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Controlled Release Innovations

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

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"The search for novel solutions to address therapeutics through new "druggable" targets and mechanistic approaches remains a matter of great concern in the pharmaceutical and biotechnology industries. New drug discovery and development platforms have been developed and optimized, resulting in an impressive pipeline of controlled release therapeutic solutions to treat a broad spectrum of disease conditions, mostly focused on autoimmune and inflammatory disorders, infectious diseases, neurological affections, and different types of cancer."

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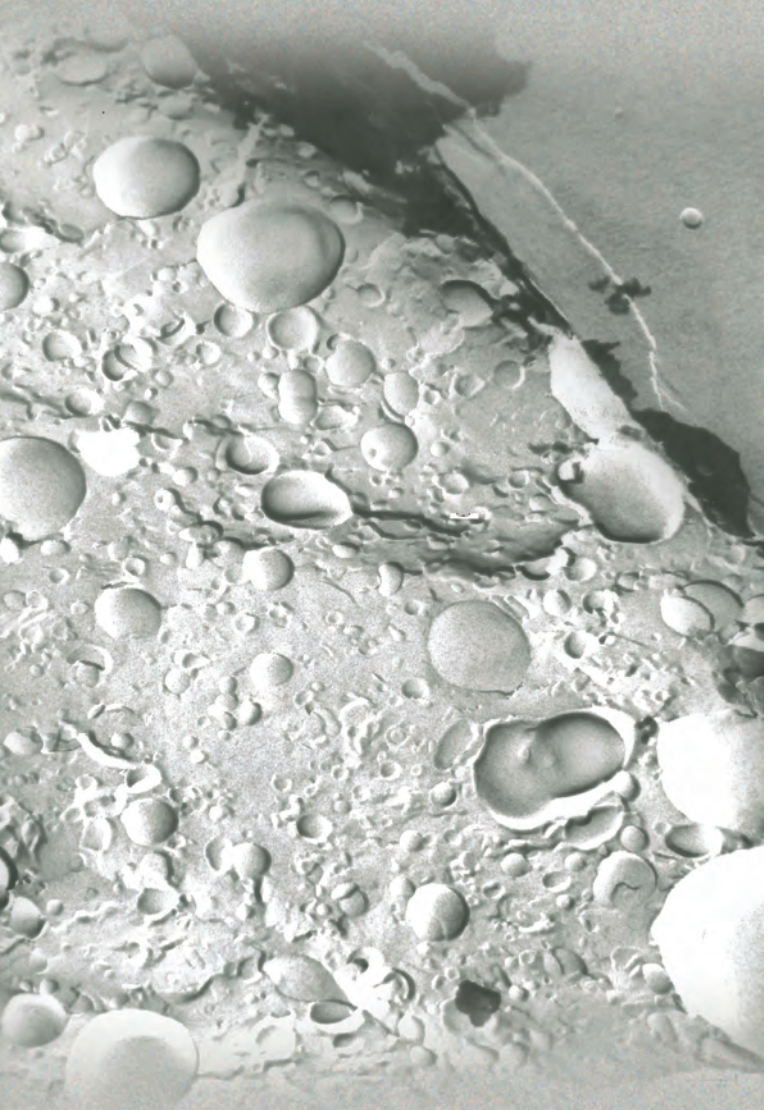

"Recently, there has been considerable renewed interest in technologies to form liposomes. Although there are few commercialized liposomal products, there are many in various stages of clinical development. The reason for the renewed interest is that both poorly soluble APIs and difficult-to-deliver biological molecules like proteins, peptides, and genes can potentially be more readily formulated as liposomes to both increase biological uptake and improve effectiveness of treatment."

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CIMA will be presenting its newest delivery technology, OraGuard Abuse-Deterrent, on July 21st at the Controlled Release Society's 40th Annual Meeting in Honolulu. If you are interested in other CIMA technologies please visit us at our booth #104.

For additional information on any of our drug delivery technologies, please contact John C. Nagel, (763) 488-4975, john.nagel@cimalabs.com or Jeremy G. Webber, (763) 488-4784 jeremy.webber@cimalabs.com

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Market News and Trends

UPM Pharmaceuticals Purchases Pfizer Commercial Manufacturing Site

UPM Pharmaceuticals, a Baltimore, MD-based drug development and contract manufacturer, recently announced it will be acquiring the 500,000-sq-foot commercial manufacturing facility that Pfizer Inc. (PFE) currently operates in Bristol, TN.

The acquisition of the Pfizer facility will provide UPM with large-scale commercial capabilities for manufacturing and packaging of solid oral dosage tablets and capsules, as well as semi-solid manufacturing of creams and ointments. The facility will also provide for comprehensive tech transfer support, pilot plant scale-up capabilities, analytical and microbial testing, as well as dedicated suites for potent compounds. As part of the purchase, UPM will continue to manufacture Pfizer's current portfolio of products within the facility for 2 years. The acquisition will allow UPM Pharmaceuticals to offer a full range of development, testing, and manufacturing capabilities to its existing and new clients.

"We are pleased to complete the sale of our Bristol site to UPM Pharmaceuticals," said John Kelly, Vice President, Strategy and Transitioning Sites. "UPM leaders have experience with this site and are familiar with our colleagues and the products we manufacture there, they share our commitment to quality and have a long history of success. We look forward to an ongoing relationship with UPM. We also think this is a boost for the Bristol community, as the managing partner of SJ Strategic Investments and Chairman and CEO of UPM is Dr. John Gregory, who is a well-known member of the Bristol community, and he and other members of his family will be involved in the ownership and management of this facility."

"The acquisition is a very exciting opportunity for our organization," added UPM's President, James E. Gregory. "With the new facility, UPM will now be able to offer clients a seamless transition from early stage formulation development to commercialization along with all associated comprehensive lab support. The new facility will give UPM the capability to annually produce 3.5 billion tablets and 680 million capsules; this will be a dramatic growth opportunity for our company and our clients."

The Pfizer facility was once home to King Pharmaceuticals before being acquired in late 2010. King Pharmaceuticals was founded by UPM's current Chairman and CEO John Gregory.

UPM Pharmaceuticals, Inc.'s history includes successful collaborative interactions with virtual to multi-billion dollar companies providing them with customized product development services and solutions. UPM focuses on drug development for dosages with oral routes of administration, in solid dosage forms such as capsules and tablets. UPM's clients enjoy service that is customized and fast with total quality management characteristic of a customer-focused business.

Novozymes's Recombinant Human Albumin Helps Innovative Dry Eye Therapy

Novozymes Biopharma recently announced that an ophthalmic solution made using its recombinant human albumin, has been approved for Phase I/II development by the FDA.

Designed by R-Tech Ueno, RU-101 ophthalmic solution is being trialed as a therapy for severe dry eye, for which no effective treatment is currently available. The recombinant human albumin is part of Novozymes Biopharma's albumin range. Novozymes Biopharma has a strong reputation in the industry for helping customers in the safe and successful commercialization and approval of new products.

The prevalence of severe dry eye, where patients suffer from instability of the tear film, continues to increase. It is the most diagnosed of all ophthalmic disorders and estimates put the market at approximately $1.5 billion. The trials for RU-101 ophthalmic solution will move ahead in two stages, the first of which will assess safety using a placebo control, and allow confirmation of the maximum dose. The second stage will then use this maximum dose for 12 weeks to evaluate the safety and effectiveness of RU-101 ophthalmic solution.

"Novozymes is dedicated to supporting our customers in the drug development and testing stages, and in assisting with the optimization of their pathways through regulatory approval procedures. We are therefore delighted that RU-101 ophthalmic solution has been approved for clinical testing," said Dermot Pearson, Marketing Director at Novozymes Biopharma.

Novozymes Biopharma's recombinant albumin is designed to provide quality performance benefits when included in drugs developed by our customers. It was selected as a key component of this novel therapy back in 2011, due to its proven high quality and enhanced safety profile. Animal-free, with an exceptional purity profile and convenient liquid format at room temperature, recombinant albumin delivers consistent levels of quality, leading to reduced lot testing and vendor auditing.

Catalent Applied Drug Delivery Institute Announces Winners of Academic Competition

The academic competition aims to identify emerging scientific talent, foster drug delivery education, and reward academic excellence. Winners were chosen from leading US and European universities with graduate programs in pharmaceutical science, including St. John's University, Rutgers University, New Jersey Institute of Technology, University of North Carolina at Chapel Hill, Purdue University and Heinrich Heine University of Düsseldorf, Germany. Competition entries consisted of original review articles addressing topics, such as drug development, delivery technologies, improving therapeutic profiles and bioavailability, pre-formulation, and pediatric drugs. The academic competition reflects the Institute's commitment to fostering education, collaboration, and adoption of drug delivery technologies to develop better treatments for patients.

The competition's grand prize of $5,000 was awarded to James Byrne of the University of North Carolina at Chapel Hill, whose winning submission focused on Treating Human Autoimmunity With Immunotherapy. Additionally, each of the following students was awarded a first place prize of $2,000 as the top submission from their university:

- Shashank Jain, St. John's University, Rationale for Selection of Solubility and Dissolution Enhancement Strategies
- Maxim Osipovs, Heinrich Heine University of Düsseldorf, Challenges for the Oral Delivery of Macromolecules
- Maxx Capece, New Jersey Institute of Technology (NJIT),Modified Release of Dry-Polymer Coated Active Pharmaceutical Ingredients.

As an investment in the future life science leaders of tomorrow, the Catalent Institute has collaborated with the American Association of Pharmaceutical Scientists (AAPS) to reward students' participation in the academic competition with a complimentary, one-year AAPS membership.

The Catalent Applied Drug Delivery Institute serves as a link between industry and academia by providing guidance, counsel, and resources on major issues pertaining to drug development, formulation, and delivery. Founded in 2012, the Institute promotes innovation, knowledge-sharing, and collaboration to enhance understanding and accelerate adoption of applied drug delivery technologies as a means to develop better treatments and improve patient care. An initiative of Catalent Pharma Solutions, the Institute is pursuing a multi-tiered approach of seed funding, strategic counsel, and educational programs to advance the adoption of emerging technologies.

Integral BioSystems to Offer Ophthalmic Formulations for Eye Therapies

Integral BioSystems LLC is developing and will offer for license its novel, platform front-of-the-eye and back-of-the-eye ophthalmic therapeutic delivery systems, OcuSurf and EySite.

Integral BioSystems' niche is in nano-engineered drug delivery systems aimed at providing solutions to long-held issues in drug products, especially in low drug absorption by target tissues due to cell impermeability and insolubility. In addition to assisting drug companies in developing their dosage forms, Integral scientists are also working on novel solutions to improve the bioavailability of Class II, III, and IV compounds.

The company has developed numerous dosage forms for ophthalmic applications. Integral BioSystems has a translational approach to drug development, customizing delivery systems to achieve the biologically effective objectives of the therapy. Dosage forms are customized to achieve sustained release or targeted, tissue-focused delivery or fast-release/instant delivery, depending upon the desired product attributes.

Once the drug-containing formulations are tested in preclinical models, the company develops an integrated CMC plan to systematically transition the project to scale up and product development. As part of product development, Integral BioSystems specializes in efficiently developing a dosage form to manufacture and test in Phase I/Phase II first-in-man trials for proof-of-concept. The company has a network of manufacturers/analytical houses for pharmaceutics that can fast-track the manufacture and release of the sterile dosage form for first-in-man trials.

Integral BioSystems is a specialty drug delivery contract research organization that offers an integrated, practical approach to formulation development projects for both small molecule and large molecule drug candidates.

Valeant Pharmaceuticals to Acquire Company for $8.7 Billion

Valeant Pharmaceuticals International, Inc. and Bausch + Lomb Holdings Incorporated, the global eye health company, recently announced they have entered into a definitive agreement under which Valeant will acquire Bausch + Lomb for $8.7 billion in cash.

Bausch + Lomb is a leading global eye health company that operates in three segments: Pharmaceutical (including prescription brands, generics, and OTC), Vision Care (contact lenses and solutions), and Surgical (intraocular lenses and surgical equipment).

Under terms of the agreement, which was unanimously approved by the Board of Directors of both companies, Valeant will pay aggregate consideration of $8.7 billion in cash, of which approximately $4.5 billion will go to an investor group led by Warburg Pincus and approximately $4.2 billion will be used to repay Bausch + Lomb's outstanding debt. Valeant expects to achieve at least $800 million in annual cost savings by end of 2014. Bausch + Lomb expects to have revenues of approximately $3.3 billion and adjusted EBITDA in 2013 of approximately $720 million. The transaction is expected to be immediately accretive to Valeant's cash earnings per share. Assuming the transaction occurred on January 1, 2013, and assuming the full realization of synergies, the acquisition would have been approximately 40% accretive to Valeant's expected 2013 Cash EPS.

Bausch + Lomb will retain its name and become a division of Valeant. Valeant's existing ophthalmology businesses will be integrated into the Bausch + Lomb division, creating a global eye health platform with estimated pro forma 2013 net revenue of more than $3.5 billion. The acquisition positions Valeant to capitalize on growing eye health trends driven by an aging patient population, an increased rate of diabetes and demand from emerging markets. The combined business will also benefit from access to a strong product portfolio and a late-stage pipeline of innovative, new products.

ADVANCED DELIVERY DEVICES

Tackling Traditional Usability Issues With Innovative Device Design

By: George Perkins

The presence of the hormone progesterone in the female body makes a vital contribution to the success rate of pregnancy. Progesterone plays a role throughout pregnancy, increasing the likelihood of conception, preparing the uterus for implantation, and aiding development of the fetus. It is becoming more and more common for mothers experiencing difficulty with natural conception to turn to In Vitro Fertilization (IVF), with about 1% of all the babies born in the US in recent years conceived as a result of IVF treatment. According to CDC's 2010 ART (Assisted Reproductive Technology) Success Rates, 147,260 ART cycles were performed at 443 reporting clinics in the US during 2010, resulting in 47,090 live births (deliveries of one or more living infants) and 61,564 infants. These numbers are set to increase as the procedures become cheaper and more common.

Women undergoing IVF are commonly given a Follicle Stimulating Hormone (FSH), which stimulates the ovaries to produce mature eggs for external fertilization. A known side effect of FSH treatment is a drop in progesterone production which, coupled with some women choosing to conceive later and later in their lives, can lead to a distinct lack of progesterone in their systems. As such, luteal support (the administration of progesterone) is a significant component of the IVF process. There are a variety of techniques for IVF, but in all cases, achieving an adequate level of progesterone is known to improve the likelihood of a successful pregnancy. The period of luteal support varies depending on each patient's natural level of progesterone, some requiring support for the first trimester, others for the full term of their pregnancy.

Typically, the patient is relied on to self-administer progesterone either by vaginal pessary (eg, Endometrin, twice daily) or intramuscular injection of Progesterone in Oil (PiO, once daily) for the specified duration of luteal support. While neither method has been proven to be more efficacious than the other, the requirement of pessary administration for patients to be horizontal for up to 20 minutes while administering the dose, the potential for inaccurate dosage due to subsequent leakage and the associated discomfort of the delivery method represent inconveniences that can sway favor toward the injection-based administration. Ignoring the negative aspects of injection, it is plausible to recognize it as a superior method of drug delivery in terms of convenience and efficacy. It is our belief at Cambridge Consultants that, by addressing the stigma and usability issues of self-administered injections, it is possible to make them the more attractive method for the administration of drugs in this and other scenarios.

FIGURE 1

THE CHALLENGE

The recommended injection site for PiO is the 'upper buttock' region, which is particularly challenging for those choosing to self-administer. Being suspended in sesame oil, PiO has a relatively high level of viscosity when compared with saline and typical injectable drugs. For manual

syringe-based administration, a user would have to exert up to 10 N for up to 120 seconds in a typical usage scenario for a 2-ml administration. The effort required to maintain this force for delivery in addition to the awkward injection site can lead to user hesitation, painful angular variation of the needle in the skin, and intermittent delivery, which prolongs the injection process. Additional issues with this delivery method can manifest as injection site irritation due to the long injection duration, discomfort due to the volume of relatively cold oil injected, and its tendency to clump into an assortment of small beads as it dissipates.

THE SOLUTION

Cambridge Consultants was first made aware of PiO and the associated usability issues while conducting user studies with healthcare professionals at US fertility clinics in 2011. Improving the user experience of PiO represented a challenging and exciting opportunity for Cambridge Consultants to showcase its in-house capabilities in the fields of innovative medical device design, product design, electronics design, industrial design, and human factors research. The drug delivery device development team set about producing a reusable device design specifically tailored to the delivery of PiO from a standard 2-ml syringe with luer-locked needle, this device was eventually to be known as 'piOna.' Utilization of the existing syringe presentation and delivery vessel is important, as it maintains consistency for users who may or may not choose to inject with the aid of a delivery device and for the pharma company who will most likely not want to bear the additional costs of certification for a new or modified syringe presentation of the hormone. A glass 2-ml syringe with luer-lock needle is seen as the 'worst case scenario' for engineers designing an auto-injector, it's large, difficult to safely retain in the device, and prone to relatively poorly controlled dimensional variation. Our philosophy was to design a device around the worst case parameters to demonstrate that any syringe can be catered for in a reusable auto-injector.

Utilizing in-house capabilities in Industrial Design and Human Factors, multiple geometries for the exterior of the device were explored and exposed to limited user studies for feedback. With the overall size of the device limited by the size of the syringe and minimum grip size for the target demographic, a variety of conceptual forms were modelled in foam to determine the most preferred handling geometry to suit the awkward delivery site. By analyzing the feedback of potential users exposed to the assorted handling models, it was possible to determine not just the optimum shape of the device for the application, but also the preferred locations for electro-mechanical controls and tactile feedback features. In addition to the physical form of the device, much attention was paid to determining a visual style for the device that would hold maximum appeal to the typical user. The intention was to break the cycle of drug delivery devices being immediately recognizable as medical devices. The approach we take to device design is two-fold. First, we determine and specify the functional requirements for a device and ensure they are satisfied, if not exceeded. Second, we strive to ensure the device is appealing to the user; it doesn't matter how well a device works if no one wants to use it!

FIGURE 2

In an effort to minimize user steps for syringe loading, a simple twist of the release collar at the waist of the device is all that is required to separate the two halves, which reassuringly 'pop' apart. The act of priming the device has been combined with assembling the two halves of the device after loading the syringe, simply pushing the two self-aligning

FIGURE 3

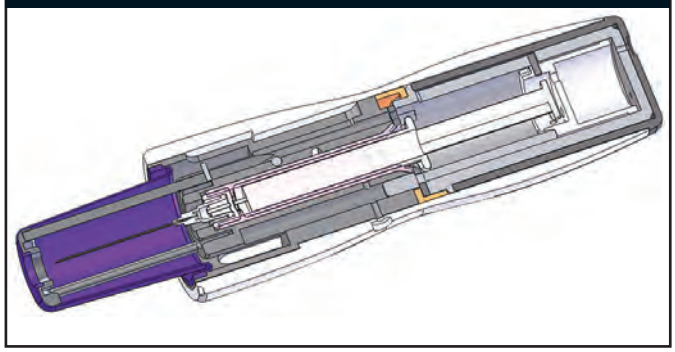

FIGURE 4

halves of the device back together will compress the piston and power spring and leave the device ready to use.

Needle phobia is a real deterrent to a significant number of potential recipients of self-administered injectable drugs. In the case of PiO, a typical needle is 22 gauge and 1.5 inches long to cater for the high viscosity of the sesame oil suspended hormone and deep intramuscular delivery. The development team addressed this issue by hiding the needle from the user until the final disposal step of the usage sequence. The needle is capped until the device is assembled, primed, and ready to use, at which point the end of the cap protruding from the needle sheath can be pulled out to remove the cap whilst the needle is hidden from view.

