantities up to a few kilograms. These are considered raw materials and can be used in GMP peptides and other non-peptidic molecules. ◆

Alliance Management

Driving Winning Partnerships: Principles & Practices

By: Matt Siefert, MBA, Manager Business Development, Eurand, Inc; with introduction by Troy Harmon, MS, MBA, VP Business Development, Eurand, Inc.

Introduction

Successful alliance management is a key indicator for top-performing pharmaceutical companies. Managing partnerships well is especially important for companies that devote significant resources to developing new products through collaboration. Eurand has a robust pipeline of such co-development partnerships and has devoted significant effort in recent years to ensuring our alliance management practices are best-in-class. Concluding a contract transaction represents only the beginning step required to build a long-term, successful co-development relationship.

Alliances and partnerships have been identified by pharmaceutical CEOs as key elements of future success within the industry.[1] Driving this change is the narrowing focus of many companies on a more circumscribed group of core competencies; therefore, increasing their dependence on external relationships for technologies and products that promote business growth. Because up to 70% of all alliances fail to meet their stated objectives, it is not simply enough for the collaborators to create an alliance; they must make it thrive.[2]

A survey by the Association of Strategic Alliance Professionals on industry collaborations found that alliance success can be attributed to cohesion and effective communication by capitalizing on each party's strengths for the welfare of the overall program.[3] To accomplish this task, all parties need to function as one cohesive unit. An effective collaboration should not be measured merely on the success of a specific product, but rather on the overall success of the entire program.

To achieve success, both companies must create a relationship based on trust and respect. The initial collaboration between companies will likely be the most difficult because a great deal of information must be shared and a high level of learning must occur within a relatively short period of time. Subsequent collaborative efforts generally move more smoothly as the foundations have been established.

To expedite the success of these collaborations, many companies are instituting the creation of long-term partnerships by adding alliance management roles within their organizations. These roles are often established to take advantage of opportunities in the business development and/or project management departments.

Alliance Management – In General

Reports suggest that up to 500 new partnerships are initiated each day. Of these, it is estimated that as many as 70% fail to meet their stated objectives. Understanding the reasons for failure serves to improve the chances for success. A number of studies have investigated the value alliance management activities provide in increasing the success of collaboration. Alliance managers who focus on interpersonal and intercompany relationships and who are directly involved in many aspects of their own and their partner's organization are generally viewed as more effective than those who are less involved.

Due diligence by both prospective partners should be conducted before the collaboration begins to determine both success factors and potential complications based on the collaborative elements. Identifying critical cultural components as quickly as possible may drive mutual understanding and unearth potential concerns that can be addressed before they become problematic.

One never has a second chance to make a first impression. This certainly applies to the first contact between collaborating

companies. Creating an open, comfortable environment in which both partners can operate is critical in optimizing the initial experience and in improving the chance of success. Many companies hold the initial meeting face-to-face at a mutually agreed upon location. It is important at this initial stage to break the ice in a relaxed setting and to encourage participants to relate both on a professional and personal level.

As no two companies and no two products are identical, no two alliances are the same. Generally, the following can maximize the chances for success:

- Open communication stimulates cohesion, two critically important areas that must be addressed and monitored to maintain a healthy relationship.
- Clear agreement regarding the reasons the companies have come together and the manner in which they will interact and function is necessary; consensus will align the two groups, creating a single team that will focus on a single task.
- Oversight and evaluation are key components in ensuring a symbiotic, synergistic team dynamic.

As the program advances, re-evaluations and readjustments may occur due to market or personnel dynamics. Continual oversight by the alliance manager to ensure the team is operating efficiently and that communication pathways are not obstructed is necessary to identify areas in need of improvement and/or whether individuals are meeting or not meeting their obligations. In the event constraints are attributable to miscommunication, rapid resolution is essential to maintaining alignment with the key objectives and to sustaining team cohesion.

At completion of each stage of the development program, it is essential to review the alliance to identify what has and has not worked. Continual improvement should be the primary goal achieved through alliance management activities designed to foster collegial teamwork, open communication, strong oversight, and full commitment.

