Drug Delivery Technology®

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RCI & Optical Microscopy

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Krishnendu Roy, PhD
Associate Professor
and Graduate Advisor,
Department of
Biomedical Engineering,
The University of Texas
at Austin

Eurand congratulates **Professor Krishnendu Roy,** winner of the 2010 CRS Young Investigator Award.

- Attend Professor Roy's presentation: *Designer Drug Carriers: Taking Cues from Physiology and Disease-Pathology*, at the Award Showcase session on Tuesday, July 13
- Eurand will present Professor Roy with his award at the Awards Ceremony on Tuesday, July 13 between 1:45-2:30 pm

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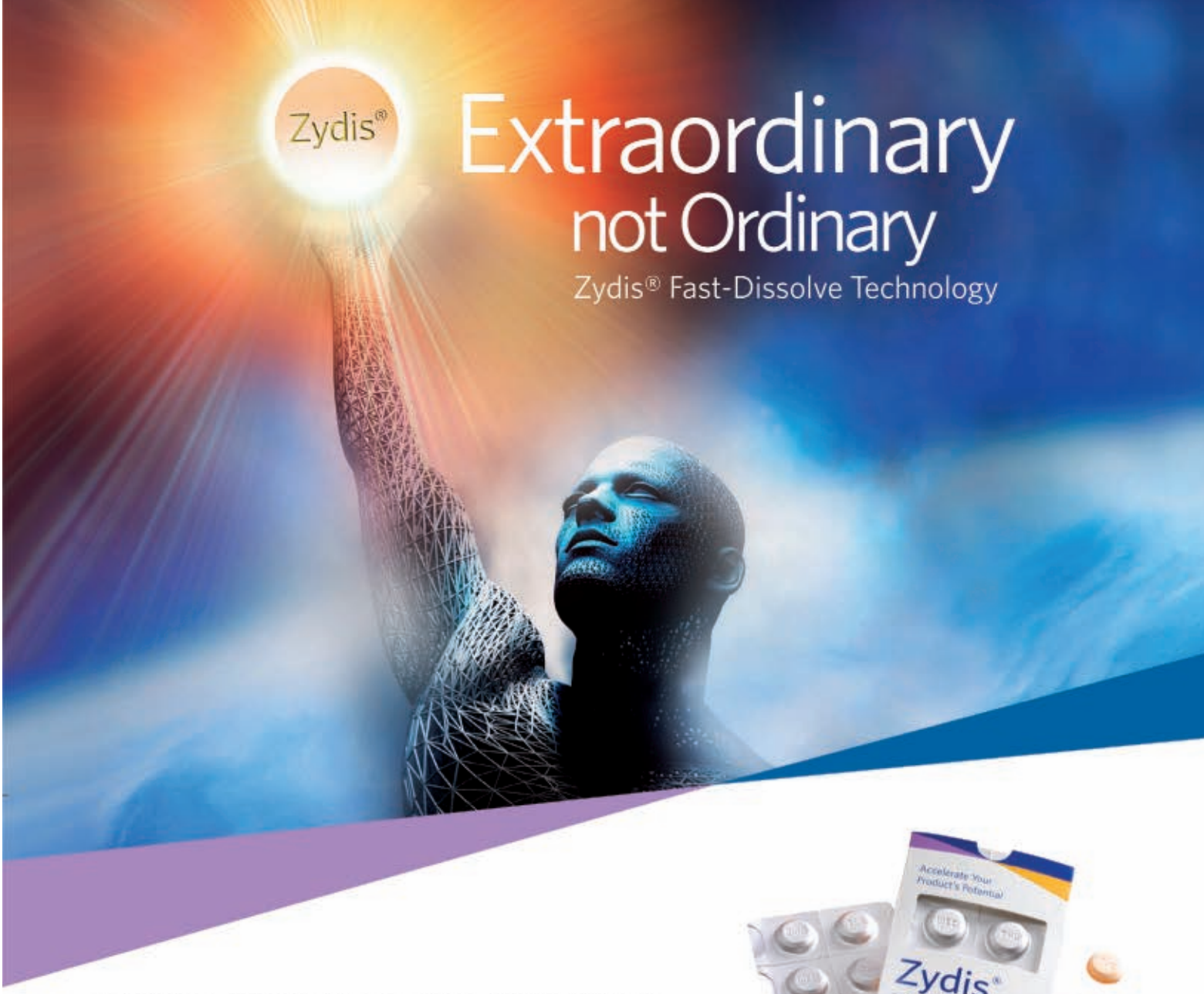