To combat the long injection duration, the development team took advantage of the in-house electronics know-how of Cambridge Consultants to develop a novel system for pre-warming the syringe and its contents prior to delivery. While docked, the piOna device is connected to a power supply, and inside the device, a custom-made PCB coupled to a flexible heating element warms the syringe from ambient to body temperature in approximately 30 seconds. The temperature is then monitored and maintained at precisely 38°C by the on-board electronics for as long as the device is docked. By only being powered in the docked state, the device is not classified as an electronic auto-injector and manages to avoid the additional regulatory burden of such a device. Once undocked, the presence of a layer of foam inside the device insulates the syringe and prevents the temperature dropping significantly over the course of the injection. In-house testing has indicated that warming PiO from 21°C to 38°C represents a 30% reduction in viscosity of the oil, and subsequently a 30% reduction of injection duration. Additional potential benefits of warming the PiO are a reduction of injection site irritation, faster dissipation of the PiO into the muscle, and the associated reduction of patient discomfort.

To combat the potential for user apprehension of the new level of technology that has been incorporated into the device, visual and audible progress indications can be integrated into the docking station to reassure the user at every step of the process, from preparation to disposal.

Adding the functionality to automatically insert the 1.5-inch needle would have significantly increased the size and cost of the device, so the development team opted to fix the needle and syringe relative to the device and utilize the novel soft touch needle shield to replicate the insertion technique of a healthcare professional. Typical advice for the insertion of a needle into the skin is to utilize a ‘swift dart-like motion’ at 90° to the skin. This technique is replicated in piOna by forcing users to overcome a high initial resistance to retract the needle shield as they push it against their skin. Once this initial force is achieved after a few millimeters of movement, the force to retract the needle sheath significantly reduces, creating the required ‘dart-like’ motion. Orientation of the device relative to the skin is aided by the wide flat front of the needle shield.

A safety interlock button is included in the device to prevent accidental triggering, the intention being that it is held down only at the beginning of insertion/delivery and can be released once delivery begins. At approximately 90% needle shield retraction, the delivery mechanism is mechanically triggered, and the contents of the syringe are expelled automatically. The button also serves as an intuitive guide as to what the development team has determined to be the optimum handling orientation for the device. Holding the device such that the thumb is over the interlock button automatically positions the fingers over the tactile feedback

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FIGURE 5

pip, a small mechanical protrusion that emerges to signify a completed delivery.

Our own user studies have shown that feedback is an important feature of any drug delivery device. Through piOna, Cambridge Consultants is hoping to demonstrate the future potential of the type of user feedback to expect from drug delivery devices. At the most basic level, there is mechanically driven tactile and audible feedback, representing the bare minimum level of feedback already seen in today's devices. The PCB on board piOna can easily be expanded to provide never before seen levels of user feedback in a drug delivery device, visual progress displays on the docking station as you inject can be implemented through wireless technology pioneered at Cambridge Consultants. Taking the technology further, integrating such a device into a network of connected health devices or even teaching it to talk to a smartphone is now well within reach.

The piOna device was conceived to not just showcase the diverse technical abilities of Cambridge Consultants, but to push the limits of expectation for existing and potential clients in terms of device performance, capability, comfort, and appeal. Typical gestation for a commercial drug delivery device development is 5 to 10 years, a timeframe that promotes a risk-adverse strategy when considering future trends. Cambridge Consultants is suggesting that drug delivery devices do not need to exist in a style space that sits outside of future trends and is inviting its clients to take the opportunity to define them.

You won't see piOna on a shelf to buy; it exists purely as a catalyst for innovative product design. We hope that piOna can help our current and future clients see the potential for their own devices and allow us to design them an equally unique solution tailored to their specific requirements. ◆

BIOGRAPHY

George Perkins is a Senior Mechanical Engineer in the Medical Technology division of Cambridge Consultants, a product development firm headquartered in the UK and with offices in Cambridge, MA, and Singapore. Mr. Perkins has been working in a consultancy environment for 17 years, directly involved in the design and development of medical devices for 5 years, including auto-injectors, dry powder inhalers, electro-mechanical delivery systems, and surgical implants.

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MARKET BRIEF

Controlled Release Technologies: Advancing Toward Targeting Therapeutics

By: Cecilia Van Cauwenberghe, MS, Technical Insights Senior Research Analyst, Frost & Sullivan

OVERVIEW

The search for novel solutions to address therapeutics through new "druggable" targets and mechanistic approaches remains a matter of great concern in the pharmaceutical and biotechnology industries. New drug discovery and development platforms have been developed and optimized, resulting in an impressive pipeline of controlled release therapeutic solutions to treat a broad spectrum of disease conditions, mostly focused on autoimmune and inflammatory disorders, infectious diseases, neurological affections, and different types of cancer. Products such as tumor necrosis factor (TNF) inhibitors for rheumatoid arthritis (RA) or glucagon-like peptide-1 (GLP-1) analogues for diabetes revolutionized pharmacotherapy by offering patients true disease-modifying benefits as opposed to simply treating the symptoms.

Nevertheless, developing safe and effective pharmacotherapeutic regimes through controlled targeted therapies represent a significant challenge for scientists and clinicians. Although oral routes of delivery remain among the most preferred regimes by patients, formulation challenges and safety specifications could discourage its utilization. In fact, some biologicals, including vaccines and certain therapeutic antibodies, need to be injected directly into the bloodstream to avoid protein structure decomposition during the digestion process. Furthermore, oral administration comes along with the systemic distribution. However, single organ or tissue localization through novel targeted therapies currently constitutes a safer approach, diminishing cytotoxicity and improving efficiency.

Figure 1 depicts the percentage of approved pharmaceutical agents according to their route of administration. Notable, oral and injectable routes still represent the 75% of the total drug delivery approaches. Figure 2, on the other hand, depicts the distribution of investigational pharmaceutical agents in reference to both route of administration and stage of development. Figure 3 broadly enlightens the technology value chain.

This article will discuss a few recent innovative approaches to controlled release technologies with a focus on some of the therapeutic areas most relevant to the current pharmaceuticals market.

KEY FINDINGS

The injectable route follows oral therapeutics in percentage of approved agents. On the other hand, subcutaneous administration is generally preferred due to its easy handling by the patient at home, especially when utilizing delivery devices, such as auto-injectors or pen-injectors. The optimization of this delivery route basically depends on the drug formulation and the device. Thus, while formulation enhancements help to reduce the frequency of administration and the required volumes, in addition to the reduction of cytotoxicity and side effects associated with the formulation, a proper design of the delivery device, including for instance a smaller needle or an auto-injector, could significantly improve handling and efficiency when the administration is performed by the patient. On that note, a myriad of companies are devoted to developing

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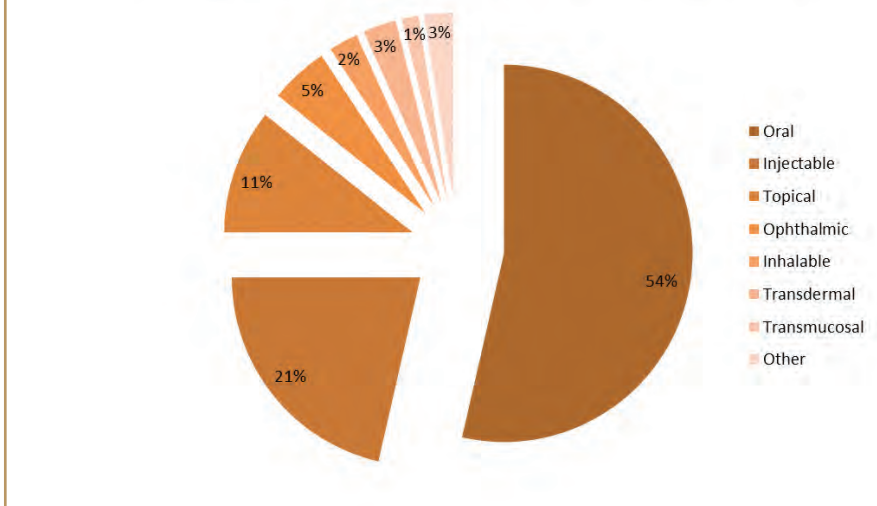
Regarding formulation, two principal release mechanisms are in the spotlight: polymer drug conjugates (PDC) and nano-enabled delivery systems (NEDS), as well as suitable combinations of both approaches. Indeed, the past decade has experienced significant research advancements around the potential opportunities of nanotechnology and nanofabrication for drug delivery, thus evolving into an even more interdisciplinary field. As it is well-known, nano-scale presents properties that could importantly differ from millimeter-scale. Indeed, size reduction implicitly involves the increasing of surface area, dissolution rate, permeability, and then intracellular uptake. Under this scope, a wide range of therapeutic opportunities have emerged as promising approaches only addressing drug formulation. Nanotech applications have demonstrated suitability when used for the optimization of the drug delivery systems and the increment of efficiency and dosage frequency diminution.

According to most scientists, beyond patient's comfort, NEDS play an important role in the drug development value chain by offering attractive solutions for addressing key challenges in managing life cycles and productivity. Importantly, a first generation of NEDS is already in the market, having overcome all trials and regulatory steps. Furthermore, NEDS can help to improve practically all the administration routes.

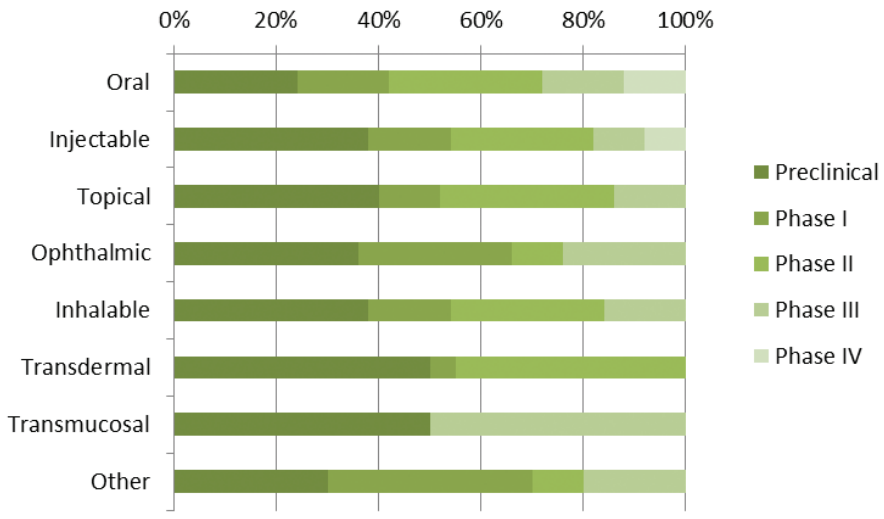
PDCs constitute other important formulation enhancers. One of the most popular methods is PEGylation, which involves attaching polyethylene glycol (PEG) to the drug. PEGylation has demonstrated effectiveness in extending the half-life of drugs, especially peptides and antibodies, thus contributing to the reduction of the frequency of administration from daily to weekly, even

FIGURE 1



Percentage of approved pharmaceutical agents by route of administration. Oral and injectable routes still represent 75% of the total drug delivery approaches. Source: Frost & Sullivan.

FIGURE 2



Percentage of investigational pharmaceutical agents by route of administration and stage of development. Source: Frost & Sullivan.

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TABLE 1

Technology	Description	Types	Advantages	Disadvantages
Liposomes	Tiny vesicles consisting of a hydrophilic core entrapped in a bi-layered hydrophobic lipid layer. Widely used for insoluble drugs and advances in conjugation technologies, liposomes constitute valuable targeted delivery systems due to their biocompatibility and possible diversity with structures and compositions.	-Conventional liposomes -Stealth liposomes -Targeted liposomes -Polymer composite liposomes -Stimuli responsive liposomes	-Passive/active targeting -Easy and rapid internalization -Low immunogenicity -Improved solubility & bioavailability -Drug protection & biocompatibility	-Rapid degradation due to uptake by the reticulo-endothelial system (RES) -Poor scale up/need for extensive modifications -Short shelf life
Polymers	Widely used for sustained release of drugs, and conjugated with functional targeting groups and other moieties.	-Stimuli responsive polymers -Multifunctional -Polymers/Co-polymers -Artificial cells -Polymer composites	-Cell mimicking -Wide range of drugs -Easy functionalization -Surface modification -Controlled release kinetics -Low cost & scalable properties	-Hypersensitivity (certain polymers) -Biocompatibility issues (synthetic)
Nanoparticles	Multifunctional, inorganic nanoparticles are being developed for targeted drug delivery and imaging applications. Hybrid drug carriers combining stimuli sensitive hydrogels and inorganic nanoparticles, and conjugation of biomolecules to nanoparticles are areas of interest.	-Silica/Alumina -Nanoparticles -Quantum dots -Gold Based (AuNPs) -Carbon based particles -Metals/Oxides/Sulfides	-Optical properties -High stability over wide temperature & pH range -Highly tunable -Evade reticuloendothelial (RES) clearance	-Toxicity issues (long-term) -Non-biodegradable (accumulation)
Cells	Direct drug encapsulation or nanoparticle conjugation for better pharmacokinetic properties, biocompatibility and higher drug loading capacity.	-Dendritic cells/Tumor cells -Microbial ghosts & Viral particles -Engineered red blood cells (RBCs) -Genetically engineered stem cells	-High drug loading capacity -Adjuvant properties -Sustained release -Biocompatible (except microbial ghosts) -Scalable and cost effective	-Potential Immunogenicity (viral, bacterial particles) for non-vaccine delivery -Storage & formulation issues -Maintaining integrity (RBCs, stem cells, macrophages)
Magnetic Particles	Micro-and nano-scale particles loaded or conjugated with drugs that are activated when exposed to an active magnetic field and release drug cargo at the target site.	-Biological -Non-biological (organic vs. inorganic)	-Evade RES clearance -Image guided delivery with MRI -Controlled drug release -Highly targeted	-Gradient loss for deep seated tissues -Accumulation of magnetic material at target site -Requirement for specialized manufacturing & QC system
Nucleic Acids/Peptides	Use of peptide and aptamer-based targeting for delivering siRNA and other nucleic acid drugs.	-Cell penetrating peptides -Peptide conjugates -DNA/RNA aptamers -DNA Origami (DNA Nanorobots)	-Highly targeted -Biocompatible -Biodegradable	-Mode of administration -Aptamer instability

Technology capability according to different carriers used for controlled release of therapeutics. Source: Frost & Sullivan.

monthly in certain cases.

As a main drawback, long-term exposure to PEG can result in immunogenicity reactions. In response to this issue, novel developments have been addressed through the use of naturally occurring biological molecules.

Oncology and neurology are undoubtedly the two most widely researched diseases for targeted drug delivery facing the blood brain barrier. Other targeted drug delivery carriers beyond polymer-based and nanoparticles are mainly constituted by liposomes, magnetic particles, nucleic-acids/peptides, or even whole cells.

Important advancements have been carried out through the investigation of liposomes as carriers. Liposomes are used for targeting highly permeable tumors; however, their use in less permeable tissues is limited. The conjugation of this technology with new approaches has evidenced some success. To this group belong nanoliposomes, stimuli responsive liposomes, and conjugated liposomes with other functional attributes, gaining important attention from researchers throughout the past 5 years.

Similarly, targeting peptides and nucleic acids capable of delivering high payloads of drugs into specific regions represents an intense area of research. Interestingly, the conjugation to a brain drug-targeting vector leads to the creation of a chimeric peptide, which could in this way penetrate the blood brain barrier.

Inhaled components have also gained

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special attention throughout the past decade. Vaccine development represents one of the typical examples of a highly active pharmaceuticals market segment. Vaccine developments for inhalation or transmucosal administration constitute a paradigm shift in clinical medicine. According to most researchers, this route not only constitutes a more pleasant administration for patients, but also possesses superior capabilities in eliciting an immune response by utilizing the same route that the pathogen has followed, principally in infections such as influenza. Similarly, controlled release of drugs in the lumen of the colon, for instance, could also be enhanced by this mean, providing topical treatment at the site of inflammation where it is needed, with reduced systemic absorption.

The next paragraphs are focused on controlled release technologies and applications, pivoting around targeted drug delivery systems.

TABLE 2

Organization/ Company	Description	Technology
Aptagen, LLC (PA, USA)	Functionalized proprietary aptamers, Aptabodies™, are used for drug delivery and diagnostics. The company is a good collaborative partner for pharma/biotech companies for delivery of peptide therapeutics.	Aptamers/Peptides/Nucleic Acids
ArmaGen Technologies, Inc. (CA, USA)	CNS targeted biological delivery. The company is developing engineered brain penetrating TNF decoy receptor therapies for acute stroke. The TNF-alpha decoy receptor is engineered as a fusion protein with a BBB molecular Trojan horse (MTH). The MTH is an engineered monoclonal antibody (MAb) against the BBB specific transferrin receptor (TfR). This MTH allows receptor mediated transport of the drug across the BBB. Using a receptor mediated transport to the brain ensures an effective and safe method of delivery of drugs to the brain.	Molecular Trojan Horse (MTH)
Arrowhead Research Corporation (CA, USA)	In house development and acquisition of targeted delivery platforms. DPCs (Dynamic polyconjugates) and RONDEL are based on polymer nanoparticles, both explored for delivery of siRNA therapeutics.	Polymer Conjugates Polymer Nanoparticles
Artificial Cell Technologies, Inc. (CT, USA)	Layer by layer assembly of polypeptide artificial biofilm nanoparticles for developing synthetic vaccines. Synthetic nanoparticles incorporating immunogenic epitopes. Artificial virus-like structures for vaccine delivery.	Virus-Like Nanoparticles
Celsion Corporation (NJ, USA)	Proprietary heat sensitive liposomal formulation of doxorubicin, ThermoDox, is already under the clinical trials stage for liver cancer and oncology indications.	Liposomes
CytImmune Sciences, Inc. (MD, USA)	PEGylated colloidal gold nanoparticles used directly as drugs via tumor targeting molecules or can be used as carriers for cancer drugs.	Gold Nanoparticles
EnGene IC (Australia)	EDV (Engene Delivery Vehicle) technology consisting of inert bacterial cell derived nanoscale minicells, conjugated with bispecific antibodies for highly targeted intracellular delivery of cancer drugs/siRNA. Currently under clinical trials stage.	Cell-based Nanocarriers
EryDel S.p.A. (Italy) ERYTECH Pharma (France)	Erythrocyte loaded drugs controlled delivery for multiple disease areas currently in clinical development.	Cell-based Carriers
Intezyne (FL, USA)	IVECT Copolymer Micelles (IVECT Method). Cost-effective, modular and highly targeted delivery platform, highly tunable for delivery of a number of drugs for varied indications. The lead candidate, IT-141, has demonstrated significant activity against a diverse number of cancer cell lines. Another formulation IT-143, is the encapsulated daunorubicin, is being assessed for the treatment of lung cancer, osteosarcoma, and ovarian cancer.	Co-polymer Micelles
Leonardo Biosystems (TX, USA)	Multistage mesoporous silica nanoparticle based platform for spatio-temporally controlled drug release. Investors and pharma companies have demonstrated increasing interest.	Inorganic Nanoparticles
LiPlasome Pharma ApS (Denmark)	Tumor targeting drug loaded lipid nanocarriers, designed to be susceptible to degradation by phospholipase A2 (PLA2), typically present in cancer microenvironment. Once degraded, the prodrug lipids are converted to active anticancer lysolipids and/or fatty acid drug derivatives, exhibiting enhanced permeability across cancer cell membranes.	Liposomes
MagForce AG (Germany)	Iron oxide nanoparticles coated with aminosilane for safe delivery of drugs to tumors upon activation by their proprietary NanoActivator™ magnetic field.	Magnetic Nanoparticles
NanoBioMagnetics, Inc. (OK,USA)	Magnetic vectored drug delivery using magnetically responsive therapeutic constructs.	Magnetic Nanoparticles
nanoTherics (UK)	Magnetic transfection method (Magnetofection™) using DNA and siRNA coupled with magnetic nanoparticles to form a complex. Upon exposure to oscillating magnetic arrays, cells show uptake of the complex via rapid endocytosis.	Magnetic Nanoparticles
Pevion Biotech AG (Germany)	Proprietary virosome-based platform for targeted drug delivery and adjuvant activity for subunit vaccines. A number of vaccines are in advanced phases of clinical trials using their VLP technology, and has also been outlicensed to several pharma players.	Virus-Like Particles
PolyTherics (UK)	Flexible polymer platform, GlycoPol™, for targeted, sustained delivery of biopharmaceuticals. Targeting glycopolymer developed by attachment of saccharides a poly (methacrylate) backbone.	Polymer Conjugates
Savara Inc. (TX, USA)	Nanonucleic technology for RNAi therapy. Condensed nanoparticles of cell penetrating peptides and RNA therapeutics for targeted intracellular delivery.	Aptamers/Peptides/Nucleic Acids
Silence Therapeutics (UK)	Silence's siRNA lipid-bi-layer delivery platform. The siRNA is combined with Silence's developed lipid moieties containing cationic lipids, co-lipids and PEGylated lipids to form nanoscale structures.	Lipid Bilayer Particles
Vascular Magnetics, Inc. (PA, USA)	Biodegradable, magnetic drug-loaded particles in combination with a magnetic targeting catheter and magnetic fields. Particles are guided to narrowed arteries in PAD (Peripheral Artery Disease).	Magnetic Particles

Case studies highlighting the impact of controlled release therapeutics in the pharma and biotech industry. Source: Frost & Sullivan.