Alliance Management – At Eurand

Eurand established an alliance management group in 2006 after recognizing the importance of cultivating long-term partnerships to derive the most value from its focus on co-development transactions. At its inception, the Eurand alliance management group was tasked to achieve two objectives: 1) to manage related business development activities and 2) to forge a single development team, comprising Eurand representatives and those of its partners, by developing trust and respect at the project team level.

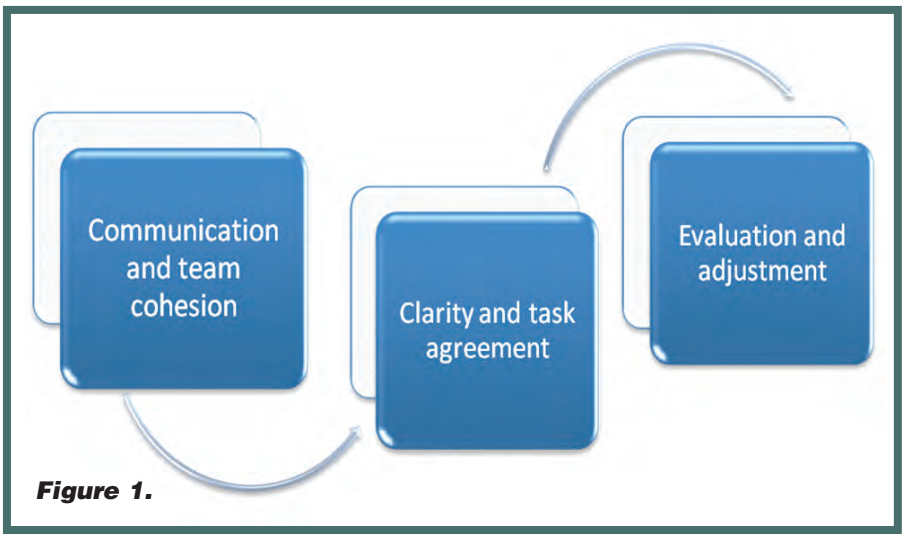
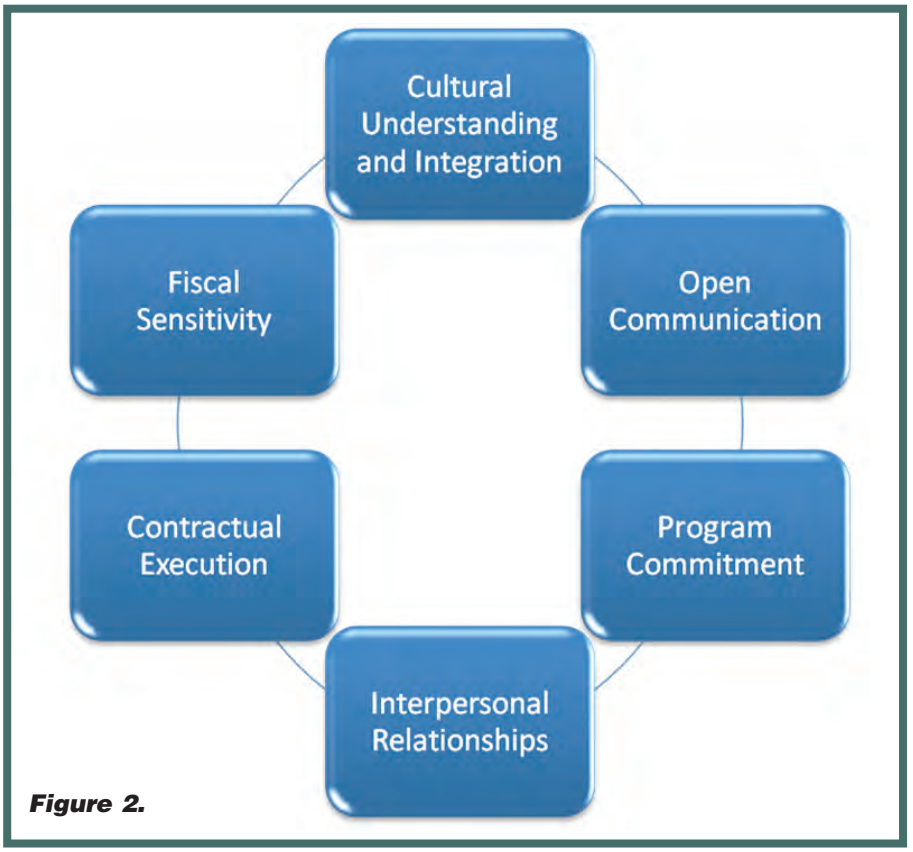


Figure 1.