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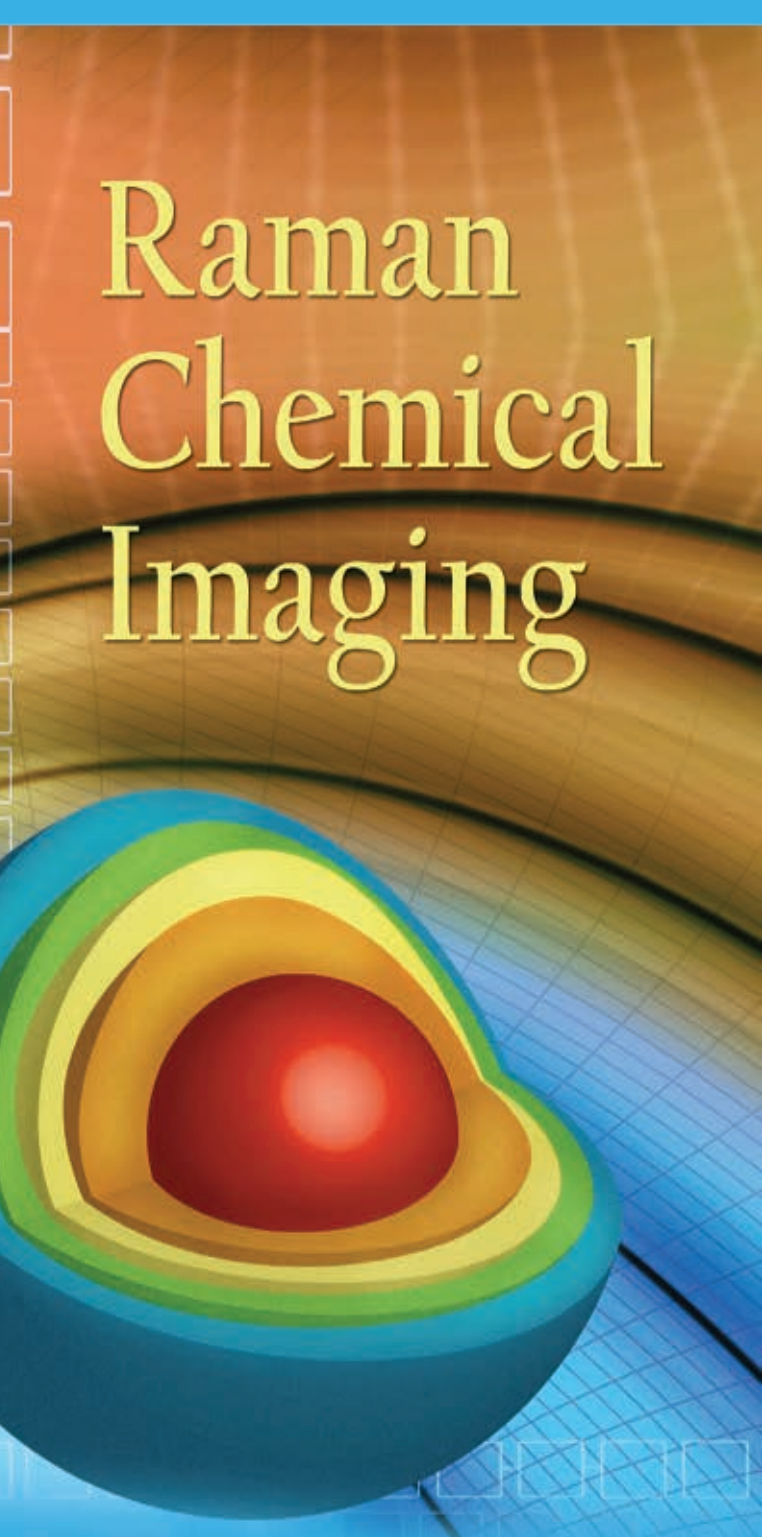

"Rich spectral and spatial information contained within the RCI data cube can provide valuable feedback during formulation and manufacturing processes and help correlate coating thickness with drug dissolution profiles. RCI technology is especially valuable for multilayer beads or for troubleshooting manufacturing processes."