FIGURE 3

Technology value chain for controlled release therapeutics. Source: Frost & Sullivan.

TECHNOLOGY DRIVERS

Among the most remarkable factors driving the technology, the need for novel, cost and time-effective solutions for the delivery of new biologics and the advent of nanotechnology and controlling, as well as, the advancements in intellectual property regimes, regulatory affairs and market entrance, can be cited.

The discovery of new biologics is rapidly progressing, especially in some areas related to cancer and central nervous system (CNS) disorders. Furthermore, the paradigm shift toward personalized medicine is changing the technology adoption scenario, promoting the appearance of new targeted and controlled release drug delivery platforms in pharmaceutical companies. The strict requirements of non-toxicity, non-immunogenicity, bio-distribution, and bio-degradability undoubtedly lead to a reduction in late stage drug failures.

This approach, which concentrates the medication in the tissue of interest while reducing the concentration in the healthy tissues, significantly increases efficacy and reduces side effects and dosage compared to the traditional therapeutics. This fact comes along with an improvement in the patient compliance and comfort.

On the other hand, the advent of nanotechnology as a disruptive technology importantly impacts the current generation of cancer therapeutics and diagnostics, thereby significantly improving the treatment of cancer and brain disorders. Currently utilized to design liposomes, nanoshells, quantum dots, and dendrimers for theranostic applications, nanotechnology plays a key role in future medicine. Nanotech advances are shaping the market through the wide range of FDA-approved nanotechnology therapeutics currently entering the market. Moreover, an important number of therapeutics, now under the clinical phase, are expected to penetrate the market in the next 2 to 3 years, driving the controlled release therapeutics market for the next 4 to 5 years. Along the same line, the impressive advances in programmed spatial/temporal setting for therapeutics delivery, as well as the new design tools and instruments to create synergistic systems, constitute an important factor for market growth.

Regarding intellectual property, patenting opportunities for targeted and controlled therapeutics is increasing as companies are now capable of applying for a patent of an already existing drug with different formulations with better efficacy and low toxicity. Similarly, regulatory approval from agencies is less extensive for a targeted drug delivery approach because of the presence of varied formulations of already approved drugs in the market. The next paragraphs exhibit some successful results and technology milestones.

TECHNOLOGY MILESTONES

Therapeutics efficiency has remarkably improved through the introduction of targeted drug delivery systems (TDDS), which attempt to increase the concentration of a drug in a specific organ or tissue. TDDS demonstrate not only enhanced therapy response by maximizing precision and modulating release, but also diminished side effects and minimized cytotoxicity.

The principal physiological barriers found by drug delivery systems are: a) blood brain barrier; b) mucous barrier; c) subcellular targeting; d) ineffective ligand targeting; e) physicochemical barriers; and f) size exclusion.

Tables 1 and 2 show the technology capabilities according to different carriers used for controlled release of therapeutics, and a number of case studies demonstrating their impact in the pharmaceutical and biotechnology industries, respectively.

FINAL REMARKS

Beyond this optimistic landscape, some challenges remain to be faced in order to guarantee the complete success of the introduction of these technologies. Regarding competition, medical devices based on targeted drug delivery currently constitute the major competitor for the non-medical device-based drug delivery market. As a principal advantage, controlled release therapeutic developments are non-invasive. Costs could represent a challenge in several systems, including antibody-based delivery carriers as well as some recombinant and fusion protein techniques. In addition, it is remarkable that the funding scenario for this technology is still lagging in comparison with drug discovery.

On the other hand, the nanotech industry has been subjected to certain criticism from health awareness groups and environmentalists regarding the long-stage effect of nanoparticles. The US Environmental Protection Agency and the International Life Sciences Research Institute are currently conducting research to develop new toxicity screening and hazard identification, avoiding speculation and obtaining reliable results.

In a more technical plane, most researchers are focused on developing combinatorial approaches, especially controlled release systems that also serve as diagnostic/prognostic tools. This amazing perspective places this technology at a step forward in achieving more personalized and efficient medicine in the coming years. Indeed, controlled release technologies, including all those synergistic approaches from the convergence of a broad spectrum of cutting-edge technologies, are expected to play one of the major roles in the future medicine landscape. ◆

BIOGRAPHY

Cecilia Van Cauwenberghe is a Senior Research Analyst with Frost & Sullivan's Technical Insights practice. She has more than a decade of professional expertise in chemical and biomedical engineering arenas, including life sciences, biotechnology, healthcare, and biomedical devices, as well as biomedical and clinical engineering. Her particular expertise in leading and executing projects relate to biopharmaceutical and biochemical modeling, simulation, and optimization; microelectronic implantable devices design; and studies in metabolic syndrome and cardiovascular diseases applications. Her expertise and professional development has grown through work with academic and healthcare institutions as well as leading firms, including the Dr. Rene G. Favaloro Foundation University, South National University, Comahue National University, YPF SA, Techint Group, and the National Institute of Industrial Technology. She has performed Doctoral Studies in Chemical Engineering, Master of Science in Biochemical Sciences, as well as a Bachelor of Science in Chemical Engineering and Mathematics.

The Second Quadrant

Out of the Shadows: Excipients Take the Spotlight; Part 1 of 2

By: Marshall Crew, PhD, President & CEO, Agere Pharmaceuticals, Inc.

A multiple-part series discussing today's most challenging issues in solubility.

Both solid dose and liquid excipients are commonly used to improve the oral bioavailability of active pharmaceutical ingredients (APIs). In addition to enhancing the solubility of drug products, they can impact the consistency and control of drug bioavailability and serve other functions, including improved physiochemical stability and manufacturability. In May of 2012, BCC Research estimated that the global pharmaceutical excipients market was $4.9 billion in 2011 and will reach $6.7 billion by 2016. While excipients comprise less than 1% of the global pharmaceutical market, from the perspective of percentage of volume of a drug product they often dominate. So whereas excipients aren't typically seen as "the main event," they play an increasingly important role in getting API stars on stage. This latest installment in The Second Quadrant series was so informative it had to be partitioned into two parts, with this month's focusing on the supporting actors on which most solubilization technologies – including melt extrusion, oral solutions, parenteral solutions, soft gel capsules, and spray drying – are critically dependent.

In an editorial in the April issue of World Pharma, Keith Horspool of

"Excipients are often considered inert ingredients, yet can play an active role… in the stability and bioavailability of the solid dose formulation."
(Jeffrey L. Shumway, Associate Director Sales Development, Bioavailability Enhancement Process Solutions, EMD Millipore - Jeffrey.shumway@emdmillipore.com)

Boehringer-Ingelheim, points out that a big issue impacting the pharmaceutical industry as a whole is that there just aren't enough excipients. The reason? It's becoming too costly due to the economic environment and the risk factors associated with the requisite FDA approval process. To overcome some aspects of the economic hurdles faced, the Vitic Excipient Database effort (https://www.lhasalimited.org/vitic_nexus/excipients/) has emerged in which leading pharmaceutical companies collaborate to share – anonymously – experimental data on different excipient formulations. The focus of this collaboration is around toxicity, but it could serve as a model for centralizing and sharing data with the goal of delivering cost advantages for solubilization. Perhaps this discussion will stimulate creative thinking around other and novel ways we can all cooperate to leverage insights and experiences related to excipients and insolubility.

To begin, we set out to learn from leading excipient manufacturing companies about their perspectives on the role excipients play in formulating and manufacturing drugs for improved bioavailability, what has and can be done differently, and how they see the industry and their specific part of the ecosystem evolving. We had such a positive response that we will focus part 1 on the role played and challenges faced by excipients and excipient provider companies in addressing solubilization. In July's column for part 2, our contributors will review major contributions over the last lustrum, and share insights into what we can expect to see as we approach the next decade. Contributing companies are Ashland Inc. Specialty Ingredients (Dr. Vivian Bi), BASF (Dr. Shaukat Ali), Croda Inc. (Serge Kechichian), EMD Millipore (Jeffrey Shumway), and Shin-Etsu Chemical Co. (Sakaé Obara).

"... it is difficult for excipient manufacturers to obtain detailed information about new APIs under development."
(Sakaé Obara, Technical Director, Shin-Etsu Chemical Co., Ltd. - obaras@shinetsu.jp)

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"…tools necessary to assess the molecular interactions [between APIs and excipients] to design a robust formulation, are lacking."
(Dr. Shaukat Ali, Technical Sales Manager, BASF Corporation - Shaukat.ali@basf.com)

CHALLENGES: THE TOP 3

Q: What do you see as the top 3 challenges faced today in formulation to achieve enhanced bioavailability directly correlated with excipients?

Dr. Shaukat Ali: Poor solubility of APIs is due, in part to, to brick dust, high melting, and hydrophobic structures. Therefore, the ultimate formulation challenges arise from (1) finding suitable excipients with the desired safety and toxicological profiles, (2) identifying appropriate technologies or solutions requiring means for downstream processing and development, and (3) the complexity due to excipient and API interactions on the stability of formulation.

Dr. Vivian Bi: When employing enabling technologies for bioavailability enhancement, typically, excipients will be used at relatively high dose levels; the lack of clinical precedence at the targeted dose level very often becomes a major hurdle in choosing excipients that contribute improved solubility. An additional challenge is the high cost and risk of developing new pharmaceutical excipients that limit the opportunities for drug solubilization innovations. Finally, there are still limited excipient choices for the safe and effective intravenous delivery of poorly soluble compounds.

Serge Kechichian: One of the top challenges faced today involves the increasing trend toward low solubility drugs with a significant percent of the APIs in the pipeline falling in BCS classes II and IV. The formulation challenge is finding the right excipient to address these low solubility classes. Another challenge is the need for new novel excipients and/or excipient combinations in the industry, especially new surfactant-based excipients for the use in oral dosage forms. Finally, when new excipients are introduced, there are hurdles within the industry exposing the use of the excipient in final formulation as pharmaceutical companies avoid being first to the market with a new excipient. The cost to prove the effectiveness of a new excipient through the amount of necessary clinicals is quite expensive, and can be a deterrent to the creation of novel excipients to the market place.

Sakaé Obara: Development of new excipients is becoming more challenging and expensive for excipient manufacturers due to regulatory issues, such as the high cost of toxicological studies. In addition, there are inherent hurdles faced when attempting to develop new technologies with better dissolution and simultaneously optimized for lower processing cost, increased stability, and an improved environmental profile. Finally, it is difficult for excipient manufacturers to obtain detailed information about new APIs under development.

Jeffrey Shumway: The top three challenges faced today in formulation to achieve enhanced bioavailability that directly correlate with excipients are Solubility, Permeability, and Targeted Delivery of APIs. Solubility and Permeability are becoming

"…there are hurdles within the industry… as pharmaceutical companies avoid being first to the market with a new excipient."
(Serge Kechichian, Key Account Manager, Health Care, Croda - serge.kechichian@croda.com)

increasingly more important topics as market overviews indicate that Pre-Clinical pipeline therapeutics are dominated by Class II and IV APIs as classified by BCS. Targeted Therapeutic methodologies are also of interest due to improved efficacies related to targeted, rather than systemic deliveries. In all three challenges, excipients can play a functional role in enhancement of solubility and permeability and can also act as targeting agents.

UNREALIZED OPPORTUNITIES

Q: Are there opportunities that go unrealized or unexplored due to lack of understanding or lack of information about what excipients can deliver?

Dr. Shaukat Ali: Excipients play an important role in the formulation dosages. But these excipients are only few and far between for application in solid dispersions. A clear understanding of chemistry between APIs and excipients, structure function relationship, and/or tools necessary to assess the molecular interactions to design a robust formulation, are lacking. Nonetheless, the formulators

"…it is important for formulators to work closely with their excipients supplier for advice and guidance."
(Dr. Vivian Bi, Technical Director, Solubilization & Contract Research Services, Ashland Specialty Ingredients - Vbi@ashland.com)

with intuition stemming from the trials and errors approaches are able to overcome some of these challenges by identifying the appropriate excipients in the formulation development. Therefore, a clear understanding of the excipients' attributes is necessary for a robust formulation.

Dr. Vivian Bi: There is no doubt that opportunities are overlooked, and in fact, such things happen probably more often than expected. For example, gamma-cyclodextrin is an effective solubilizer for many new APIs by forming inclusion complexes. With more high-molecular weight APIs emerging from the drug-discovery pipeline, gamma-cyclodextrin with a larger inner cavity could be a good solubilizer for many new APIs. Regardless of its proven safety, lack of familiarity with this excipient has resulted in its limited use in pharmaceutical applications. Therefore, it is important for formulators to work closely with their excipients supplier for advice and guidance.

Sakaé Obara: Our excipients for solubilization enhancement have been used for coating applications for many years. Throughout this period, we have encountered several quality issues that had never been considered when dealing with coating. So we continue to evolve and enhance our offerings based on new information.

Jeffrey Shumway: One of the more often unexplored opportunities related to the impact of excipients on solid-dose formulations are considerations related to stability from two distinct perspectives. The primary consideration related to stability is the preservation of the active API and the prevention of chemical degradation. An additional and equally applicable consideration is preservation of the amorphous state of difficultly soluble APIs. Excipients are often considered inert ingredients, yet can play an active role, not in terms of the performance of the formulated API, but in the stability and bioavailability of the solid dose formulation. This excipient "functionality" is currently supported by a limited knowledge base and is simply in the primary stages of being explored; improved characterization, regulatory considerations, and process control and analytics may play a critical role in understanding effects related to

stability. When considering the percent composition of many solid-dose formulations, excipient content is generally >50%, and in some cases, excipient content approaches 90% of the formulated dose, which can have measurable implications on stability and bioavailability.

OPPORTUNITIES FOR COLLABORATION

Q: Could excipient providers collaborate with each other or with other members of the pharmaceutical ecosystem to ensure the industry is better informed or more able to leverage the benefits solubilization excipients can offer?

Dr. Shaukat Ali: Mutual collaborations between the excipient manufacturers and drug manufacturers bear the hallmarks of many industries, namely BASF's collaborations with companies specializing in solid dispersions and offering solutions to customers struggling to identify the appropriate technologies for increasing solubility and enhancing bioavailability of poorly soluble drugs. Like BASF, other companies are also forming alliances with CROs/CMOs and/or drug manufacturers to bring new chemical entities (NCEs) in drug development, manufacturing, and commercialization.

Dr. Vivian Bi: Such collaborations are ongoing and not limited to solubilization excipients. Frequently, these collaborations aim at influencing regulatory authorities to eliminate hurdles that may be preventing pharmaceutical scientists from accessing effective novel excipients.

Serge Kechichian: I believe there are opportunities in the industry for collaboration, but the value seems highest with the collaborations between excipient manufacturers and pharmaceutical/biotech companies. These collaborations provide more transparency and clarity with regard to the need of the formulator, resulting in novel excipient solutions that can be utilized and commercialized on a quicker time scale.

Sakaé Obara: Increased collaboration would be ideal; however, due to confidentiality of techniques and formulations, collaboration on the whole has not yet been well developed.

Jeffrey Shumway: As many solubilization-enhancing excipients are not new, and have gained regulatory acceptance by historic application, many collaborative opportunities exist to better define functionality from a material science perspective as to potential indication and application with pipeline therapeutics. In addition, increased regulatory pressures associated with Supply Chain transparency are encouraging all members of the pharmaceutical ecosystem to collaborate from a chain-of-custody perspective. Development of improved or novel excipients may also provide grounds for collaboration by providing a unified approach to characterize and gain approval of emerging technologies.

NEXT STEPS

To ensure The Second Quadrant serves as a forum for interactivity and collaboration, please send your reactions, thoughts, and suggestions so we can continue the dialogue. As always, I look forward to hearing from you, and together moving toward greater solubilization. ◆

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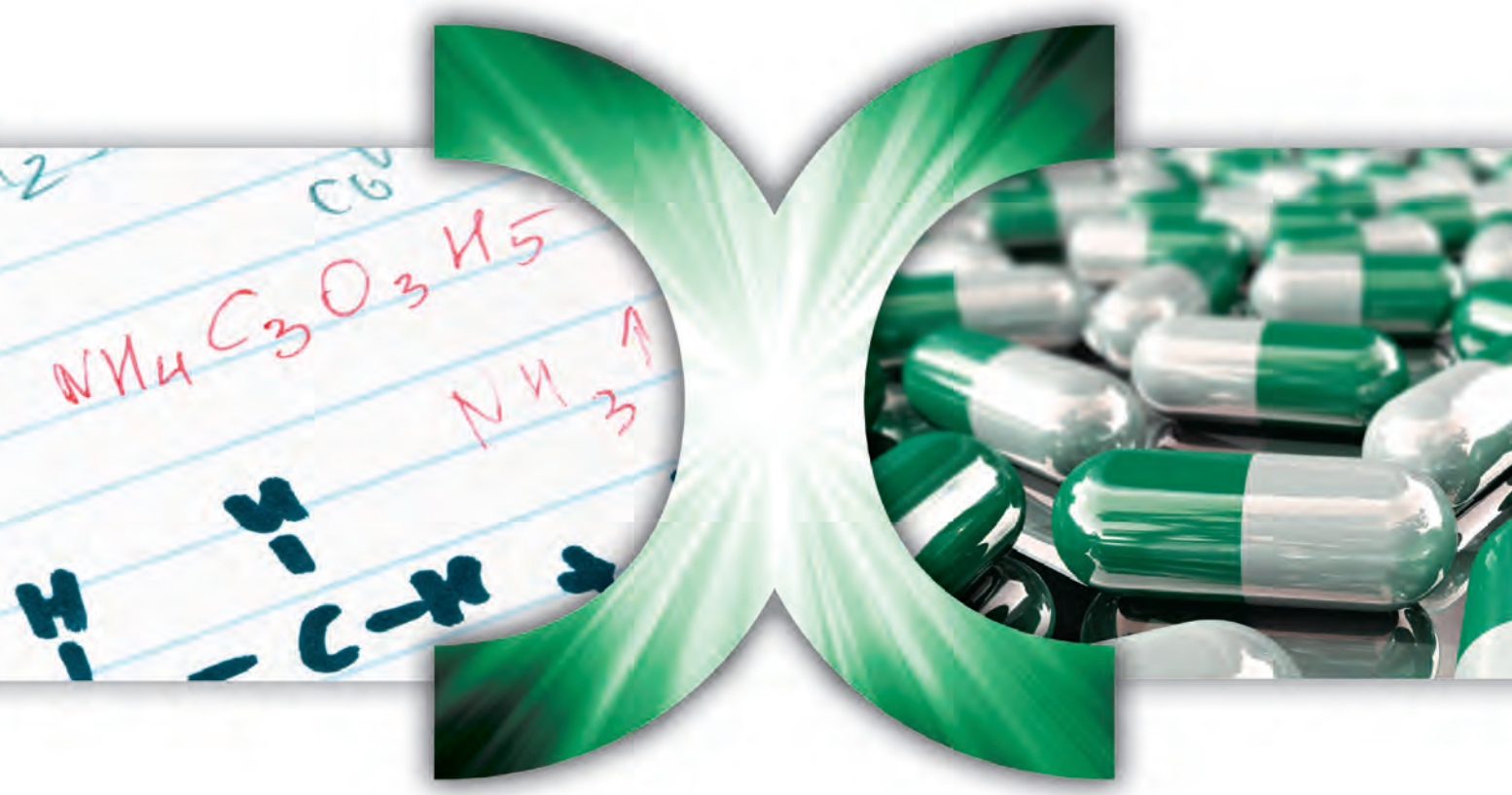
https://www.linkedin.com/profile/view?id=17815140



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Next generation HPMC capsules greatly expand pharmaceutical uses

by Dominique Cadé, PhD

A powerful alternative for pharmaceutical dosage forms

Polymer choices in pharmaceutical dosage forms have always been a balancing act between performance and development time, and historically has been shaped by the interactions of gelatin. The first generation of HPMC capsules, which relied on a secondary gelling agent, were recognized by formulators as having issues with dissolution performance and product stability. Fortunately, new scientific discoveries in polymers and capsule manufacturing have resulted in the creation of the next generation of HPMC capsules – one that offers better performance and reduced development time compared to gelatin and first-generation HPMC capsules.