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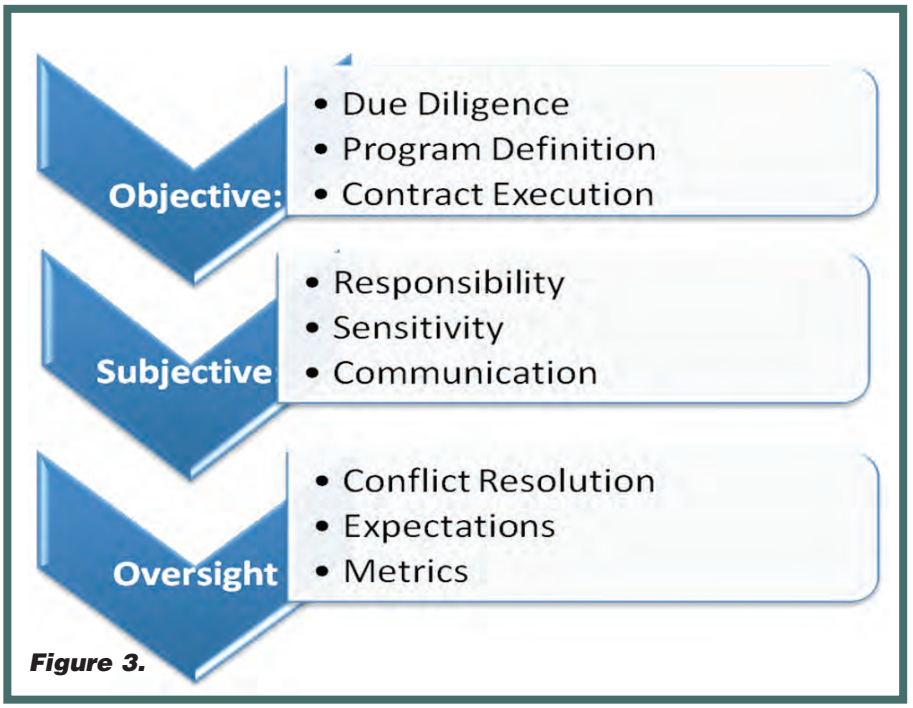

Figure 3.

Eurand crafted Alliance Management Best Practices after examining more than 15 years of collaborative effort with several diverse partners, specifically looking at the dynamics of partnerships that empower alliances to gain the highest level of support, and thereby increasing their probability of success.

Eurand's Alliance Management group strives to manage alliances from the outset by instituting a joint understanding of each party's goals, creating a framework for interaction and providing a system for communication. The group is charged with fostering a team-lead program powered by open communication, strong risk-mitigation plans, and a clear roadmap to enhance the program experience.

Collaborations are initiated using a three-step process: Objective, Subjective, and Oversight. In the Objective phase of the partnership, due diligence is performed by both companies. Partners are asked to respond to a questionnaire designed to better understand their objectives, driving points, and sensitivities. Data from this questionnaire are analyzed in conjunction with Eurand's best practices to evaluate how the groups will best integrate. From experience, Eurand has found that early assessment and understanding of these critical items facilitate a clearer understanding and provide the knowledge that can be a resource in developing the connections necessary to creating a strong alliance. Upon execution of the partnership agreement, a kickoff meeting provides a starting point for the parties by aligning the group and creating one cohesive team. Program goals and contract commitments are discussed at this meeting so that the team members understand their individual obligations as well as the limitations of their roles.

The Subjective phase assesses the personality of the alliance and the individual parties. Identification and discussion of responsibilities of team members and subsequent agreement must occur to mitigate potential "off-scope work" and to support an efficient development process. Corporate and cultural sensitivities of each party also are discussed. An open communication pathway is established based on the objectives and identified risks of the program. Good communication is critical to providing the information to move the program forward as well as to identify and address problems.