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Market News and Trends

Marinomed Achieves Preclinical POC for Allergy & Allergic Asthma Drug

Marinomed Biotechnologie GmbH, a company focused on the development of innovative therapies for respiratory diseases, recently announced that MAM-06.301 has achieved preclinical proof-of-concept for the treatment of allergy and allergic asthma.

The compound, also referred to as beta-escin, was identified through screening as a potential anti-allergic compound. In the present study, MAM-06.301 was investigated in vivo in two mouse models for early and late-stage allergic reactions (passive cutaneous anaphylaxis and allergic asthma). In both models, beta-escin showed a potent dose-dependent inhibitory effect.

"Serious allergies can be extremely debilitating life-long problems, and there is evidence that their incidence is increasing," said Dr. Andreas Grassauer, CEO and Co-Founder of Marinomed. "The current array of treatment options, such as steroids, antihistamines, and mast-cell stabilizers, suffer from issues of low patient compliance. We therefore hope that MAM-06.301 will be a safe alternative with high compliance in the future and plan to initiate a clinical trial in due course. "

Marinomed Biotechnologie GmbH was founded in 2006 and develops therapies against respiratory diseases based on an innovative technology platform. The usability of this safe and effective technology has been proven by its first marketed product: an anti-viral nasal spray. The huge potential of the technology is reflected by Marinomed´s additional products concentrating on influenza, combination products for asthmatics, and other high-risk patients. In addition, the company develops a novel treatment against type I allergy and autoimmune diseases. Marinomed Biotechnologie GmbH is a spin-off from the Veterinary University Vienna and is located in Vienna, Austria.

Oramed Pharmaceuticals Reports Results of Phase IIb Trial of Oral Insulin Administration to Type 2 Diabetes Patients

Oramed Pharmaceuticals Inc., a developer of alternative drug delivery systems, recently reported results for its completed Phase IIb non-FDA clinical trial of its flagship oral insulin capsule, ORMD-0801.

The randomized, double-blind, placebo-controlled, multi-centered study conducted in South Africa evaluated responses of 29 type 2 diabetes patients to ORMD-0801. Insulin-loaded or placebo capsules were administered to patients who were closely monitored throughout the 6-week study period. Safety, tolerability, and efficacy parameters of Oramed's oral insulin were assessed.

ORMD-0801 was found to be well-tolerated and exhibited a positive safety profile. No cumulative adverse effects were reported throughout this first study of extended exposure to ORMD-0801. In addition, the percentage of subjects demonstrating clinically relevant reductions in insulin, c-peptide, fasting blood glucose, and Hb1Ac levels was always higher in the ORMD-0801 cohort, when compared to the placebo. Moreover, mean decreases in insulin and CRP levels were found to be statistically significant following the 6-week, once-daily ORMD-0801 treatment period. These findings suggest that ORMD-0801 attenuates insulin oversecretion, reprieving beta cells from their heightened activity. The reported results substantiate the safety and tolerability of ORMD-0801 and demonstrate that oral insulin has a relevant clinical impact at the tested dose. The data collected from this trial will help to further the development of ORMD-0801 in future, pivotal trials.

"The results of this trial once again underscore the safety of Oramed's oral insulin preparation," said Harold Jacob, MD, a member of the Oramed Board of Directors. "These results show a positive trend of efficacy for the tested oral insulin preparation."

"This study, as well as data from our earlier studies, suggests that Oramed's technology is an effective and well-tolerated delivery platform that will potentially make a significant clinical impact on diabetes management. We are proceeding with confidence toward IND approval in the US," added Nadav Kidron, Chief Executive Officer of Oramed Pharmaceuticals.

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Genzyme Receives FDA Approval for Lumizyme for Pompe Disease

Genzyme Corporation recently announced the FDA has granted US marketing approval for Lumizyme (alglucosidase alfa), produced at the 4000-liter bioreactor scale at its manufacturing facility in Geel, Belgium. Lumizyme is the first treatment approved in the US specifically to treat patients with late-onset Pompe disease.