Capsugel, the market leader in research and development in this area, is now offering these second-generation HPMC capsules under the trade name, Vcaps® Plus capsules.

In a number of studies, Vcaps Plus capsules have been shown to deliver optimized compound stability and predictable *in vitro* dissolution while also helping to eliminate the complexity in formulation development. Known globally for their reliable and predictable performance, Vcaps Plus capsules are well suited for over-the-counter (OTC) or off-patent products as well as for new chemical entities (NCEs).

True pH and ionic media independent performance

Traditionally, HPMC capsules were created using secondary gelling agents and ionic gel promoters, which have been found to interact with dissolution media and delay compound release from the capsule. The activity of the gelling agent kappa-carrageenan, for example, is enhanced by potassium and calcium cations contained in many foods. The extent of the resulting delay in dissolution time was shown in an *in vitro* test in which caffeine-filled traditional HPMC capsules were dissolved in a number of dissolution media. In the simulated normal acidic environment of the stomach (pH 1.2 USP), 90% of the caffeine was dissolved within approximately 15 minutes (Figure 1). Adding 2 g/L of potassium chloride (KCl) to this medium resulted in no dissolution after 15 minutes and a caffeine dissolution between 70% and 80% after more than one hour. Increasing the KCl content to 9 g/L delayed caffeine release even further, with a dissolution rate of just over 10% in 45 minutes. Results with simulated milk fluid were equally disappointing. Similar delays in dissolution times were observed and attributed to carrageenan in an independent study (Ku et al., 2011). Of course, such long delays in capsule dissolution are unacceptable particularly for rapid-relief products.

Capsugel addressed this situation by developing a proprietary new thermal gelation manufacturing process for Vcaps Plus capsules that eliminates the need for gelling systems all together and provides true pH and ionic media independence in disintegration. *In vitro* tests showed that these second-generation HPMC capsules had similar rates of dissolution at pH levels of 1.2 and 6.8 and with simulated milk fluid, achieving a nearly complete dissolution of the caffeine contents within approximately 30 minutes (Figure 2). Even adding 2 g/L or 9 g/L of KCl to the dissolution medium did not affect the performance of Vcaps Plus capsules, with dissolution of over 90% within 30 minutes, even under the most disadvantageous condition.

These findings were supported by an independent study that compared the dissolution performance of traditional and second-generation HPMC capsules (Ku et al., 2011), and underscores the superior performance of Vcaps Plus capsules.

Ideally suited for moisture sensitive compounds

While gelatin capsules have been effectively used for over a hundred years, due to their excellent flexibility and highly desirable dissolution properties, they are not typically the polymer choice for moisture sensitive compounds. Vcaps Plus capsules on the other hand have a three-fold lower moisture content than gelatin capsules and are less hygroscopic. That equates to fewer broken capsules due to brittleness and less of a chance of drug degradation compared to gelatin capsules.

Figure 1

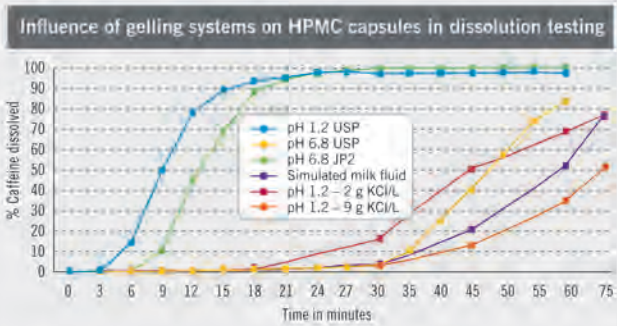
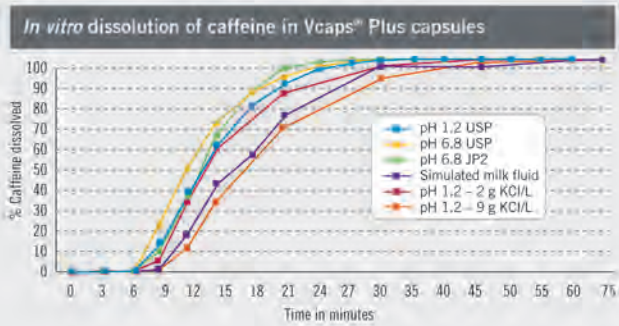


Figure 2



Improved stability at high and low temperatures

Capsugel in-house studies and an independent study conducted at Wyeth (Ku et al., 2010) have demonstrated the superior stability of Vcaps Plus capsules. An exposure of up to one week to temperatures ranging from 4°C to minus 18°C did not change the appearance or performance of unfilled Vcaps Plus capsules in closed high-density polyethylene (HDPE) bottles. The same stability was found with empty Vcaps Plus capsules in fully-filled glass bottles that were heated for 24 hours to temperatures ranging from 40°C to 60°C.

In long-term storage condition studies, including a 6-month storage at 40°C and 75% relative humidity and 2 years at either 25°C and 65% relative humidity or 30°C and 70% relative humidity, Vcaps Plus capsules disintegration and dissolution characteristics remained unchanged.

The wider temperature capabilities of Vcaps Plus capsules make them the perfect choice for longer term storage and when used in progressively unpredictable home environments.

Superior machinability

Traditional and second-generation HPMC capsule attributes have been compared on many common high-speed capsule filling machines (Ku et al., 2010). With respect to filling and rejection rates, Vcaps Plus capsules performed much like gelatin capsules and were superior to traditional HPMC products. In addition, Vcaps Plus capsules can be adapted for use with liquid compounds.

Wide regulatory and industry acceptance

Vcaps Plus capsules are manufactured in certified ISO 9001 facilities and in accordance with IPEC's (International Pharmaceutical Excipient Council) Good Manufacturing Practice (GMP) Guide for Bulk Pharmaceutical Excipients. They are acceptable for use in pharmaceutical and dietary supplement oral dosage applications in major markets of the US, Canada, EU, Japan, and Australia. In addition, Vcaps Plus capsules are certified Kosher Ko and Halal by IFANCA, and are approved for vegetarians by the Vegetarian Society.

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Vcaps® Plus

For more information about Vcaps® Plus capsules visit VcapsPlus.com.

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ORALLY DISINTEGRATING TABLETS

Novel Controlled Release Formulation for Orally Disintegrating Tablets Using Ion Exchange Resins

By: Abhijit Gokhale, PhD, and Praba Sundararajan

INTRODUCTION

Oral disintegrating tablets (ODTs) are designed to disintegrate rapidly in the mouth upon contact with saliva (≤ 30 seconds) and allow oral drug delivery without chewing or a need for water.[1] These formulations offer increased convenience and ease of use with the potential to improve patient-dosing compliance - especially in certain patient populations (eg, pediatric, geriatric, mentally disabled, and bed-ridden patients), for which swallowing conventional solid oral dosage forms may be difficult or impossible.[2] In addition to convenience and improved patient compliance, ODTs offer accurate dosing; enhanced bioavailability by greater pre-gastric drug absorption in the mouth, pharynx and esophagus, and often a better safety profile by reduced likelihood of choking or suffocation.[3]

The popularity of ODTs has surged in the past decade, and currently, more than 50 medicines in various cardiovascular, psychiatric, analgesics, and antihistamine indications are available as ODT formulations.[3,4] Further, marketing studies have shown that greater than 50% of patients prefer ODTs compared with other solid dosage forms, and roughly 70% purchase ODTs, even though liquid and tablet formulations of a drug are also commercially available.[5] This may, in part, be attributed to known ODT advantages that include portability, convenience, ease of swallowing, and a pleasant taste that often masks the bitterness of most orally bioavailable active pharmaceutical ingredients (APIs).

PROPERTIES OF ODTS

Not every medication is amenable for ODT formulation. Ideally, ODT formulations should not require water to swallow and will dissolve or disintegrate in the mouth. These formulations should allow high API (drug) loading, be compatible with taste-masking and other excipients, have a pleasing mouth feel, leave little or no residue in the mouth after administration, possess sufficient strength and physical properties to withstand pharmaceutical manufacturing and packaging processes, and exhibit low sensitivity to environmental factors such as temperature and humidity.

Drugs that are typically not amenable to ODT formulations include those that present taste-masking difficulties or that require controlled or sustained release.[3-6] However, as the demand for ODTs continues to grow, formulation scientists are exploring ways to adapt ODT formulations for drugs that require controlled or sustained release for optimal therapeutic benefits.

ION EXCHANGE RESINS IN ODT FORMULATIONS

Ion exchange resins (IERs) are water-insoluble cross-linked polymers containing a salt-forming group at repeating positions on the polymer chain.[7] Synthetic IERs are usually cast as porous beads with considerable external and internal pore surfaces for loading. The resins are typically

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DD Patent 74,413 DD Patents	**Keyword** Keywords	**UK: EMC** 5,171 Products
Discovery Technology 1,036 Discovery Technologies		**EU: EMA** 5,452 Products
Keyword Keywords		**New Zealand**
		Supply Chain (NZ Medsafe) 11,323 Products
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spherical in shape and 0.5 to 1.0 mm in diameter. The structure of these IERs is quite porous at a molecular scale to achieve the drug loading.

IERs are broadly classified into two main categories: cation exchange resins and anion exchange resins, which have the ability to exchange counter-ions within aqueous solutions surrounding them.[7] Cation exchange resins contain either strong acidic groups (eg, sulfonic acid groups) or weak acidic groups (eg, quaternary amino groups). Anion exchange resins contain either strong basic groups (eg, carboxylic groups) or weak basic groups (eg, amino groups).

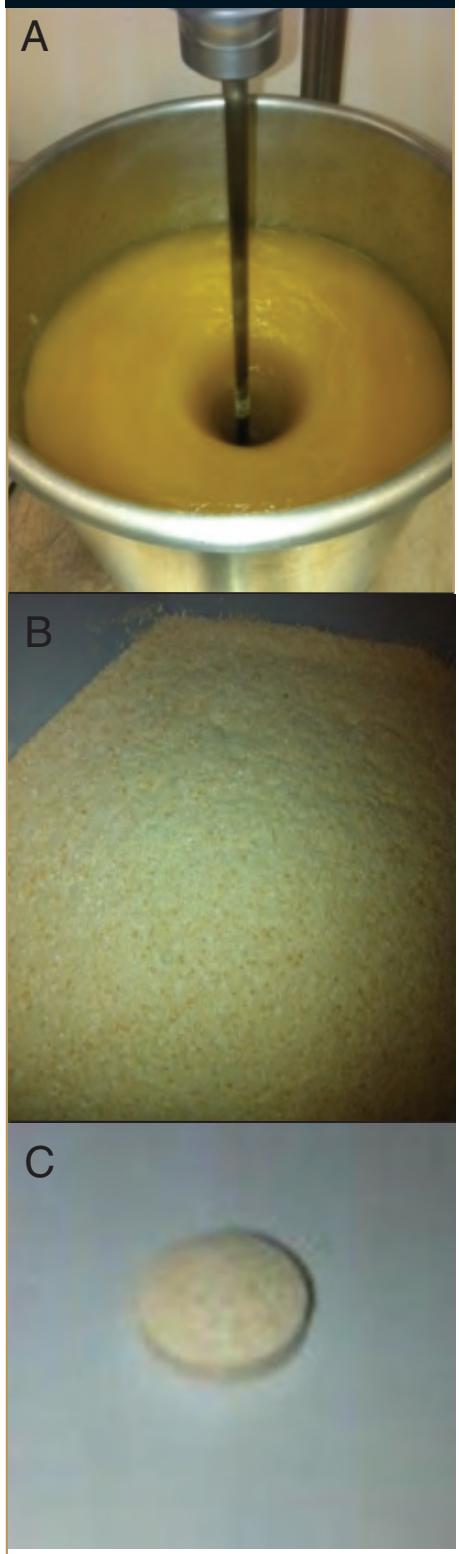
Selection of an appropriate IER is largely dependent upon the exchangeable ion properties of a specific drug. When choosing an IER for the sustained-release application, two main factors must be considered: cross-linking properties and drug loading capacity.[7,8] The typical range of cross-linking is 4% to 16%. For drug loading considerations, the resin acid/base strength and counter-ion selectivity are important.[7,8]

Drugs are loaded onto the resins via an exchange reaction, forming drug-resin complexes called resinates. Insoluble resinates are formed through weak ionic bonding with oppositely charged drugs so that release of a drug from a resinate does not occur at salivary pH (~ 6.7).[7-9] The resins are not absorbed by the body due to their high molecular weight and water insolubility and are therefore inert; making them ideal drug delivery vehicles. To that end, ion exchange resins are used for a variety of applications in the pharmaceutical industry, such as:[8,10]

- Taste-masking
- Disintegrant /Superdisintegrant
- Solubility improvement
- Drug stabilization
- Improved flow rates
- Modified-/Sustained-release profiles
- Therapeutics

Junyaprasert et al formulated sustained-released suspensions of diltiazem (a short half-life calcium channel blocker) using strong cation exchange resins.[11] Likewise, Steel et al studied a novel combination vector consisting of the adenovirus conjugated to liposomes bound to cation-exchanging microspheres as a sustained release gene therapy delivery vehicle.[12] Jeong et al investigated the complex formation between drugs and cation exchange resins and the effects of coating by various aqueous polymeric dispersions on the complexes to develop new sustained-release ODTs of the cough suppressant dextromethorphan.[13,14] All these aforementioned studies show the successful sustained release of drug molecules using IER technique.

FIGURE 1A,B&C



Visual pictures of the coating process to include Drug Loading (A), Coated Resinates (B), and the Final Tablet (C).

TABLE 1

Ingredients	Formulation A	Formulation B
Drug Loaded Resins		
Model Drug	10.3%	10.3%
Amberlite™ IRP69	41.1%	20.5%
Functional Coating		
Eudragit® RS	3.3%	2.0%
Eudragit® RL	1.4%	0.9%
Triethyl Citrate	0.5%	0.3%
Talc	2.4%	1.4%
Tablet Ingredients		
Mannitol	27.9%	43.9%
Ac-di-Sol®	4.1%	6.5%
Citric Acid	4.1%	6.5%
Sodium Bicarbonate	4.1%	6.5%
Mg Stearate	0.8%	1.2%
Total	**100.0%**	**100.0%**

Formulation Details

EXPERIMENTAL METHOD & MATERIALS

In the present study, a strong cation exchange resin, Amberlite™ IRP69, was used to form IER-drug resinates. Amberlite IRP69 was considered to be suitable for the model drug compound based on the drug properties. The model drug used in this study was a very bitter-tasting HCL salt, making it difficult to formulate in ODT formulations.

The Amberlite IRP69-drug resinates were created by mixing hydrated ion-exchange resin particles and different concentrations of the model drug substance. Mixtures were stirred for 6 hours to maximize drug loading onto the IER particles. The samples were taken at 1, 2, 4, and 6 hours to investigate the drug loading. The drug loaded resins were then dried in an oven and coated with a combination of methacrylate polymers to further control the release profile by reducing the initial burst. Figure 1 shows the manufacturing process.

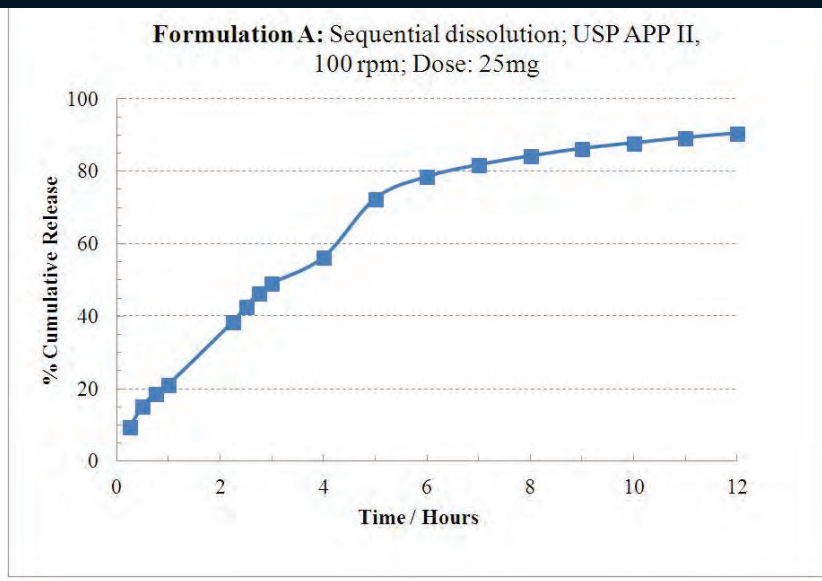
Formulations were developed by varying the material composition and optimizing the process parameters. Croscarmellose Sodium (Ac-di-Sol®) was used as a super-disintegrant to obtain tablet disintegration within 15 seconds. Mannitol, citric acid, and sodium bicarbonate helped to mask the taste of the bitter drug compound as well as to enhance the disintegration time along with Ac-di-Sol. Table 1 provides the details of the two formulations. The blend was then compressed using 11/32" round tooling into 250-mg tablets. Both formulations have a dose of 25 mg. The physical properties of both of the formulations are presented in Table 2.

RESULTS & DISCUSSION

Both formulations were tested in standard sequential dissolution (2 hours in pH 1.2 buffer followed by 10 hours in pH 6.8 buffer) to investigate the release characteristics. Figures 2 and 3 show the dissolution profiles of the formulations. Both formulations exhibit sustained drug-release characteristics. The comparison of the dissolution profiles is demonstrated in Figure 4.