The Oversight process is used to accentuate an understanding of rules and how to work through issues if they arise. At this stage, effective conflict resolution is discussed, expectations from senior members of both organizations are shared, and metrics are agreed upon and established. These metrics focus on the relationship quality of the program as well as the achievement of technical milestones. The process is considered to be an overall successful if the parties clearly understand their objectives, are able to communicate effectively, and demonstrate trust of and respect for each other.

Alliance Management – In Action

Even when collaboration is thought to have been organized correctly, the following example illustrates the importance of productive personal relationships and open communication pathways. Eurand's US-based development group was working with a European pharmaceutical company on a product targeted for foreign markets. The client brought two project teams to the collaboration: the product champions and lead contacts based in Europe and a technical team based outside Europe. The three teams formed a partnership that needed to function effectively across multiple time zones. At the kick-off meeting, all parties reviewed and agreed upon activities, the work plan, and other topics as had been previously discussed. Development moved forward with minimal issues for the first few months. Then, early signs of disconnect were detected as new regulatory expectations from the ex-European group were identified that would significantly change the scope of work, significantly affecting timelines and costs, and leading to confusion among the European-based product champions and Eurand. While the regulatory expectations had not changed, they had not been clearly conveyed. Both parties were developing a product without having all of the relevant information, an extremely risky situation. The new information was going to lead to

additional work, additional costs, and additional time, all of which were potentially damaging to the success of the program.

Because the relationships established at the beginning of the alliance enabled a comfortable and uninhibited channel to correspond, the conflict resolution process was quickly implemented. Through open communication, all parties were able to discuss whether the program's scope required reshaping. It became evident the technical plan was not sufficiently clear from a regulatory standpoint, and that this was the main factor necessitating changes in program scope. Compounding the issue was that the communication pathway had not been working as well as it should; therefore, the teams were not effectively communicating to move the program forward. The entire process needed to be simplified. Fortunately, all of these issues were identified early on and were worked through during a strategically important period, resulting in the realignment of certain objectives without jeopardizing the team or the program. This experience illustrates the inestimable value of good personal relationships, as open communication is critical to managing challenges.

Asking the Right Questions

Eurand continually evaluates each alliance by implementing periodic status checks through questionnaires. These "spot-check" questionnaires evaluate how well the alliance is performing by eliciting information from both parties. Two key areas assessed are communication and coordination. This review raises awareness of problems and concerns as early as possible so the parties can resolve them before the alliance is negatively affected.

Questionnaires have proven effective when other methods of oversight and evaluation have not, as is illustrated in the following example. An alliance between Eurand and a US-based pharmaceutical company developing a life-cycle management product for worldwide distribution started off successfully. A few months into the program, a questionnaire was distributed to the partners to understand how the program was developing, how the alliance was working, whether there was alignment, and if there were any impending issues. After reviewing the data, it was revealed there was a misalignment in communication. Eurand had rated communication as excellent, while the partner had rated communication as just okay. The alliance manager spoke to the client to elicit additional feedback regarding the luke-warm response and learned the partner had been receiving updates during regularly scheduled project team meetings, but felt the updates were too infrequent based on the nature of the program, potential risks, and culture of their organization.

Changes in the communication process were immediately implemented; these included more frequent updates and expanded sharing of information. A follow-up questionnaire fielded a month later demonstrated the changes implemented had successfully addressed the problem.

What Have We Learned?

Both aforementioned examples demonstrate that open communication is of critical importance for the success of an alliance. As long as there are open channels among the alliance partners, and all are encouraged to be forthcoming in expressing their concerns, issues can be quickly identified and problems addressed in a timely manner.

Eurand conducts a full review at the completion of a partnership. This assessment evaluates how effectively the program has been managed and how key learnings can be used to improve current practices. Eurand's overarching goal is to be a Partner of Choice and to make the collaborative experience efficient, professionally rewarding, and profitable. ◆

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Mr. Matt Siefert is Manager, Business Development, for Eurand with a primary role of alliance management of the company's co-development partners. In this capacity, he has developed the Best Practices for Alliance Management that Eurand currently uses. He also is responsible for general business development activities, including the management of transaction terms, arising intellectual property, budget, work plan changes, partnership steering committees, and negotiation of contract amendments and supply agreements. Prior to joining Business Development, Mr. Siefert was a Formulation Scientist from 1998 to 2005. In that role, he worked as the lead formulator on Eurand's R&D collaborations in the US, developing products, managing the technical interactions of partnerships, and assisting in advancing Eurand's intellectual property portfolio. He earned his BS in Chemistry from Wilmington College in Wilmington, Ohio, and his MBA from Wright State University in Dayton, Ohio.