"This is an important day for the Pompe community, especially for those patients with late-onset Pompe disease in the US who are awaiting treatment for this devastating disease," said Genzyme Chairman and Chief Executive Officer, Henri A. Termeer. "We are grateful to the FDA for their efforts to approve Lumizyme ahead of its scheduled PDUFA date."

Lumizyme (alglucosidase alfa) is a lysosomal glycogen-specific enzyme indicated for patients 8 years and older with late (non-infantile) onset Pompe disease (GAA deficiency) who do not have evidence of cardiac hypertrophy. The safety and efficacy of Lumizyme have not been evaluated in controlled clinical trials in infantile-onset patients, or in late (non-infantile) onset patients less than 8 years of age.

Genzyme began work on a therapy for Pompe disease 10 years ago, and the company has invested nearly $1 billion to support the development program. In 2006, Genzyme received approval for Myozyme (alglucosidase alfa) in Europe and in other countries outside of the US manufactured at a 2000-liter bioreactor scale and indicated to treat all patients with Pompe disease. At this time, Genzyme also received FDA approval for Myozyme manufactured at a smaller 160-liter bioreactor scale in the US, which because of its limited capacity, has been reserved for children and infants in the US. In 2009, Genzyme received approval outside of the US for manufacturing Myozyme in 4000-liter bioreactors at its state-of-the-art manufacturing facility in Geel, Belgium, and began to transition patients globally to the product manufactured at this larger scale. To prepare for growing demand for alglucosidase alfa, Genzyme has installed a third 4000-liter bioreactor in Geel with an anticipated approval in 2011.

Genzyme has worked closely with patients and physicians in the US Pompe community during the preapproval period to ensure that the most severely affected late-onset patients could access therapy in advance of Lumizyme approval. In May 2007, Genzyme began providing alglucosidase alfa free-of-charge to patients in the US through a program known as the Alglucosidase Alfa Temporary Access Program (ATAP). Nearly 200 severely affected adults in the US with Pompe disease are currently receiving treatment under the ATAP program. Genzyme will now work closely with the treating centers and prescribers to ensure that patients in the ATAP program can continue to access therapy during the transition to commercial supply. Genzyme will also begin working with US healthcare professionals to help adult patients who have been waiting to access treatment. In effort to preserve 160-liter scale product for infantile-onset patients, Genzyme will begin to transition eligible patients who are receiving Myozyme onto Lumizyme.

Because Genzyme will market two approved alglucosidase alfa products in the US, a Risk Evaluation and Mitigation Strategy called the Lumizyme ACE (alglucosidase alfa control and education) Program will be implemented for Lumizyme to ensure appropriate use for the intended patient populations. All prescribers of Lumizyme, and healthcare facilities where Lumizyme will be dispensed and administered, are required to be certified and enrolled in the Lumizyme ACE Program prior to treating patients with Lumizyme. Prescribers must also ensure patients enroll in the Lumizyme program prior to receiving therapy. Genzyme will begin this process immediately to certify and enroll prescribers and healthcare facilities and to help prescribers to enroll all patients that they intend to treat with Lumizyme.

Pompe Disease is a progressively debilitating disease that manifests as a broad spectrum of clinical symptoms. All patients typically experience progressive muscle weakness and breathing difficulty, but the rate of disease progression can vary widely depending on the age of onset and the extent of organ involvement. When symptoms appear within a few months of birth, babies frequently display a markedly enlarged heart and die within the first year of life. When symptoms appear during childhood, adolescence, or adulthood, patients may experience steadily progressive debilitation and premature mortality due to respiratory failure. They often require mechanical ventilation to assist with breathing and wheelchairs to assist with mobility.

to-BBB Technologies Announces Brain Drug Delivery Pilot Study With Janssen Pharmaceutica for CNS Diseases

to-BBB, the Dutch drug brain delivery company, recently announced it is entering into a pilot study with Janssen Pharmaceutica NV (Janssen) to enhance delivery of drugs to the brain for Central Nervous System (CNS) diseases.

"We are very proud to join forces with Janssen," says Pieter Gaillard, CSO of to-BBB. "to-BBB's brain delivery technology combined with Janssen's rich history in neuroscience discovery and broad range of potential compounds for brain diseases, will hopefully lead to new therapeutic options for patients."