Both formulations presented in the study had a tablet hardness of 15 KP and were identical in all aspects except the

FIGURE 2



Sustained-release properties of Formulation A.

ratio of Amberlite IRP69 to drug substance. The amount of Amberlite IRP69 in the formulations varied, and the tablet weight was maintained by adjusting mannitol quantity to obtain the dose similar formulations. The dissolution profiles of both of the formulations showed that the drug release is independent of the concentration and exhibits Fickian characteristics. Each of the formulations disintegrated in less than 15 seconds, demonstrating the ODT nature of the tablets.

The friability of both of the formulations was 0.02%. The flowability of the granules was acceptable for both of the formulations and no undesired bridging, rat holes, or sticking to the tooling were observed during compression.

TABLE 2

	Formulation A	Formulation B
Tablet Disintegration	<15 seconds	<15 seconds
Tablet Hardness	15 KP (± 1KP)	15 KP (± 1KP)
Tablet Shape	11/32" Round	11/32" Round
Tablet Friability	0.02%	0.02%

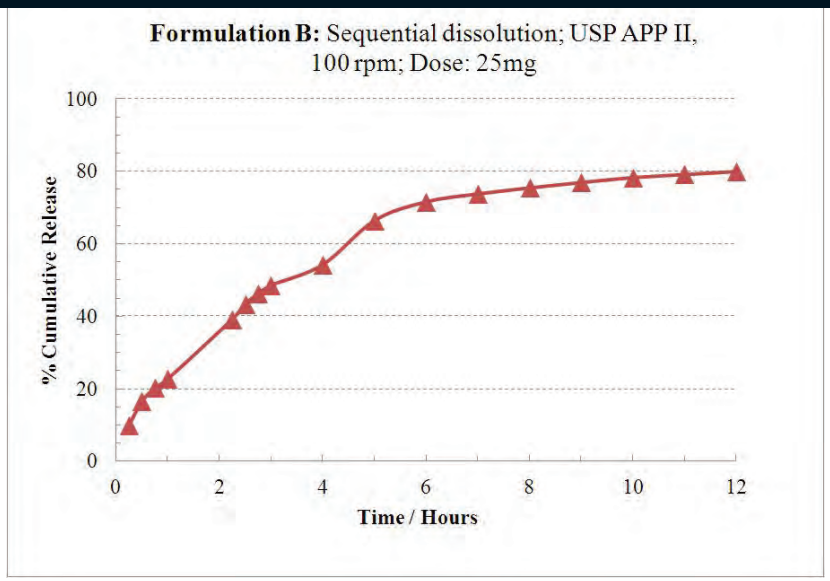
Physical Properties of Formulations

CONCLUDING REMARKS

The drug formulation technique described in this article is simple and easily scalable. Because of the availability of a wide range of anionic and cationic IERs, a vast array of pharmaceutical drugs can be formulated using this technique to achieve sustained release of drug molecules.[15] In addition, IERs can be used as taste-masking agents and super-disintegrants in ODT formulations.

Combining the taste-masking and sustained-release characteristics of IERs to formulate ODTs will help to improve drug dosing compliance among pediatric, geriatric, bedridden, and non-cooperative patients.[16,17] Moreover, the popularity of ODTs amongst members of the general population is likely to increase because of their portability, ease of use, and convenience.

FIGURE 3



Sustained-release properties of Formulation B.

ACKNOWLEDGEMENTS

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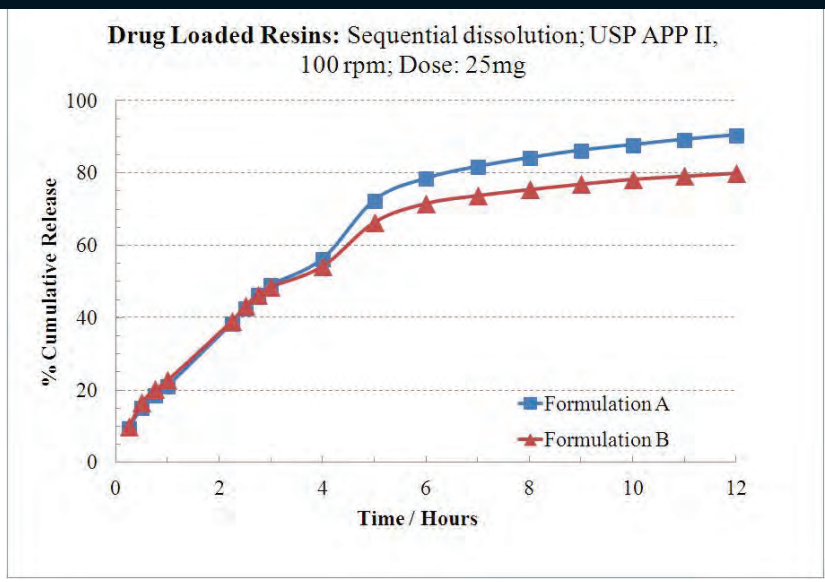
FIGURE 4



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BIOGRAPHIES

Dr. Abhijit Gokhale is a Senior Scientist (Formulations and Process Development) employed at Patheon Pharmaceuticals since May 2011. Dr. Gokhale has over 12 years of drug development experience in both academic and industrial environments. He has extensive experience in formulating pharmaceutical drugs for both controlled release as well as bioavailability improvement applications. Dr. Gokhale has authored several papers and patents in the field of nanoparticle-based drug delivery and several cutting-edge technologies used in formulations.

Praba Sundararajan is a Specialist (Formulations and Process Development) employed at Patheon Pharmaceuticals since April 2007. Mr. Sundararajan has over 12 years of drug development experience in pharmaceutical drug development. He has extensive experience in formulating pharmaceutical drugs for controlled release and technology transfer.

Freeze Fracture Electron Microscopic (*ff* EM) Examination & Analysis of Liposomes Produced by Covaris AFA Technology

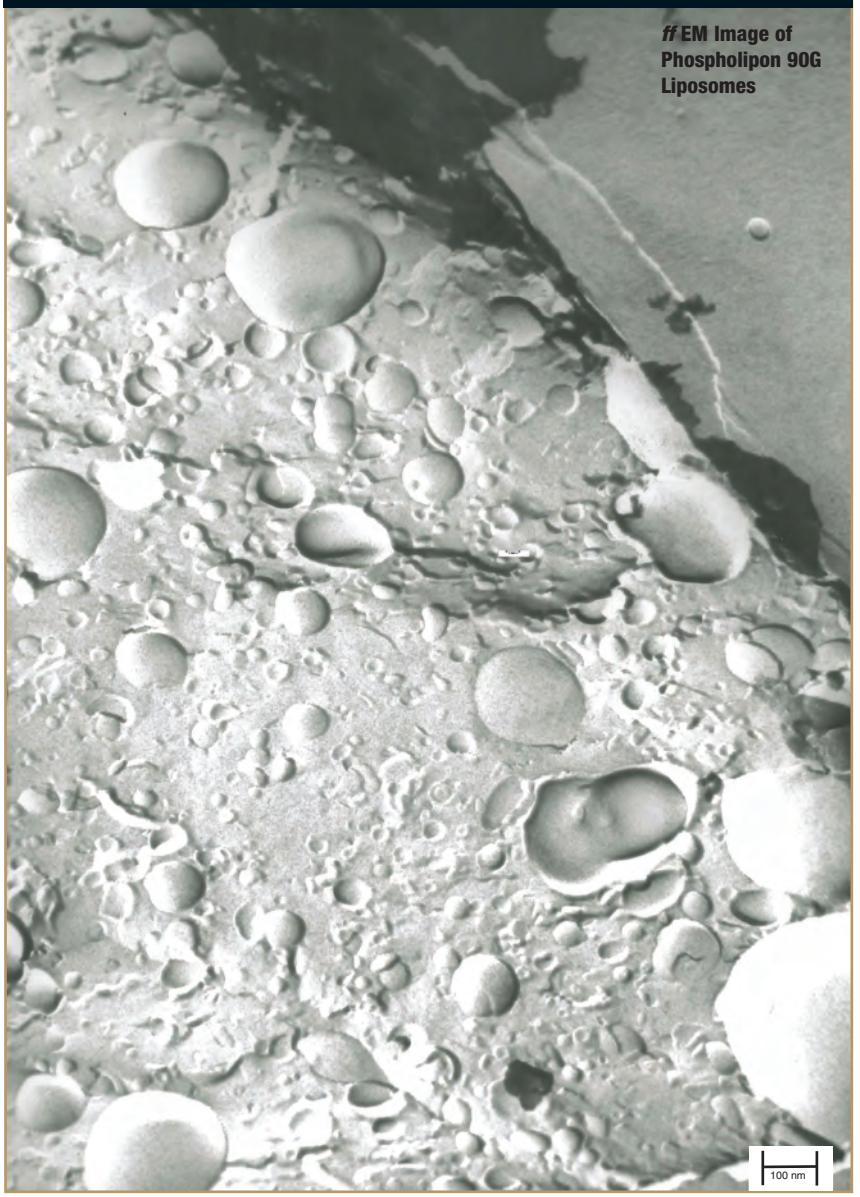
By: Srikanth Kakumanu, PhD, and Rajeev A. Jain, PhD

INTRODUCTION

Recently, there has been considerable renewed interest in technologies to form liposomes. Although there are few commercialized liposomal products, there are many in various stages of clinical development.[1,2] The reason for the renewed interest is that both poorly soluble APIs and difficult-to-deliver biological molecules like proteins, peptides, and genes can potentially be more readily formulated as liposomes to both increase biological uptake and improve effectiveness of treatment. This potential quicker formulation would accelerate more efficient and more cost-effective candidate screening.

The traditional liposome preparation methods, including detergent depletion, ethanol injection, reverse-phase evaporation, and emulsion methods, all have intrinsic limitations. Depending on the moieties to be packaged and the desired mechanism of action, liposomes can be prepared in three forms: Multi Lamellar Vesicles (MLV), Large Unilamellar Vesicles (LUV), and Small Unilamellar Vesicles (SUV). MLVs have a more complex structure than LUVs and SUVs.[1-3] Processing methods include high-pressure homogenization, extrusion, and traditional ultrasound. The major disadvantages of these preparation methods include the requirement for significant volumes of

FIGURE 1



volatile organic solvents and their subsequent solvent evaporation, multiple lengthy processing steps, contamination, and potential degradation of the samples due to heat exposure.[3-5] These limitations can be problematic for the delivery of some types of active materials, most notably solvent- or temperature-sensitive biological compounds.

Traditional ultrasound, which is unfocused and low frequency, has been in use for preparing liposomes for many years.[1] However, it has fundamental limitations as a process technology due to inefficient energy conversion and poor control to obtain a desired pressure flux, and the inherent long wavelength precludes effective process control. An alternative ultrasonic processing technology, based on Covaris' Adaptive Focused Acoustics™ (AFA), allows manufacturing of liposomes of predetermined sizes and offers an efficient, isothermal, and non-contact process.

Formation of liposomes using AFA has been described in previous articles.[3] AFA utilizes a concave transducer to converge emitted acoustic energy to a precise point inside a processing vessel without direct contact. This enables processing vessels to be loaded with liposome-forming materials and buffers and simultaneously exposed to an active acoustic focal point. This allows control of cavitation and streaming energy to form liposomes of particular sizes. Temperature of the sample is maintained by immersion in a water bath, which is connected to a chiller with a preset temperature. The AFA process employs focused bursts of ultrasonic acoustic energy at frequencies 20 to 40 times higher than traditional sonicators. The high frequency of AFA produces a wavelength of only a few millimeters, which enables the ultrasonic acoustic energy to be focused into a discrete zone within a sample vessel immersed in a water bath. AFA Focused-ultrasonicators are highly controllable and may be independently programmed for the power intensity, duration, and duty factor of these bursts. The versatility in power settings supports a wide variety of applications, from low-power gentle mixing and enzyme acceleration, to high-power DNA shearing, tissue disruption, and compound management, including dissolution, formulation, and emulsification.

AFA technology enables a simple and efficient liposome preparation workflow, and provides effective thermal control with no cross-contamination when compared to other available liposome preparation technologies.[3-8]

In this article, blank liposomes were produced using AFA technology, followed by characterization using Dynamic Light Scattering (DLS) and *ff* EM (freeze fracture Electron Microscopy) techniques. Although in previous articles, the particle size distribution of liposomes was analyzed using DLS, a more detailed confirmation of liposome structure is required.[3] *ff* EM techniques are widely used to assess the surface morphology of liposome formation and provide a more detailed evaluation of liposome construction using AFA.

Three different lipid (liposome) formulation samples were prepared and formed. To evaluate structure of liposomes formed below phase transition temperatures, the third liposome sample was prepared using DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine), which has a phase transition temperature above 55°C (Tc of DSPC is 55°C to 58°C).9 This liposome sample was formed upon chilling the phospholipid to 3°C and maintaining the sample temperatures below 20°C during preparation. Critical questions of the Covaris liposome process include:

1. Can AFA liposomes be prepared without organic solvents?
2. Is the particle size of the AFA liposomes as small as the liposomes prepared using traditional methods?
3. What is the structure of AFA liposomes formed at temperatures below the gel-to-liquid crystalline phase transition temperature (Tc) of the lipid?

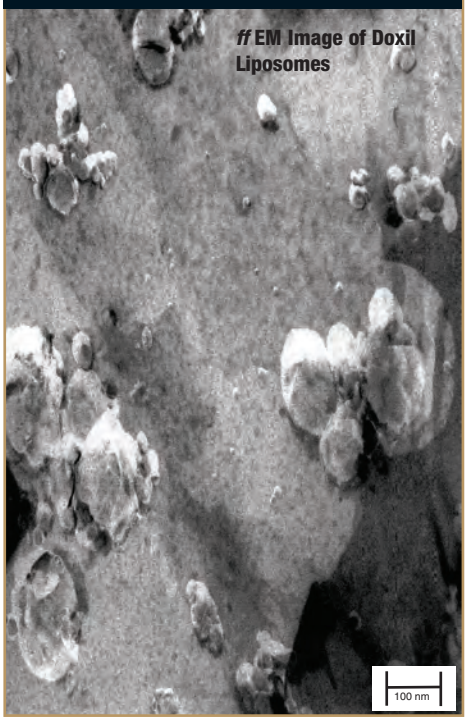
TABLE 1

No.	Sample	Particle Average Diameter (nm)	Comments
1	Phospholipon 90G	20…170…810 (1400-2300)	High concentration of liposome with large size range; smaller liposomes bud off from outer bilayers of larger ones; MLVs.
2	HSPC, PEG, DSPE & Cholesterol	15...90…200 (220...330…640)	Edgy liposomes below 200 nm in diameter, liposome associates with diameters up to 640 nm.
3	DSPC	9…30…50 (70…250…1170)	High concentration of small particles and smaller particle aggregates, some larger particles/aggregates.

Particle Analysis by *ff* EM

***Particle Average Diameter represents major size range of particles found, and values in parenthesis represents either the MLV (Sample 1) or agglomerates (Samples 2 & 3).**

FIGURE 2



MATERIALS

Phospholipon 90G (EP-80) by Lipoid (Newark, NJ); Doxil lipids, ie, HSPC [L-α-phosphatidylcholine, hydrogenated (Soy)], DSPE-PEG2000 [1,2-distearoyl-sn-glycero -3- phosphoethanolamine -N-[methoxy(polyethyleneglycol) -2000] (ammonium salt)], and DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine) from Avanti lipids (Alabaster, AL), cholesterol and 0.1M Phosphate-buffered Saline (PBS) from Sigma (St Louis, MO); Covaris focused-ultrasonicator Model S220x in closed 2-ml sample processing vessels (PN 520056) both from Covaris, Inc. of Woburn, MA.

PREPARATION OF AFA LIPOSOMES

The respective lipids were weighed and added to 2-ml glass vessels. Sample 1 was processed for 12 mins using the S220x acoustic settings of 75-Watt Peak Incident Power (PIP), 50% Duty Factor (DF), and 1000 Cycles per Burst (C/B). Samples 2 and 3 were processed for 1 hr using the S220x acoustical settings of 150-Watt PIP, 50% DF, and 1000 C/B. 20 mg/ml of phospholipon 90 G is used in Sample 1. In Sample 2, 11.4 mg HSPC was used with 4.5 mg of PEG DSPE and 4 mg of cholesterol. In Sample 3, 20 mg/ml of DSPC was used. Respective lipids were washed into process vessel and topped off with 0.1M PBS, followed by tightening the vessel cap and loading into the S220x for processing at 3°C chiller temperature.

PREPARATION PROCEDURE (NANOANALYTICAL LABORATORY STANDARD TEST METHOD STM - 001)

The *ff* EM was performed by Nano Analytical Laboratory (San Francisco, CA). The samples were quenched using the sandwich technique and liquid nitrogen-cooled propane. Using this technique, cryofixation at a cooling rate of 10,000°C/sec is reached, and ice crystal formation and artifacts possibly caused by the cryofixation process are minimized. The cryofixed samples were stored in liquid nitrogen for less than 2 hrs before processing. The fracturing process was carried out in JEOL JED-9000 freeze-etching equipment, and the exposed fracture planes were shadowed with Platinum for 30 secs in an angle of 25 to 35 degrees and with carbon for 35 secs (2kV/ 60 to 70 mA, 1x10-5 Torr). The replicas produced this way were cleaned with concentrated, fuming nitric acid for 24 hrs followed by repeating agitation with fresh chloroform at least 5 times. The replicas were examined using a JEOL 100 CX electron microscope. Multiple micrograph images were taken for each sample. Information on the evaluated samples is provided in Table 1, and images are shown in Figures 1 through 3.

RESULTS

Sample 1 - EP-80 Liposomes

DLS measurement analysis is presented in Table 2. Figure 1 shows the surface morphology by *ff* EM analysis, and Table 1 represents the sizing analysis by ff EM. The particle average diameter (Z-average) as measured by DLS is 360 nm, while *ff* EM analysis shows it to be around 170 nm. Budding of smaller liposomes from larger sizes is observed. A significant number of smaller particles are found. These EM pictures show MLV, LUV, and SUV and their transformation from one shape to another, which suggests that the sample may be only partially processed, and additional processing may result in more complete convergence on a specific size distribution.

Sample 2 - Doxil Liposomes

DLS measurement analysis is presented in Table 2. Figure 2 shows the surface morphology by *ff* EM analysis, and Table 1 represents the sizing analysis by EM. The Z-average as measured by DLS is 142 nm, while *ff* EM analysis shows it to be around 90 nm. Even here, bilayer particles were found. Particles had agglomerated due

to storage conditions (4°C) before performing the EM analysis.

Sample 3 - DSPC Liposome

DLS measurement analysis is presented in Table 2. Figure 3 shows the surface morphology by *ff* EM analysis, and Table 1 represents the sizing analysis by EM. The Z-average as measured by DLS is 198 nm, while *ff* EM analysis shows it to be around 30 nm.

DISCUSSION

Electron micrographs taken from several freeze-fracture preparations show all three samples contain overall spherical particles in high concentrations. Because most of these particles display their shadows mainly in front and behind their structures, they showed bilayer-coated structures such as liposomes.

The average diameter of these liposomes is largest at 170 nm in Sample 1 (EP-80), followed by the diameter in Sample 2 (Doxil Lipids) at 90 nm, and the smallest diameter in Sample 3 (DSPC) of 30 nm. The size range of the particles is very large in the EP-80 sample (from 20 nm to 2.3 micrometers) and smaller in the Doxil lipids sample (from 15 to 640 nm) as well as the DSPC sample (from 9 nm to 1.2 micrometers). Size ranges in Samples 2 and 3 may read higher due to agglomeration, which results in DLS representing a group of particles as a single entity (especially in Sample 2). The observed distribution of particles matches the polydispersity index (PdI) values obtained by DLS analysis. This value for EP-80, Doxil, and DSPC liposomes were 0.514, 0.390, and 0.276, respectively. Agglomeration in the 3 samples was observed. As reported in the literature, this agglomeration occurred primarily due to the 4°C sample storage condition.[8-10] In addition, agglomeration could have benefited from dilution before characterizing with *ff* EM.