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Mr. Troy Harmon is currently Vice President, Business Development for Eurand, a specialty pharmaceutical company focused on the development of novel drug delivery technologies and products. Mr. Harmon joined Eurand in 2002, and his responsibilities include business development, marketing, and licensing efforts for Eurand in North America. Prior to joining Eurand, Mr. Harmon was Director, Business Development at Delsys Pharmaceutical in Princeton, NJ, where he was responsible for marketing and partnering the company's electrostatic powder deposition technologies worldwide. In addition, Mr. Harmon has served as Director, Business and Product Development at FEI Technologies, a company specializing in implantable drug delivery systems, and as Sr. Scientist at Summit Technology, an innovator in laser vision correction procedures. Mr. Harmon earned his BS from the University of Kentucky, where he was elected to Phi Beta Kappa and received the University's first prize for undergraduate academic research. He earned his MS in Physical Chemistry from Cornell University and his MBA from Villanova University.

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Up to My Blank in Alligators: A Short Story of a Youngster & The Unprofessional

By: Dan Marino, MSc

About a year-an-a-half ago, I was called on the phone by a young man from a public relations firm who was looking to promote one of his clients in our publication. He was nice and explained in detail how the company he was representing was a perfect fit for our magazine and its readers. He had done his homework.

After a few minutes, he asked if there was any type of information we sought for our readers other than press releases on mergers, acquisitions, licensing, etc. Eventually, we had both come up with a great idea for a series of columns on a very specific topic. The column was extremely popular and a great success.

I say success for several reasons. First, our readers were provided with editorial content they could use in their every day professional lives. Second, the client of the public relations company that provided the content was afforded exposure to our subscribers (their potential customers) as well as the thousands who visit our website each month. In addition, the public relations company was justly paid for finding the opportunity and doing exactly what it was supposed to do. Not to mention, we even got some advertising out of the deal. It was a win-win. Boy, if we could only get the economy to work this simply.

I will not mention any names in this column, so I will refer to the public relations employee as the Youngster. Our relationship lasted for quite some time as he had other clients related to our publication. And because we both knew exactly what the other wanted and needed, the relationship was very low maintenance, yet very effective and productive.

Then one day, I called the public relations firm looking for my buddy and was given every excuse in the book as to why he couldn't come to the phone and that he would call me back. My phone never rang. Most, if not all, of us out there know from our personal lives what that feeling is like. Did I do or say something wrong? After several more attempts in trying to reach out to the Youngster, I was put in touch with his Replacement! I guess the Youngster got the boot.

I gave it my best as I am sure the Replacement did, who also never wanted to talk about the Youngster and where he had gotten off to. Needless to say, it wasn't the same. As time went by, the companies the public relations firm represented directly related to us began to dwindle, and in just a short period of time, the relationship just fizzled. It was sad, but it was also time to forge ahead.

I will not go into the specifics on why I had to do it, but I needed to get in touch with the President of the public relations company. The first several times I called, I was told he was out of the office, never thinking of asking for his voice mail as I left my messages with his assistant for him to call me back. The next time I called, I asked for his voice mail, and his assistant was more than happy at this point to put me there. When the message came on, it said, "I can't come to the phone right now, I'm up to my butt in alligators!" I used the word butt because this is a family-oriented magazine, but the word on the machine was more graphic.

The picture at this point became very clear to me. The President, who I will call the Unprofessional for never calling me back and that ridiculous message, was still losing clients and very valuable employees, ie, the Youngster. Did he actually believe he was helping his situation? I wonder how many potential clients who may have wanted to do business with him heard that message and hung up the phone? I'm not going to sit here and say that I have been professional every single step in the staircase of my career, but I can tell you one thing, a message like that is like hanging a permanent sign on your door that says….Out of Business! ◆

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