Drug development for CNS disorders is hampered by the blood-brain barrier (BBB), which prevents the delivery of many drug candidates to their disease target in the brain. to-BBB's proprietary G-Technology is a safe technology for drug delivery to the brain. It is based on liposomes that are coated with the tripeptide glutathione at the tips of polyethylene glycol (PEG) to safely enhance the delivery of free drug to the brain. Proof- of-concept with the G-Technology is demonstrated in several disease models, including pain, brain tumors, and viral encephalitis.

Janssen Pharmaceutica NV is an international pharmaceutical company under the Johnson & Johnson group. With more than 80 drugs to its name, Janssen is one of the most innovative pharmaceutical companies in the world and its products have found major applications in human medicine. The pilot study with to-BBB will allow researchers of Janssen to investigate the capabilities of the G-Technology to enhance delivery of their investigational compounds to the brain.

to-BBB is a Dutch biotechnology company in the field of enhanced drug delivery across the BBB. The company is developing novel treatments for brain disorders by combining existing drugs with its proprietary brain drug delivery platform. The company's vision is that the treatment of currently unserved brain diseases will be best achieved by safely enhancing the blood-to-brain delivery of drugs.

Market News and Trends

Transave Issued Key Composition of Matter Patent for ARIKACE

Transave Inc. recently announced the US Patent and Trademark Office has issued an important composition of matter patent (US Patent No. 7,718,189) for liposomal aminoglycoside formulations, including its lead compound, ARIKACE (liposomal amikacin for inhalation). The company expects that the patent will provide exclusivity for ARIKACE until October 1, 2026.

"The issuance of this composition of matter patent significantly strengthens the intellectual property estate around ARIKACE and represents a valuable asset for Transave," said Tim Whitten, Transave's CEO. "We are continuing to secure and expand our proprietary position for ARIKACE, which has the potential to become an important treatment for cystic fibrosis (CF) patients with Pseudomonas lung infections, non-CF bronchiectasis patients with Pseudomonas lung infections, and patients with nontuberculous mycobacteria (NTM) lung infections. We look forward to moving to Phase III as soon as possible."

The company also announced that the US Patent office granted another patent (US Patent No. 7,544,369) last year covering ARIKACE for the sustained release of antibiotic and once-daily treatment of Pseudomonas lung infections.

ARIKACE is a form of the antibiotic amikacin, which is enclosed in nanocapsules of lipids (liposomes). This advanced pulmonary liposome technology prolongs the release of amikacin in the lungs while minimizing systemic exposure. The treatment uses biocompatible lipids endogenous to the lung that are formulated into small (0.3 micron), neutral liposomes that enable penetration of the biofilm. ARIKACE is administered once daily using a customized Investigational eFlow Nebulizer System (PARI Pharma GmbH), a novel, highly efficient, and portable aerosol delivery system enabling more effective distribution in the lungs.

Positive results were announced in October 2009 from pooled results of two Phase II clinical trials in the treatment of CF patients with Pseudomonas lung infections. The company also previously announced positive Phase II results in September 2009 in the treatment of non-CF bronchiectasis patients who have Pseudomonas lung infections.

ARIKACE has been granted orphan drug status in the US by the FDA, and has received an orphan drug designation in Europe by the European Medicines Agency for the treatment of Pseudomonas infections in patients with CF. ARIKACE has also been granted orphan drug status by the FDA for the treatment of bronchiectasis in patients with Pseudomonas or other susceptible pathogens.

Transave, Inc., is a biopharmaceutical company focused on the development of innovative inhaled pharmaceuticals for the site-specific treatment of chronic lung diseases. The company's major focus is on developing antibiotic therapy delivered via proprietary advanced pulmonary liposome technology in areas of high unmet need in lung diseases.

First Orally Bioavailable Anti-Obesity/Diabetes Peptide Drug Candidate to be Presented

Data demonstrating the efficacy of the first and only anti-obesity and anti-diabetic peptide drug candidate not requiring injection will be presented at the Endocrine Society Annual Meeting in San Diego, June 19-22 by Dr. Patricia Grasso. In 2000, researchers at Albany Medical College, in Albany, NY, under the direction of Dr. Grasso, made the discovery that injection of very small fragments of leptin, representing less than 6% of the total leptin molecule (a protein hormone exerting a critical role in curbing appetite), was effective in controlling appetite, blood glucose levels, and weight gain.