In Samples 1 and 2, liposomes consist of several bilayers (MLVs). The particles in Sample 3 are mostly unilamellar (SUVs), although they are at the lower end of the particle size of SUVs. In Sample 3, some particles that are even smaller than the smallest liposomes are visible (9 to 14 nm), showing shadows mostly behind their structures, which may well represent phospholipid micelles. This finding is not surprising and most likely due to the low processing temperature used in preparing liposomes that include a phospholipid that has a high phase transition temperature (Tc = 54°C) in which the lipid bilayer is in the gel state.

In addition to these observations, every sample exhibited some special characteristics. Smaller liposomes seem to "bud-off" from the most outer bilayers of larger liposomes (Figure 1). AFA process with EP-80 at low power produced liposomes that have more than one bilayer (multiple layers). This would be useful in increasing the loading of entrapped API. Liposomes formed are circular in shape. This shows that first, larger particles are formed and then the smaller liposomes bud off from the large ones. Based on previous liposome processing using AFA, if this sample was processed for only 2 to 3 mins, larger particles would result. Likewise, if

FIGURE 3

***ff* EM Image of DSPC Liposomes (formed at 3°C chiller conditions)**

the sample was processed for more than 12 mins (ie, 24 mins or longer), smaller particles would be formed, and the number of bilayers and size of vesicles would most likely decrease.

Most of the liposomes appeared edgy, such as seen clearly in Samples 2 & 3. Even though the Doxil liposomes are agglomerated particles, the Z-average is around 90 nm, which is near the reported particle size of 87.5 nm for Doxil formulation.[7]

Small DSPC liposomes (around 30 nm) are produced by AFA. This confirms that liposomes can be formed below the phase transition temperature of DSPC (Tc = 54°C) because the chiller temperature was maintained at 3°C, and the sample temperature was measured to be between 16°C to 20°C. Most of the particles are single or represent small-numbered associates (Sample 3). There are few areas visible where these small particles are not totally separated from larger units (Figure

TABLE 2

No.	Sample	PdI	Z-avg (nm)	Volume (nm)	Comments
1	Phospholipon 90G	0.514	360.4	814 (51.8%) 518.7 (width) 160.4 (51.8%) 60.46 (width) 4673 (5.9%) 984.2 (width)	EM & DLS measurements matches.
2	HSPC, PEG, DSPE & Cholesterol	0.390	141.5	343 (8%) 108.6 (width) 68.42 (91.4%) 34.73 (width) 5264 (0.6%) 730.9 (width)	Particles around 90 nm which matches with the analysis done by DLS.
3	DSPC	0.276	197.8	108.9(68.9%) 44.77(width) 403.9(30%) 157.2(width) 5099(1.1%) 801.6(width)	Particles around 30 nm are observed with EM. Bigger particles than observed with DLS may be due to agglomeration observed.

Overview of DLS Measurements (Malvern ZS-90)

3). Sample 3 supports the concept of forming liposomes with the bulk fluid temperature below Tc.

CONCLUSION

AFA-based formation of liposomes is confirmed in all three samples. Indeed, even in the DSPC sample processed below the phase transition, liposomes were formed. Overall, there was a fairly good agreement in the sizing data (Z-average values) between DLS and EM for the EP-80 and Doxil liposomes. For the DSPC liposomes, a large discrepancy between the two methods was observed.

By simply changing the process conditions of AFA, both the size and distribution of the liposome population can be changed. Preparation methods are simple and convenient, and offer dramatic improvements over current methods. For example, the elimination of solvents and subsequent rehydration of the lipid offers considerable time savings over existing methods.

In conclusion, the AFA technology offers a viable new delivery system method for potentially formulating biologically active liposomes, especially for temperature- and solvent-sensitive molecules. ◆

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BIOGRAPHIES

Dr. Srikanth Kakumanu earned his PhD from the Department of Biomedical Engineering and Biotechnology at University of Massachusetts in 2010. Since June 2010, he has been working as a Research Scientist at Covaris, Inc., where he heads the research in the application of Adaptive Focused Acoustics in formulations (Dissolution, Micronization, Nanosuspensions, and Liposomes). His major focus of research is scaling the AFA process to pilot scale and continuous flow processing.

Dr. Rajeev A Jain joined Covaris, Inc. in 2013 as Manager of Business Development – Formulations. Dr. Jain has more than 15 years of broad experience in various drug delivery technologies, formulation/process development, technology transfer, scale-up, and product outsourcing. Previously, he has held scientific and technical positions at Lonza Biologics, Fleet Laboratories, Acusphere Inc., and Elan Drug Technologies. Dr. Jain has authored or co-authored a variety of abstracts and publications. Over 8 patents and patent applications have been issued or filed under his name. Dr. Jain earned his MS in Pharmacognosy and his PhD in Pharmaceutics from The University of Rhode Island.

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Technology & Services *Showcase*

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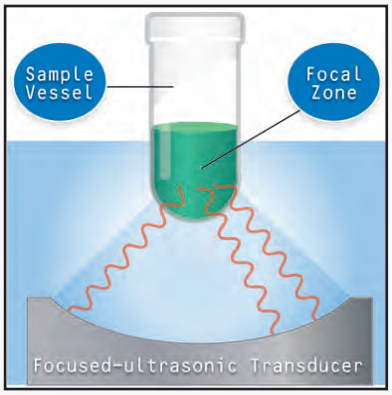

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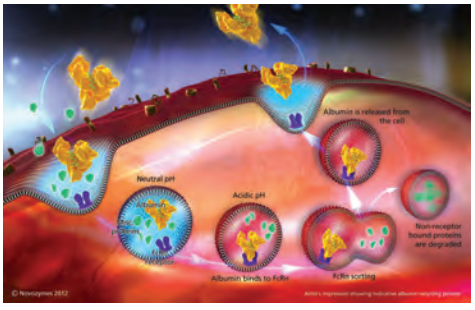
Tunable Half-Life Extension Technology



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Management Insight

Digital Soup

By: Derek Hennecke, CEO & President, Xcelience

Part 5 of a 6-part series offering an overview of this year's six best business books with insights into what they can teach the Pharma industry.

In 2010, I had a carotid dissection. It's a rare thing – the innermost wall of my left carotid artery came loose and for a 3-inch section it was flapping sporadically through the currents of my blood, occasionally blocking the flow completely. I went to the ER with stroke-like symptoms, and it took 3 days to diagnose me. The condition is so uncommon that 75% of the time it is diagnosed in autopsy.

As I recovered, I visited numerous highly qualified specialists. None had seen more than a couple of carotid dissections. They couldn't tell me what caused it. They couldn't tell me how long I could expect my recovery to take. They couldn't estimate what the chances of reoccurrence were.

Then, 2 years ago, I came across a forum just for people who had been diagnosed with this uncommon condition. In the space of 2 hours, I compared notes with hundreds of patients and learned that the condition almost always comes from intense exertion during exercise. I learned that recovery took most people between 6 months and 2 years. Mine was 6 months. I learned that once the artery healed, the chance of recurrence is essentially non-existent.

What I had stumbled on, of course, was a mini, self-generating clinical study specific to my condition that no pharma company would ever economically conduct. Of course, I realize there was no blinding, and the responders were self-selecting, but the information was still valid for my purposes. Think about this for a moment. What do you think it means for the future of medical care? For research?

The Digital Revolution is upon us. If this is a brave new world, then we are in the primordial soup. The quality and quantity of information that has become available at little or no cost to anyone anywhere just in the past 5 years – it's massive. It's unprecedented. Change is everywhere. Our nice tidy ways of innovating are being swept up into a massive digital soup. Opportunity is everywhere, for those who can grasp not just the new technologies, but more importantly, the new mindset.

This is the core message of James McQuivey's new book, *Digital Disruption*. In the past, innovation occurred through physical things, McQuivey explains, like an assembly line. An innovation was a commercial jetliner, a heart transplant, or a flat panel LCD screen. Because innovations involved physical things, the disruptions they caused were few and far between. A new innovation necessitated massive inflows of capital to build factories and to achieve the scale of production necessary to make them affordable. All this took time, and oodles of cash.

Not so in the digital soup. Innovation is cheap. Travis Kalanick turned the taxi business upside down overnight with a mobile app that brought drivers and passengers together more quickly than ever, saving time, trouble, and fuel. Mr. Kalanick told *The Wall Street Journal* that users of his Uber service take in $10,000 more than those who don't.

Similarly, Kevin Moller single handedly created fuel price competition at major airports around the world with an app called FuelerLinx. In the olden days (about 5 years ago) pilots just fueled up wherever they landed, regardless of cost. Prices for fuel were variable from place to place and hard to predict. Today, FeulerLinx collects data from airports around the world and suggests where the best prices are.

Mr. Moller founded the app by entering 1,800 locations into a huge Excel spreadsheet every Wednesday morning. Now, the data is generated automatically and accessed by pilots everywhere.

"Five years ago, the processors and Internet speeds and tools weren't

there. Now all of it has come together," Mr. Moller told *The Journal*.

These innovations are popping up everywhere, from the "Lose It" app that has upended the weight loss market, to high-frequency trading, which has made the stock market a very different place for small investors.

DIGITAL INNOVATION IN BIOTECH

Let's say a promising young scientist named Random Researcher has a great idea for a new mechanism of action. A few years ago, Random would've needed a large company to vet the idea, finessing it through the appropriate corner offices until a staff and a budget was assigned to develop it. Months to years would pass in the process. Not so in the Digital Soup. Now Random can line up a couple of investors, and for maybe $500,000, he can hire companies to develop a prototype. Once the prototype shows promise, investors should line up and Random's idea will be on the market faster and more cheaply than was ever possible before. With a process this easy and cheap, biotech innovation is poised to explode; anyone anywhere can access knowledge and share ideas to develop a concept.

How much innovation will this unleash? "I'll make it as simple as possible," McQuivey writes in Digital Disruption. "Imagine that with all the free tools and platforms available… we get 10 times as many people bringing innovative ideas to market – a highly conservative estimate. Then assume that the average cost to develop and test those ideas falls to one-tenth as much per idea as in the past (also conservative). The result would be 100 times the innovation power."

FERROKIN

FerroKin is a young start-up that develops molecules with just 11 researchers working from their homes and outsourcing lab work. Because of their small scale and infinitesimal overhead, they can focus on molecules with smaller paybacks that big pharma couldn't even consider because of their massive infrastructures.

Models like this have huge appeal to investors. Today's investors are getting more and more frustrated with the return on investment (ROI) offered by large pharma. Large pharma investors supply massive injections of cash for results that are becoming renowned for mediocrity. Some $135 billion is spent annually in R&D and all that money turns out only about 30 drugs a year. Then investors must sit idly by and watch as Pfizer crushes a 750,000-sq-ft facility in Groton, CT, seemingly throwing money into the wind, and Astro Zeneca closes an R&D lab in Atterly Park, then opens a half-billion dollar facility in Cambridge, MA.

What returns investors do eek out of large pharma are largely gained by increasing the cost of treatments. There is a ceiling, however, to what can be charged per treatment. At some point, people just won't/can't pay it. It's like a roulette table. Gamblers who lose at the roulette table try to double down on their next bet in an effort to earn their money back. When they lose the second bet, they'll double again on the next bet. This is called the Martingale Gambler's Ruin. Every casino sets a house limit on each table. Such a limit protects the house against bankruptcy. Society, similarly, will come to protect itself from healthcare bankruptcy. What is that house limit? 40% of GDP? 60% of GDP?

If the proof of FerroKin's virtual strategy lies in its sale price, then the evidence is convincing. Shire bought this little company a few months ago for $100 million upfront with promises of as much as $225 million more coming for reaching certain milestones.

RISING TO THE TOP IN THE DIGITAL SOUP

If there was a clear way to grow some legs or fins and rise up out of the soup, I'd be too busy making millions of dollars to write this article. But McQuivey does offer some pointers that seem like reasonable starting points.

Becoming a digital disrupter is all about mindset. It's not about individual technologies so much as the way that people who truly operate in the digital world think. In the digital environment, tools are free and ideas are openly exchanged, explored, and expounded upon. Digital technology is making the corporate meeting room, and in fact the office, obsolete (take note, commercial real estate investors). Such open access to markets and ideas eliminates traditional barriers to entry and advantage. Any company that is not embracing this new mindset is missing a fundamental ground shift.

What is this mindset precisely? "Relying on their altered sense of reality, digital disruptors innovate differently, building different products, using a different model for partnerships to make it all happen," McQuivey writes.

Put yourself in the shoes of your customer, McQuivey advises, and design your product accordingly. Don't make huge "pie-in-the-sky" jumps into new products and systems; move "adjacently" by making slight adjustments to existing products and gradually shifting into new territory. I'm not sure Steve Jobs would've agreed with this approach, but for a lot of people, this is sound strategy. He then recommends, "depending on convergent adjacencies" and "persisting on the path to innovation." Through this process, he develops an essential understanding of innovative ideas and delivers a total product experience that "wraps around and through a product, even a very analog product, to amplify, expand, and digitally redefine the way customer experiences the product."

Digital Disruption is not a book about new technologies. You can find that information anywhere. It is, however, a solid grounding in the processes that companies can use to identify and capitalize on some of the opportunities that surround them in the digital soup - opportunities just waiting for someone who understands the digital context and can turn the proliferation of new and cheap ideas into products. ◆

BIOGRAPHY

Derek G. Hennecke is President and CEO of Xcelience, a CDMO in formulation development and clinical packaging located in Tampa, FL. Mr Hennecke launched Xcelience as a management buyout in 2007, and the company has more than doubled in size. Prior to starting Xcelience, Mr. Hennecke worked for DSM as a turn-around manager in the global drug development community, managing an anti-infectives plant in Egypt, technical and commercial operations in a JV in Mexico, and a biologics facility in Montreal. He developed the formulation and business strategy of several drug compound introductions such as clavulanic acid, erythromycin derivatives and Tiamulin. A Canadian, he covets the Florida sun, but can't be kept away from the rink for long. He is an avid fan of the Tampa Bay Lightning.

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President & CEO,
Radius Health, Inc.

Radius Health, Inc. is a biopharmaceutical company focused on developing advanced therapeutics for healthy aging. The company's mission is to improve the quality of life in older adults by treating age-related conditions with new solutions that target osteoporosis and other women's health conditions. Michael S. Wyzga, President and Chief Executive Officer of Radius Health, Inc., formerly served as Executive Vice President, Finance and Chief Financial Officer of Genzyme, where he held primary responsibility for the firm's financial management worldwide and provided leadership in the successful $20.1 billion sale of Genzyme to Sanofi - the second-largest acquisition in biotechnology history. Drug Development & Delivery recently interviewed Mr. Wyzga to discuss what Radius is bringing to the underserved market for women's healthy aging solutions.

Q: According to the National Osteoporosis Foundation, the prevalence of osteoporosis is continuing to grow, yet the disease is still significantly under-recognized and under-treated. Do you see this changing in the future?

A: I believe there are three trends that will drive changes in this market. To start, we are seeing osteoporosis treatments that build and repair bone for the first time as opposed to only slowing the resorption process. Previously, there was little that could be done to rebuild the lost bone mass for patients with osteoporosis, but new therapeutics have the potential to move patients out of the fracture zone and keep them out with a "build and hold" strategy.

Second, big pharmaceutical companies like Amgen, Merck, and Eli Lilly are working on their own treatment systems to target osteoporosis. The fact that these major players in the industry are taking action underscores the unmet need of this large and growing market.

Finally, the population is aging and

"With BA058-TD, the transdermal patch, we expect the current 6-month trial to show that it is as effective as the subcutaneous delivery method. There is reason to believe it may even be more effective when delivered transdermally in highly vascularized skin, because doing so allows the administered drug to absorb into the system at a faster rate. If the transdermal works as well as the subcutaneous, we will have not only the best-in-breed anabolic drug, but also a convenient, patient-preferred delivery method we believe will improve compliance."

maintaining an increasingly mobile lifestyle. People in their 60s and 70s are remaining very active, and they are demanding better osteoporosis treatment options. We should not accept the treatment limitations of the past.

Q: The range of treatment and prevention options for osteoporosis has expanded in recent years. Can you elaborate on the new types of treatments and explain what Radius Health, Inc. is currently doing to develop new therapeutics in this area?

A: As we know, bones are constantly forming and resorbing, and this balanced process keeps bones from becoming brittle. In an osteoporosis patient, particularly postmenopausal woman, the resorption process continues, but the formation mechanism becomes weaker. Bones become brittle and more prone to breaking. The process typically begins in thinner bones like the vertebrae, where it may manifest in backaches, then moves to more dense bones, like the hip. The majority of osteoporosis treatments currently on the market are antiresorptive, which means they slow down the resorption process. However, anabolic agents assist in the building of bone and offer a solution beyond slowing resorption.

Our treatment, BA058, is a novel, synthetic proprietary peptide analog of human parathyroid hormone related protein or PTHrP, a bone-building anabolic compound. This treatment is currently in a Phase III clinical trial for a version delivered via subcutaneous injection, as well as a Phase II trial for a transdermal delivery method.

Q: In 2011, Osteoporosis International published results of a study indicating that patients' preferences for osteoporosis medications are strongly influenced by the mode of administration. What are pharmaceutical companies doing to move toward patient-preferred solutions?

A: There's an old saying in biotech: "It's a fascinating drug, but only if somebody uses it." We know that a drug's mode of administration is key, and a drug is only effective if it is used for an appropriate time period. If the treatment mechanism is cumbersome or painful, patients won't use the drug. For example, the only available anabolic for the treatment of osteoporosis is delivered by daily subcutaneous injection and must be refrigerated. Our data suggests that the inconvenience of daily injection and the need for refrigeration significantly affects compliance rates. Between the hassle of refrigeration and the unpleasant self-injection delivery, many just give up.

Amgen has a treatment that must be administered monthly in the doctor's office, in a series of two to three separate 1-mL injections. These injections are administered with significantly larger needles, and the patient has the added inconvenience of having to travel to the doctor's office.

Our treatment, BA058-SC, currently in Phase III testing, is delivered via at-home subcutaneous injection as well, but one key difference is it does not have to be refrigerated, which offers the potential to keep patients using it for a longer period of time. The real game changer is BA058-TD, the transdermal delivery option currently in Phase II testing. We have an exclusive agreement with 3M Drug Delivery Systems to develop and commercialize this convenient, short wear time patch that uses a Microstructured Transdermal System (MTS) from 3M Drug Delivery Systems. Studies with the BA058-TD have shown that a 5-minute wear time of the patch delivers peak drug levels consistent with subcutaneous injection. Patients can apply the patch in the morning as they are getting ready for their day and leave it on for about 5 minutes without having to deal with large needles, refrigeration, or scheduling monthly doctor visits. We believe by utilizing 3M's innovative technology, BA058-TD has the potential to improve patient compliance significantly.

Q: What results have you received so far in the testing for BA058, and what are your expectations for the new product once it is commercialized?

A: One major difference we've seen compared to the currently available anabolic is that BA058 works faster. Results have shown that bone mineral density (BMD) levels increase significantly in both vertebral and non-vertebral areas. We are studying this further in the Phase III testing.

With BA058-TD, the transdermal patch, we expect the current 6-month trial to show that it is as effective as the subcutaneous delivery method. There is reason to believe it may even be more effective when delivered transdermally in highly vascularized skin, because doing so allows the administered drug to absorb into the system at a faster rate.