Additionally, this potential new drug is unique in that it also stimulates release of a natural peptide hormone that prevents bone loss during weight loss. Unexpectedly, subsequent studies revealed that these same beneficial effects were maintained when the drug was administered by a simple nasal spray, and most recently, in an oral form as well, using Aegis' patented Intravail® technology, offering the prospect of a highly effective pill to treat obesity in humans, with potential applications in treating diabetes as well. Other leptin-based drugs currently in development require injection as with insulin.

"Peptide drugs are particularly exciting for chronic disease applications because they metabolize to natural amino acids and thus are intrinsically devoid of the chemical toxicity issues that have plagued many of the earlier anti-obesity and anti-diabetic drugs," said Dr. Edward T. Maggio, CEO of Aegis Therapeutics. "The combination of Albany's highly effective peptide with Aegis' non-invasive Intravail peptide delivery technology promises to lead to the first orally active peptide anti-obesity and diabetes drug."

A number of issued and pending patents provide a broad commercial franchise for this drug and related peptides as well. Aegis and Albany Medical are now seeking appropriate pharmaceutical and biopharma company partners interested in the obesity and diabetes markets.

Aegis Therapeutics commercializes its patented drug delivery and drug formulation technologies through product-specific licenses. Its Intravail technology enables the non-invasive delivery of a broad range of protein, peptide, and non-peptide macromolecular therapeutics that can currently only be administered by injection with exceptionally high and unmatched bioavailability. Its ProTek® technology provides proprietary, easily manufacturable, aqueous dosage forms that are stable at elevated temperature and that reduce unwanted immunogenicity of many protein and peptide therapeutics.

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Market News and Trends

Intellipharmaceutics Announces Significant Advance in its Abuse-Deterrent Oxycodone Program

Intellipharmaceutics International Inc. recently announced it has achieved a significant advance in its program to develop and manufacture drugs incorporating abuse-deterrent characteristics. The company advises that it has taken delivery of and fully qualified its primary manufacturing equipment for the manufacture of an abuse-deterrent formulation of controlled-release oxycodone hydrochloride, and that the manufacture of clinical batches using that equipment has commenced. The successful manufacture of clinical batches is required to make the drug eligible for Phase I studies, and to establish a clinical program in cooperation with the FDA in order to facilitate advancement of the drug through the application process.

The drug delivery platform, branded Rexista, produces a unique dosage form designed to be deterrent to the well-documented abuses associated with currently marketed oxycodone products, such as the abuse of these drugs by nasal inhalation when crushed or powdered, and by injection when combined with solvents. Rexista products are also designed to deter release of the entire dose when consumed with alcohol, a significant problem with some opioid drugs. In 2008, controlled-release oxycodone drugs had US sales of approximately $2 billion.

“The qualification of this equipment is a significant step in our Rexista program,” said Dr. Isa Odidi, CEO of Intellipharmaceutics. “It involved the very difficult design and modification of certain aspects of the equipment to accommodate the novel and proprietary dosage form which we have developed for our Rexista drug program, namely a paste in a capsule. We have now commenced the manufacture of clinical batches of our oxycodone CR product using this novel delivery platform. The overall success we are having, including with Rexista and our two filed ANDAs for generics of Focalin XR and Effexor XR, is reflective of the capabilities and versatility of our proprietary technology platforms and our scientific and regulatory teams."

The company has announced that it and its licensee and development partner Par Pharmaceutical, Inc. received confirmation that the previously announced stays of the patent litigation concerning a generic version of Novartis' Attention Deficit Hyperactivity Disorder drug, Focalin XR (dexmethylphenidate hydrochloride), expired without regulatory intervention, and that the parties have stipulated to a dismissal of the litigation.

The parties, Intellipharmaceutics, Par, Novartis Pharmaceuticals Corporation, Novartis Pharma AG, Celgene Corporation, Elan Corporation, PLC, and Elan Pharma International Ltd., have also entered into license agreements in conjunction with the settlements of the litigation concerning the company's generic drug application in the FDA for 5-, 10-, 15-, and 20-mg strengths of dexmethylphenidate hydrochloride.

Intellipharmaceutics’ management presently expects that marketing of generic versions of the products will commence no sooner than the fourth quarter of 2012. The company has a 10-year profit-sharing agreement with Par for the sale of dexmethylphenidate hydrochloride XR capsules in the US, which commences with the commercial launch of the product by Par. Details of the license agreements remain confidential. In 2008, Focalin, including Focalin XR, had US sales of approximately $350 million. Intellipharmaceutics' application for approval of a generic version of Focalin XR remains subject to FDA approval.

The FDA has accepted the filing of the company's ANDA for a generic version of the antidepressant Effexor XR (venlafaxine hydrochloride). The company's application will now proceed to full review by the FDA. No assurance can be given as to whether or when the FDA will approve the company's generic version of Effexor XR. Intellipharmaceutics is actively seeking a commercialization and distribution partner for this product in the US. Total combined sales in the US in 2009 for Effexor and Effexor XR branded products were approximately $3 billion.

3M Drug Delivery Systems Introduces 3M™ Nasal MDI

3M Drug Delivery Systems is introducing the 3M™ Nasal Metered Dose Inhaler (MDI), a no-drip method of nasal drug delivery designed to drive patient preference. This new nasal inhaler has been shown through research to be patient preferred, with no post-nasal run-off, aftertaste, or drip, giving pharmaceutical partners a novel and effective way to deliver inhaled corticosteroids for allergic rhinitis and other nasal treatments.

The current use of aqueous pump sprays for allergic rhinitis has significant drawbacks for patients, as sprays that run back down the nose and drip down the throat are unpleasant both in sensation and taste, as well as unhygienic. These systems also have a short shelf-life once opened. The 3M Nasal MDI overcomes these limitations, however, with an evaporating spray technology that eliminates run-off, leaves no aftertaste, and won't irritate patients' throats. This delivery method can also increase a drug's shelf-life, and gives patients confidence the drug has been effectively delivered. The device's twist-and-lock cover cannot be misplaced, and its contemporary, non-breakable design makes it intuitive to use and improves hygiene.

For pharmaceutical companies, the device can help deliver a valuable competitive advantage versus aqueous pump sprays. The system does not require an aseptic manufacturing environment, and is compatible with existing valves and the 3M Integrated Dose by Dose Counter, contributing to its cost-effectiveness. It also utilizes technology that is familiar to regulators, developed utilizing 3M's more than 50 years in the MDI category. The 3M Nasal MDI offers pharmaceutical partners important life cycle management options for molecules coming off patent, as well as new molecules targeting nasal allergies.

In research, patients preferred the 3M Nasal MDI's no-drip system and sleek design to aqueous pump sprays and other nasal MDI designs, giving pharmaceutical companies an innovative way to differentiate their offerings. 3M is ready to perform initial feasibility studies combining partners' treatments with this new device.

3M Drug Delivery Systems partners with pharmaceutical and biotech companies to develop pharmaceuticals using 3M's inhalation or transdermal drug delivery technology. 3M offers a full range of feasibility, development, and manufacturing capabilities combined with regulatory guidance to help bring products to market. In-house resources, including toxicology, regulatory expertise, quality assurance, operations, and marketed product support, are available for each step of the development and commercialization process. This depth of resources is one reason why more than 50% of all MDIs worldwide and 80% of all transdermal systems in the US utilize 3M drug delivery technology.

Evaluation of In Vitro Dissolution Methods for the Assessment of Drug Release From Hydrophilic Extended-Release Matrices Based on Polyethylene Oxide

By: Marina Levina, MSc, PhD; Dasha Palmer, MSc; and Ali R. Rajabi-Siahboomi, PhD

INTRODUCTION

Hydrophilic matrices represent a popular and widely used approach for oral extended-release (ER) drug delivery. Hypromellose (hydroxypropyl methylcellulose, HPMC) remains the polymer of choice as the rate-controlling carrier.[1] In addition to HPMC, polyethylene oxide (PEO) has more recently been studied as a matrix-forming polymer.[2,3] This is mainly attributed to its availability in a range of molecular weight/viscosity grades, wide regulatory acceptance, and unique swelling and erosion characteristics, which are utilized for modulating release of drugs with different solubility and doses.