If the transdermal works as well as the subcutaneous, we will have not only the "best-in-breed" anabolic drug, but also a convenient, patient-preferred delivery method we believe will improve compliance.

Q: An estimated 2 million women undergo menopause every year in the US, totaling around 50 million postmenopausal women. What is currently being done in the pharmaceutical industry to address the needs of this demographic?

A: Radius has two potential products focused on helping these patients. In addition to the osteoporosis treatment, we have a product currently in Phase II testing for the treatment of "hot flashes" called 1901. While the statistics of osteoporosis are very sobering, many women seem to be equally or even more concerned with hot flashes. It's a quality of life issue.

Hot flashes often last 4 to 5 years, and in about 20% of women, hot flashes may never go away. The night sweats and daily discomfort can be quite significant, and the currently available hormone replacement therapies with estrogen and/or progesterone have been associated with increased risks for malignancy and cardiovascular disease. We saw the need for better options, and we are developing RAD1901, a selective estrogen receptor modulator. We've completed a 4-week, Phase IIa study that established clinical proof of concept, and achieved a statistically significant reduction in frequency of moderate and severe hot flashes. As an alternative to conventional estrogen therapy, this treatment is very promising. It functions as an estrogen agonist in the body, promoting normal estrogen, except for in the uterus and the breast where it actually functions as an antagonist, which is what you want in order to avoid the problems associated with other therapies. This treatment will soon go into Phase IIb, another 90-day efficacy and safety study, focused on the frequency and severity of hot flashes in postmenopausal women.

Q: With several programs currently in the pipeline focused on treating osteoporosis and menopause, what can we expect to see from Radius Health, Inc. in the future?

A: We are projecting approval for BA058-SC, the subcutaneous anabolic bone builder, in 2016. The BA058-TD patch should have approval about a year later. As resources permit, we will focus on RAD1901.

We also have a drug in the preclinical phase, a selective androgen receptor modular SARM, which is a potential treatment for age-related muscle loss, frailty, and wasting-type disorders. Very often in patients with cancer or HIV, we see issues that have less to do with the primary disease than with the associated weight loss and frailty, which makes the patient susceptible to many more problems. This fits well within our focus area of healthy aging, and we look forward to making progress with this treatment. ◆

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Cell Culture Media

Addressing Variability in Dry Powder Mammalian Cell Culture Media

By: Jörg von Hagen, PhD, Head of R&D Process Development, Merck Millipore

Introduction

Mammalian cell culture technology has become a major field on its own within the biopharmaceutical industry as the quality of culture media has a great impact on many important processes, ranging from cell growth in the R&D setting to critical quality attributes of new biological entities (NBEs).[1,2] Biotherapeutics, such as monoclonal antibodies and recombinant proteins, are being produced in manufacturing facilities that utilize large-scale cell culture production processes for both clinical and commercial use, and the bioprocessing industry is increasingly relying on ready-to-use dry powder media.[1]

The ability to deliver high-quality, reproducible good manufacturing practice (GMP) cell culture media relies on three critical elements: formulation optimization, quality of raw materials, and the production process. Although two batches of media may technically contain the same formulation, cell culture performance may be vastly different if the quality of the raw materials and/or the production process differs. The proper selection, qualification, and pre-processing of raw materials is essential for ensuring that the starting materials are of the highest quality in support of optimal media performance; the production process, including milling, mixing, and packaging, must be controlled and gentle enough to avoid degradation of the raw materials. It is therefore critical for media manufacturers to have a process in place that can consistently deliver raw material and process quality in order to be able to deliver batch-to-batch consistent dry powder cell culture media that are scalable from kilograms to tons.

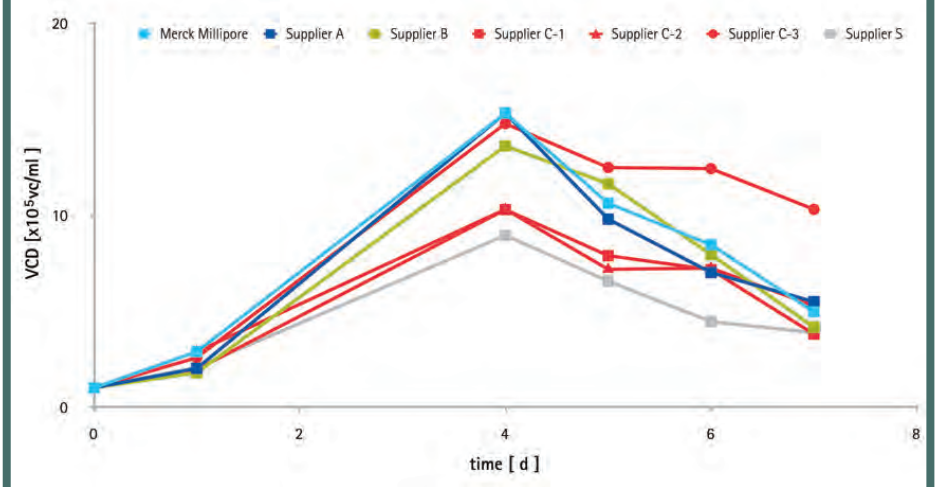


Figure 1. **CHO-S batch culture performance testing using DMEM/F12 dry powder media from various suppliers.**

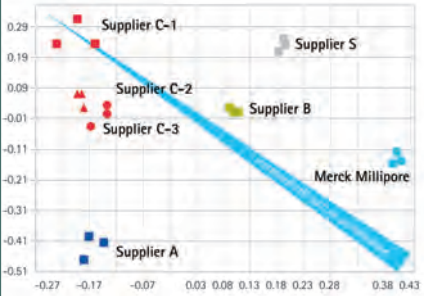


Figure 2. **Principle component analysis: Correlation of cellular performance and NIR analysis.**

Dulbecco's Modified Eagle Medium (DMEM/F12) is a commonly used mammalian cell culture medium that contains a standard dry powder formulation among suppliers. Merck Millipore conducted a DMEM/F12 benchmarking study in order to assess the variability of this common medium among suppliers despite having a standard formulation. Dry powder DMEM/F12 was obtained from several suppliers, and numerous physico-chemical and performance tests were conducted.

Not So Standard

Despite having a standard formulation, DMEM/F12 dry powder media produced by various suppliers appear very different as the powder ranges in color from white to pale yellow to pink. Because the formulation is the same, these color differences are likely the result of variations in the quality of raw materials and/or production processes used by the various suppliers, and imply that important physico-chemical properties, including pH, osmolality, humidity, and particle size distribution, may also vary across samples. Each of these properties is a critical parameter in mammalian cell culture as even small deviations could impact media performance.

Maintaining optimal pH (7.4) and osmolality (0.29 osmol/kg) of culture media is critical for cell viability and growth. One cell culture medium, Supplier S, varied significantly in both of these parameters; in particular, the osmolality of this sample was, on average, 0.4 below the standard osmolality expected based on the DMEM/F12 recipe. No precipitates were observed in any of the samples following solubilization; therefore, all powders were very soluble.

The water content, or humidity, in dry powder media has a direct impact on stability and storage. In addition to selecting the right packaging materials, it is important for media manufacturers to have an optimized production process in place, one that begins with and maintains a very low water content (~1%) to avoid supporting microbiological growth throughout production and storage. For this reason, water content should be routinely monitored throughout production. All DMEM/F12 samples were analyzed for water titer by Karl Fischer titration. Variability for humidity was observed among the samples, with a few approaching or exceeding a water titer of 1.2%.

Particle size distribution is a vital element that must be controlled in the production process because it has implications for demixing effects, solubility, oxidation, and microbial degradation as dry powders are not produced under sterile conditions. Each DMEM/F12 media sample was analyzed for particle size distribution using air jet sieving, and two types of particle size reduction effects were observed: one group of samples followed a linear distribution; another group of samples more closely followed a logarithmic scale. Demixing effects are observed to be lower for dry powder cell culture media that follows a more linear distribution.

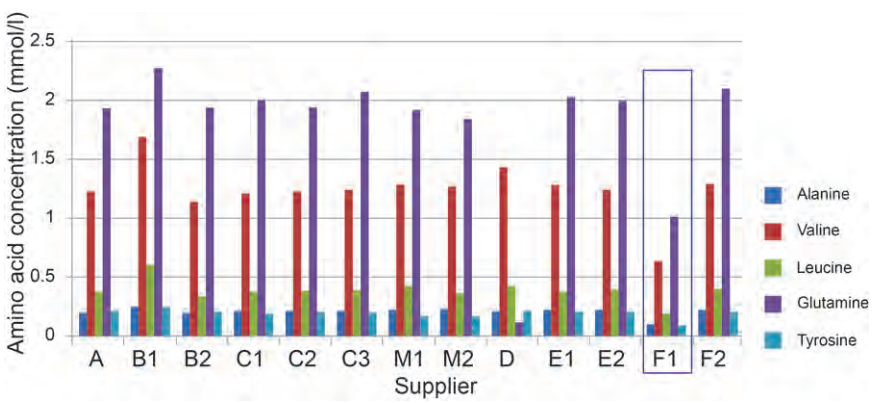


Figure 3. **Amino acid quantification of DMEM/F12 dry powder media from various suppliers as analyzed by NMR profiling.**

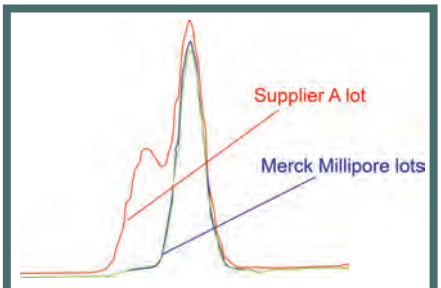


Figure 4. **Degradation of a raw material during the DMEM/F12 dry powder media production process as analyzed by UPLC.**

In addition to the pysico-chemical characterization assays, Chinese Hamster Ovary (CHO-S) batch culture performance testing was conducted to measure media performance. Approximately $1x10^5$ viable CHO-S cells per mL were seeded and allowed to grow over several days. Viable cell density varied by as much as 50% across DMEM/F12 samples after four days (Figure 1).

Together, the physico-chemical and performance data from this DMEM/F12 benchmarking study conclude that "standard" formulation dry powder cell culture media are not in fact standard in their physico-chemical and performance characteristics across suppliers. In addition to formulation optimization, media manufacturers must also have the right high-quality raw materials and production processes in place for optimal media performance.

Predicting Media Performance

Although informative for measuring media quality and performance, the analytical assessments used in the DMEM/F12 benchmarking study are very labor-intensive and time-consuming, especially if full testing is run for each new batch of medium. Merck Millipore has adopted much simpler "fingerprinting" technology that can predict media performance quickly and accurately without requiring full analytical testing. These methods include principle component analysis (PCA), nuclear magnetic resonance (NMR) profiling, and ultra performance liquid chromatography (UPLC).

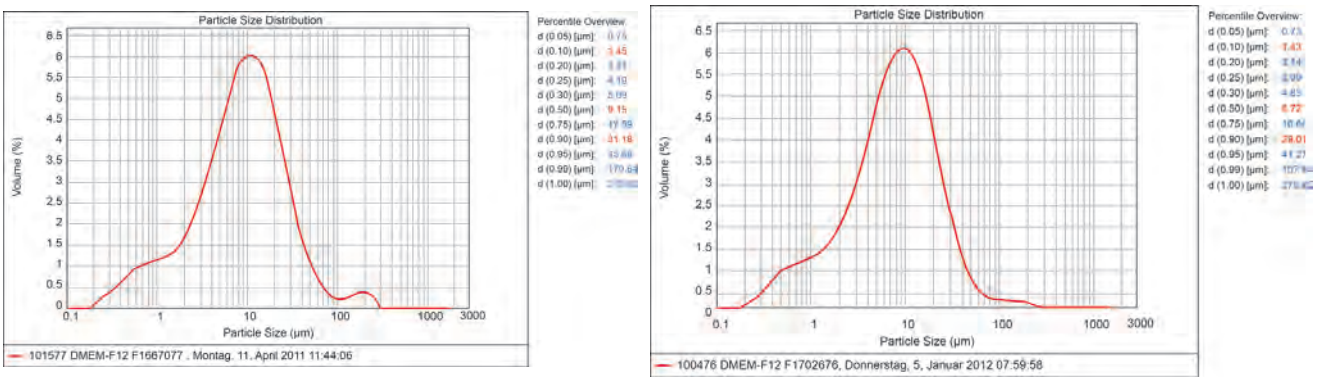
Principle component analysis is a standard tool used in data analysis that extracts relevant information from complex data sets. With respect to media performance, PCA revealed that near-infrared spectra (NIR) of media samples contain enough physico-chemical information to be a robust predictor of media performance (Figure 2). This predictive tool can be used to identify quality differences and lot-to-lot variability among batches. A particular PCA score does not necessarily define high- or low-performing media; rather, experience is needed from historical batches so that a particular PCA score can be mapped to higher and lower performing batches. In this model, an increase in cell culture performance is predicted as data moves from the upper left hand quadrant to the lower right hand quadrant.

If PCA testing predicts low performance, then the issue with the media could lie with impurities in the raw materials or with degradation of the raw materials as a result of the production process. These issues can be further analyzed using methods such as NMR profiling and UPLC - and then appropriately addressed.

NMR profiling was conducted on an extended set of 13 different batches of DMEM/F12 media from various suppliers to quantify the amount of each amino acid present in each sample. Of this set, five amino acids – L-alanine, L-valine, L-leucine, L-glutamine and L-tyrosine – proved to be of particular interest due the variability of their concentration among some of the samples (Figure 3). For example, some batches of media were found to contain only half the concentration of L-valine and L-glutamine as predicted by the DMEM/F12 formulation. UPLC was conducted on the same set of DMEM/F12 media to identify potential impurities that could impact performance (Figure 4). A pre-peak was identified in one of the media batches, which suggests that degradation of a raw material during the production process had occurred (this was later confirmed by NMR analysis). Therefore, once a low-performing batch of a medium has been identified, or predicted by PCA testing, potential impurities can be qualitatively and quantitatively analyzed.

In summary, high-quality raw materials, a gentle production process that preserves these critical raw materials from

Set A



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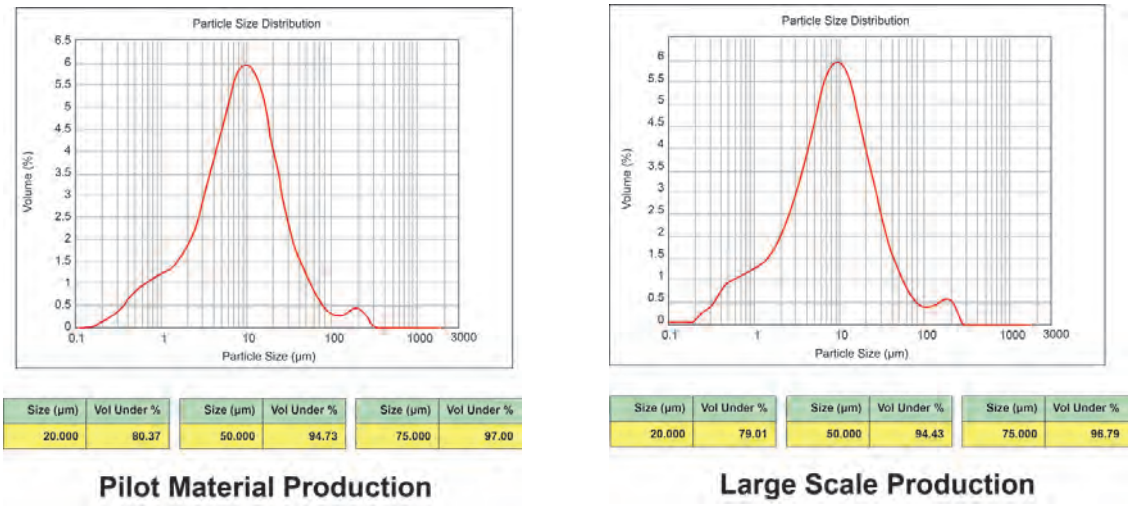

Figure 5. **Particle size consistency demonstrates 5a) batch-to-batch consistency when using different raw material sets 5b) scalability from pilot to large-scale production. Raw material set A and B are fully different batches throughout all ingredients (Δt > 1/2 year). Particle sizes are measured by laser diffraction.**

degradation, and having the right analytics in place for predicting media quality are all highly desired attributes for media manufacturers. These attributes are critical for the ability of manufacturers to deliver dry powder cell culture media that are consistent from batch-to-batch and scalable from kilograms to tons.

From Kilograms to Tons

Scaling up the production of dry powder cell culture media is an important topic for most large-scale biopharmaceutical producers because of the need to ensure batch-to-batch consistency of these large-scale productions. Merck Millipore frequently supplies tailored cell culture media in batches of up to 2.5 tons using state-of-the-art cGMP production facilities and raw materials sourced from qualified suppliers who can fulfill the requirements for our quality standards. These raw material qualification standards ensure batch-to-batch consistent delivery of the individual ingredients.

Merck Millipore assessed the reproducibility and scalability of DMEM/F12 dry powder medium, ranging from 1 kg to up to 2.5 tons, using only qualified raw materials. Dry powder medium was produced from one set of raw materials (set A) with pin-mill technology as lab-scale (up to 1 kg), mid-scale (up to 100 kg), and large-scale (up to 2.5 tons) batches. Using the same formulation and production process, but a completely different set of raw materials (raw material set B, purchased 6 months later) another

large-scale batch was produced within 6 months. Each batch was then evaluated for pH value, osmolality, solubility, particle size distribution, and cellular performance.

All of the physico-chemical parameters were similar, regardless of the scale or raw material sets used. As shown in Figure 5, particle size consistency remained nearly identical from pilot material to large-scale production or when different batches of raw materials were used (raw material sets A and B), demonstrating both scalability and batch-to-batch consistency, respectively. These data confirm that the scale-up and large-scale production of dry powder cell culture media at Merck Millipore is a very highly controlled process. Additionally, a world-class battery of analytics is used to achieve high levels of reliability and security.

Conclusion

The DMEM/F12 benchmarking study demonstrated that despite having a standard formulation, significant variability exists among dry powder media produced from different suppliers. Thus, formulation alone does not determine media performance; the quality of raw materials and the production process play critical roles in the delivery of consistent, high-quality GMP dry powder cell culture media. These elements are also critical for ensuring scalability while preserving the desired parameters.

There are three factors that contribute to the success of quality raw materials: a raw material manufacturing process that adheres to best practices; a raw material qualification program that ensures consistency of the individual components, and a raw material pre-treatment process that ensures each component has the proper surface area for optimal solubility. Batch-to-batch consistency begins with consistency of the raw materials used. Additionally, there are three factors that contribute to a successful production process: a gentle milling technology that does not degrade the raw materials, an optimal mixing time, and a packaging process that controls for humidity. Merck Millipore has a very tightly controlled process in place that incorporates all of these elements, enabling smooth transitions from pilot-scale to commercial-scale cell culture production. ■

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Head of R&D Process Development
Merck Millipore

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Evaluation of a Needleless Injection Technique for Treatment of Peyronie's Disease: a Feasibility Case Study

By: Jeffrey Marotte, MD, FACS

Introduction

Peyronie's disease (PD) is a progressive disorder characterized by a tunica albuginea inelastic scar resulting in a variety of penile deformities often coexisting with erectile dysfunction and pain. PD has historically been thought of as a rare, insignificant disease relegating physicians to take an observational approach and to reassure men that the disease can spontaneously resolve over time. However, the truth is that the natural history of PD is often progressive in severity, leading to significant emotional distress and psychological burden.[1]

Current trends in diagnosis and management in PD are even more disconcerting. Despite clear evidence that oral agents like Vitamin E and potassium para-aminobenzoate are no more effective than placebo, oral therapies are routinely offered as primary treatment.[2] Recent literature indicates that multimodal therapy (oral plus intralesional injections and/or iontophoresis plus mechanical stress) could be a promising treatment protocol for PD.[3,4] Iontophoresis or electromotive drug administration (EMDA) is the use of an electrical current to drive positively charged medication into the underlying tissue.[5] Early in the introduction of EMDA, researchers were optimistic about its use but it has not proved promising as a viable treatment option. Levine's 2003 study using EMDA was able to detect varying amounts of verapamil in the tunica albuginea, but his 2007 double-blind, placebo controlled study using verapamil and EMDA indicated no statistically significant difference in decreases of curvature.[3] Experts in the field recently reviewed the current PD literature and made guideline recommendations on all therapies for PD based on graded, evidence-based criteria. This systematic analysis revealed the strongest level of evidence in support of non-surgical therapy was for intralesional therapy (ILT), specifically interferon (Grade B).[6] Despite these recommendations, a minority of men with PD receives ILT. When men receive ILT, it is uncommon that the local urologist performs the treatment; rather, he is referred to a practice focused on surgical treatment of PD.[2]

For 4 decades, urologists have overlooked a potentially effective manner to infiltrate Peyronie's lesions with ease.

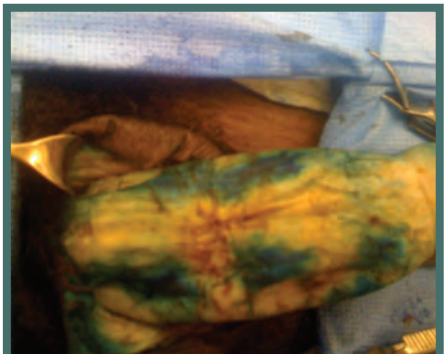

Figure 1. **Hematoxylin from one, three, and five needleless injections penetrates the tunica and disperses radially from the injection site.**

Beginning in 1968, 21 patients were treated with a needleless injector with corticosteroids with 64% having improved curvature.[7,8] While steroids have fallen out of conventional PD ILT use, the Madajet® injector is a readily available instrument in the urologists' armamentarium in the burgeoning area of needleless anesthesia for the no-scalpel/no-needle vasectomy and circumcision.[9,10] The Madajet is an FDA-approved device historically used for mass immunizations but now commonly utilized as an anesthetic tool in dentistry, podiatry, dermatology, and recently, urology. Depending on the application, the device ejects the anesthetic under high pressure at a consistent depth of penetration of 2 to 6 mm below epithelium and makes a wheal at the base of injection of 5 to 6mm in diameter.[9] The device could provide the urologist with a vital tool for intralesional injections for Peyronie's using well-studied, established preparations like verapamil, interferon, and collagenase. This study's aim was to present a proof of concept that the Madajet may be a suitable instrument to inject medication into Peyronie's plaques.

Methods

The study design was reviewed by the institution's Internal Review Board and determined to not fall under the IRB review process, because it did not rise to the level of human subject research under the FDA definitions. Three cadaveric intact male penises were embalmed up to 3 months prior to the study. Each penis was divided into six sections on the left and right side of the midline of the dorsal penis, to be injected into left and right corporal bodies. One, three, and five needleless injections of approximately 0.2 ml of hematoxylin were performed in the left and right side of a formalin fixed cadaveric penis at the distal, mid, and proximal shaft, respectively.

Immediately following the injection of hematoxylin, the penis was degloved exposing the underlying Buck's fascia and tunica albuginea of both dorsal corporal bodies to the level of the penoscrotal junction ventrally and penile ligament dorsally (Figure 1). Core samples were obtained using a dermal 5-mm circular punch biopsy through the entire tunica albuginea (TA) into the cavernosum over the respective injection sites on each corporal body. Specimens were fixed in formaldehyde and processed by a pathology technician using hematoxylin in the traditional H&E staining method. Hematoxylin stains only nuclei of cells; therefore, the depth of hematoxylin staining was evaluated grossly on core sampling and microscopically by indentifying hematoxylin stained cells in the cross-sectional thickness of the TA (Figure 2). Though collagen staining could have been performed, endothelial cells are present throughout the entire TA; therefore, their staining is a valid demonstration of hematoxylin penetration.

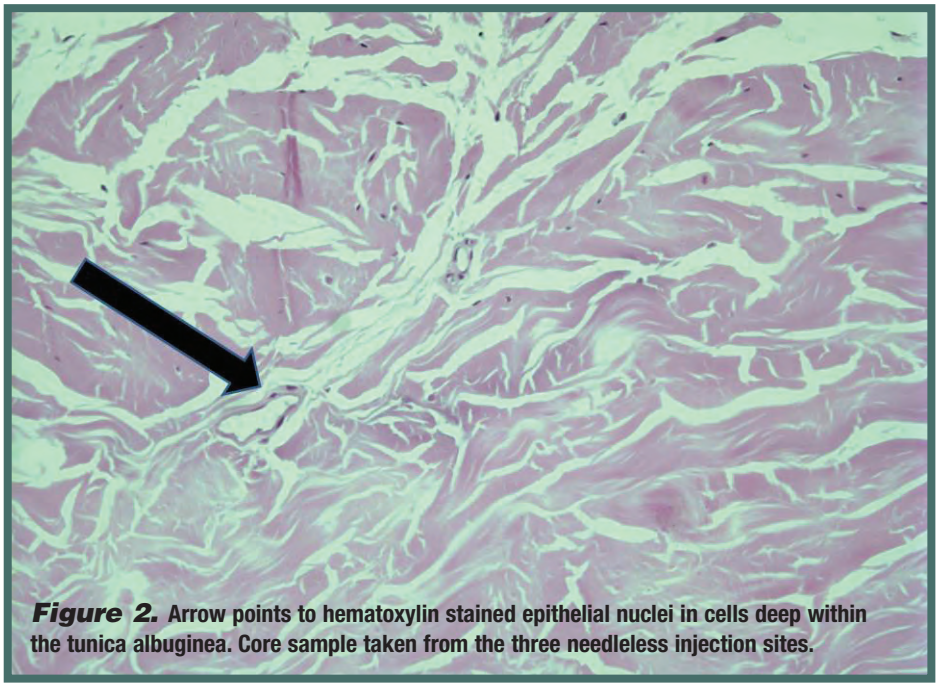

Figure 2. **Arrow points to hematoxylin stained epithelial nuclei in cells deep within the tunica albuginea. Core sample taken from the three needleless injection sites.**

Results

Hematoxylin in all three specimens completely penetrated the skin. Upon gross and microscopic evaluation, the one needleless injection of hematoxylin penetrated greater than 50% of the TA, but the three and five needleless injections penetrated 100% of the TA. The dermal layer had a drug entry point with a 3-mm

radius of hematoxylin stain that radiated outwardly to a more diffuse 4-mm circumference on the superficial layer of the TA to a 7-mm circumference on the deep layer when three and five fires were performed. There was minimum uptake by the skin. The neurovascular bundles were not inspected.

Discussion

Since oral agents for PD have demonstrated minimal to no effectiveness, and surgical therapy is only performed in a minority of patients, a large proportion of men with PD will continue to be undertreated. Since 2007, more compelling clinical trials have shown that ILT has, at least, consistently proven to stabilize the deformity or, at best, reduces the curvature.[11-13] It is unclear whether it is the inaccurate belief that PD spontaneously resolves or that nothing can be done to treat the disease that limits the opportunity for men to receive ILT.[14] Epidemiological reviews of PD don't fully explain why only the minority of urologists offer ILT. Lack of adoption could be skepticism of the effectiveness of ILT or reluctance to perform the procedure due to lack of formal training in the technique.[15] Patient factors may limit its use too. Many men with PD may not consent to the procedure after the conventional needle technique is described to them or may decline ILT over concerns of the possible increased costs incurred by off label use. An easier and potentially less painful way to administer the medicine has been attempted with topical verapamil therapies, but none have proven definitively that the drug permeates the plaque.[16]

Intralesional therapy has been used in the treatment of PD for over a half a century with recent evidence-based analysis supporting that ILT has the most robust data for non-surgical treatment.[6] Despite potential benefits of ILT, one of the impediments is the negative reaction of most men to the thought of a needle inserted into the penis. The needle injection technique requires an anesthetic penile block followed by a total of seven to eight separate needle "sticks" to administer 10 ml of diluted drug.[15] Plaques are often very hard and can be calcified, making it difficult to penetrate the plaque. Drug dispersal into the plaque is accomplished by backing the needle out and pushing the drug into the created needle track. Scores of needle injections over weeks of injections into the tunica plaque raises some theoretical concerns of increasing injury to the dorsal nerves and arteries of the penis.

The results of this case study demonstrate the efficacy of the Madajet in delivering hematoxylin into the TA. The molecular weight of hematoxylin (302 g/mol) is not significantly different than verapamil (455 g/mol) or interferon alpha-2b (244 g/mol); therefore, the needleless technique may be a viable option for drug dispersal. The limitation of this study is that the mechanism of drug transportation is different in cadaveric than human tissues. Additionally, formalin may alter the resistance of cadaveric tissues allowing solution to pass with less resistance than live TA with plaques. If there is more resistance from live tissue, more than five needleless injections may be needed to penetrate the entire thickness of Peyronie's plaques. The Madajet can administer a volume of approximately 1.5 ml in seven needleless injections, potentially getting higher concentrations of the drug at lower volumes of solution while encompassing a broader field of the plaque.

The Madajet technique also may offer an advantage over needle injection in terms of drug delivery in cases of PD with extensive fibrosis, plaque formation, and calcification. Conventional injection techniques are limited with extensive calcification, fibrosis, and plaque formation, requiring higher gauge needles and administering drugs only on exiting the needle tract. The pressure generated by the device far exceeds that what can be obtained with a syringe, and as a result, may provide more effective drug delivery through these challenging plaques. In contrast, needleless technique may not provide the mechanical fracturing of plaques that needles can achieve, indicating that the published success in ILT may be secondary to the physical insertion of needles itself, which lead to traumatic plaque destabilization and clinical improvement.

The Madajet may have another

advantage over conventional needles in terms of its safety. The needleless technique potentially could be less likely to traumatize the neurovascular bundle that usually sits on top of the major area that forms plaques. Using the device also poses less risk to the corpus spongiosum with ventrally located plaques, whereas a needle presents the risk of penetrating the corpus spongiosum causing hematuria or urethral trauma.

The Madajet injector operates a spring-loaded piston that generates about 2000 psi in the fluid chamber and disperses the approximately 0.2 ml of solution radially into the tunica albuginea, creating shear forces into the target tissue. The mechanical/physical forces delivered by the Madajet have a promising therapeutic advantage over conventional needle injection treatment in that the high forces produced by the quick bursts of fluid potentially creates plaque distention and disruption of the abnormal aligned collagen fibers. A mechanical/physical approach to treating Peyronie's is not a new paradigm; ESWL, counter flexion of the penis after ILT, and traction devices are at the forefront of PD management. Further molecular rationale for a "pugilistic" approach is supported by studies of Duptyren's contracture, PD's genetic and analogous counterpart, which demonstrated upregulation of "antifibrotic" genes by applying stressors to the abnormal collagen.[17]

Urologists and their patients with PD anticipate the possible FDA approval of histoplasmiticum collagenase if Phase III trials demonstrate its effectiveness. If approved, it will be the only drug of its class approved for PD, creating a high demand for its use. Nevertheless, many men may still defer treatment because of the aversion to needles. The Madajet technique has the capability of addressing the shortcomings of the ILT needle technique by making the needleless ILT therapy a simple and relatively painless mode of drug delivery.[18] With its benefits and ease of use, a higher percentage of urologists would offer ILT in their practice.

Conclusion

The Madajet needleless injector penetrated cadaveric penile skin and infiltrate the entire tunica albuginea in less than 1.0 ml of solution. The relative ease of applying a less invasive needleless technique to men with PD may not only increase the number of men receiving ILT over those receiving less effective therapies but also provide an easier method than conventional needle techniques. Further study of needleless techniques in vivo is required to compare with traditional needle techniques with regard to its efficacy, drug dispersion properties, and physical structural effects to the plaque architecture. ■

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Dr. Marotte is a urologist in private practice in Arkansas and is a Clinical Adjunct Instructor at the University of Arkansas for Medical Sciences in the Department of Urology. In 2005 he completed his urologic residency at Stanford University after publishing a number of manuscripts in urology pertaining to urologic oncology and pediatric urology. Currently, he is a fellow of the American College of Surgeons, President of the Arkansas Urologic Society, and Representative to the SouthCentral Section of the American Urologic Society. Aside from his busy clinical practice, Dr. Marotte is focused on innovative urological surgical techniques and urological devices and holds a patent pending in a new urological device. He also is interested in novel drug delivery systems with urologic applications and is the lead scientist in a study evaluating testosterone replacement therapy with Bioject, Inc.

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The Performance Report

By: John A. Bermingham

I hate Performance Reports! In my experience dealing with these reports, I have always found that, on their own, they are too little, too late and the cause for more problems than they are worth. I say this for several reasons.

1. The rating system is typically a 1 to 5 score with 5 being a "walks on water" rating, and 1 being a "you better start looking for a new job" rating. The problem is that in a person's mind, receiving a rating of 3 is a failure and patently unfair. But if you read the definition of a 3 in most report forms, the definition states that a 3 meets all expectations in the category under review. That's a great rating. I would say that the score relates to a B+ or an A-.

2. The reviewer and reviewee are going to be in an unavoidable conflict during and after the review. The reviewer will normally take the position that he or she is being generous with the ratings and hoping to motivate the reviewee, while the reviewee will become upset because he or she will believe the reviewer does not see the values and benefits they are bringing to the company and why they are not receiving all 4s and 5s.

3. The Performance Report is generally a once-per-year review, and this can often be a shocking experience because the reviewee believes that everything is wonderful because nothing negative has been said to them all year. The reviewer, on the other hand, knows that no one is perfect, so certain shortcomings have to be brought to the reviewee's attention.

4. Most managers have never been trained or counseled on how to conduct a Performance Report meeting, and they often degrade into a confrontation of varying degrees.

When I was with AT&T, we had an annual performance review. It was an extensive document that covered multiple areas and had the standard 1 to 5 rating scale. The problem with AT&T's Performance Report was that if you did not receive a 5 in every category, then you were considered a failure. So what benefit is a Performance Report if everyone is rated as "walks on water" in every category? It might make a person feel good, but it is a fraudulent rating that makes it valueless.

A Performance Report should be a document in which you and the person you are reviewing take the opportunity to talk about that person's job performance not just from your perspective but from the reviewee's perspective. The person being reviewed will often have a different perspective from yours, and you should both talk this through. ◆

Biography

John A. Bermingham
Chief Operating Officer
1st Light Energy & Conservation Lighting

John A. Bermingham is currently the COO of 1st Light Energy & Conservation Lighting. He was previously Co-President and COO of AgraTech, a biotech enterprise focused on chitosan, a biomaterial processed from crustacean shells (shrimp, crawfish, crab, etc), as well as President & CEO of Cord Crafts, LLC, a leading manufacturer and marketer of permanent botanicals. Prior to Cord Crafts, he was President & CEO of Alco Consumer Products, Inc., an importer of house ware, home goods, pet, and safety products under the Alco brand name and through licenses from the ASPCA and Red Cross. He successfully turned around the company in 60 days and sold Alco to a strategic buyer. Mr. Bermingham was previously the President & CEO of Lang Holdings, Inc. (an innovative leader in the social sentiment and home décor industries) and President, Chairman, and CEO of Ampad (a leading manufacturer and distributor of office products). With more than 20 years of turnaround experience, he also held the positions of Chairman, President, and CEO of Centis, Inc., Smith Corona Corporation, and Rolodex Corporation. He turned around several business units of AT&T Consumer Products Group and served as the EVP of the Electronics Group and President of the Magnetic Products Group, Sony Corporation of America. Mr. Bermingham served 3 years in the U.S. Army Signal Corps with responsibility for Top Secret Cryptographic Codes and Top Secret Nuclear Release Codes, earned his BA in Business Administration from Saint Leo University, and completed the Harvard University Graduate School of Business Advanced Management Program.

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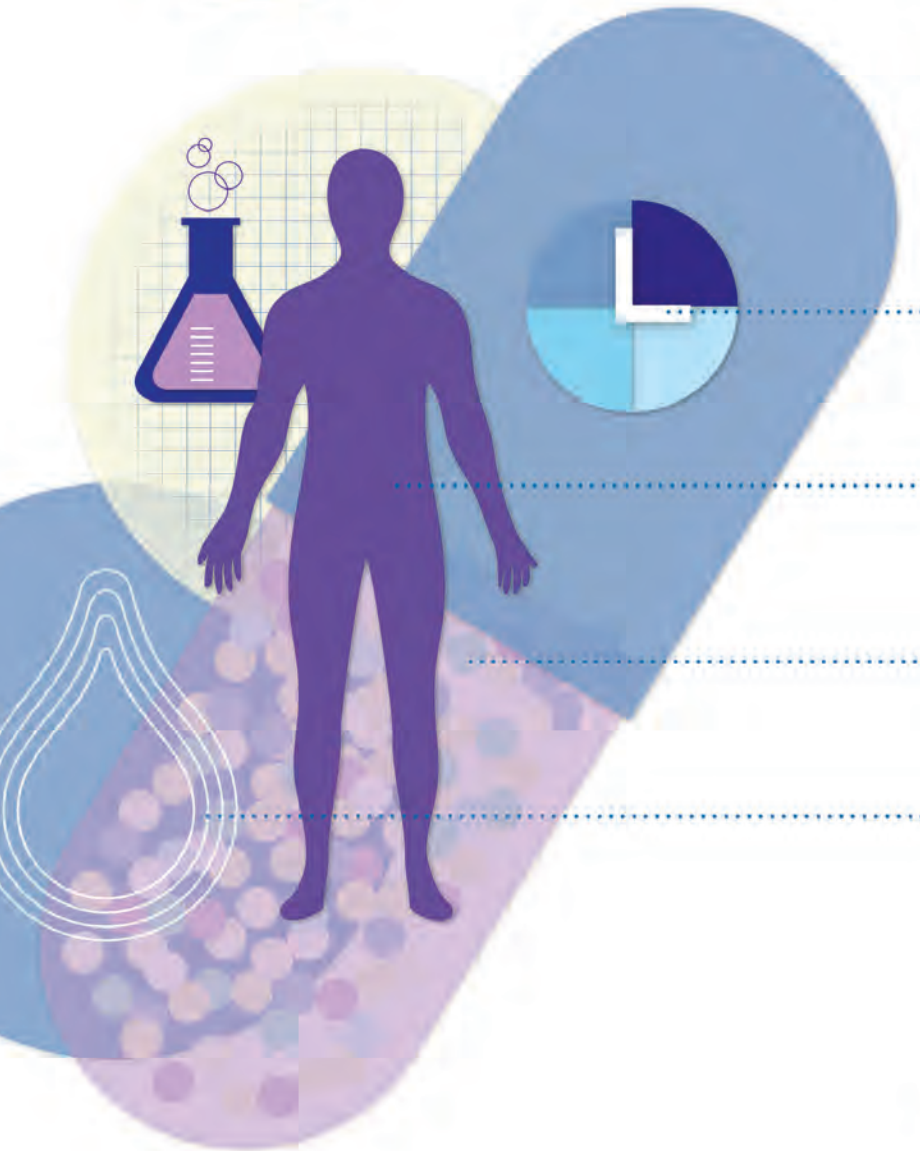

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