When in contact with water, PEO hydrates rapidly, swells to a larger extent than HPMC, and, similar to hypromellose, forms a gelatinous barrier layer around the wetted tablet.[4] Drug release occurs by diffusion of the active through the gel layer and/or by gradual erosion of the gel, exposing fresh surfaces for the drug to dissolve and release in the medium. The rates of wetting, swelling, and erosion are controlled by polymer molecular weight.

Polyethylene oxide is commercially available as POLYOX™, water-soluble resins, in a range of molecular weights (MW) for hydrophilic ER matrix system applications (Table 1). The in vitro drug release from hydrophilic matrix tablets may be affected by various factors and is often dependent on the hydrodynamic conditions used during dissolution testing.[1] Different dissolution apparatus operated at varying agitation intensities create different hydrodynamics.[5] This causes varying degrees of mechanical stress on the hydrated matrix, which may lead to alterations of polymer erosion rate, as well as a change in the thickness of the diffusion layer on the surface of the hydrated tablet.

Here, the influence of different dissolution methods and hydrodynamic conditions in a dissolution machine on the release of a freely soluble drug, metformin HCl, from an ER matrix formulation containing PEO as the rate-controlling polymer was evaluated.

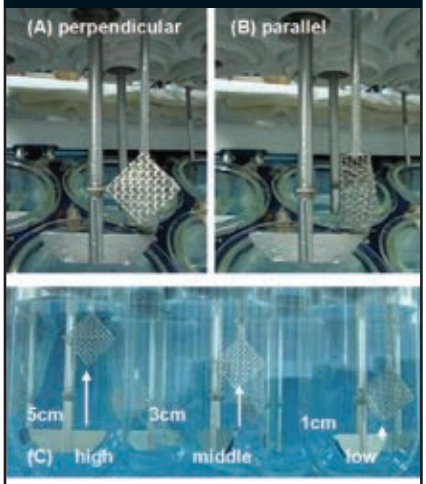
EXPERIMENTAL

Formulation, Manufacture & Testing of ER Matrices

A formulation containing 50% w/w metformin HCl (AMRI, India) as a freely soluble model drug, 30% w/w PEO (POLYOX WSR-1105, Dow Chemical Co., USA), 19% w/w microcrystalline cellulose (Microcel 102, Blanver, Brazil), 0.5% w/w fumed silica (Aerosil 200, Evonik, Germany), and 0.5% w/w magnesium stearate (Peter Greven, UK) was prepared. Microcrystalline cellulose (MCC) and fumed silica were screened together through a 35-mesh (500 micrometer) sieve. All ingredients except for the magnesium stearate were then blended in a Turbula mixer (Switzerland) for five minutes at 32 rpm. Magnesium stearate was finally added, and the formulation was blended for an additional one minute at the same speed.

Tablets with a target weight of 1000 mg were manufactured by direct compression using a 10-station rotary Piccola press (Riva, Argentina), fitted with 7 x 18 mm caplet tooling and operated at 20 rpm and 20 kN compression force.

FIGURE 1



Position of QBs in the dissolution vessel relative to the paddle.

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Tablet breaking force values (n = 20) were obtained using a hardness tester (AT4, Dr. Schleuniger-Pharmatron, Germany). Friability (n = 20) was determined using a friabilator (Copley, UK); at 25 rpm and four minutes running test time.

Drug Dissolution Testing

Drug release was measured in an AT7 (Sotax, UK) dissolution bath using a range of dissolution techniques at 100 rpm:

- USP I (baskets)
- USP II (paddles)
- USP II (paddles) with sinkers (11 x 31 mm, Sotax)
- 2.38 mm (8-mesh) stationary quadrangular baskets (QBs)[6] from Quality Lab Accessories (USA) and positioned within the dissolution vessel using the following configurations:
- Perpendicular or parallel to the shaft of the paddle (Figure 1A & 1B)
- In a low, middle, or high position (ie, 1, 3, or 5 cm) above the paddle (Figure 1C)

Finally, the effect of paddle speed (50, 100, 150, and 200 rpm) was evaluated for QBs positioned perpendicular and 3 cm above the paddle.

The dissolution medium was 1000 mL of purified water at 37.0 ± 0.5°C. Samples were analyzed with a dual beam spectrophotometer (PerkinElmer, USA) using 0.1 mm quartz cells at a wavelength of 233 nm. Measurements at each time point were performed in triplicate, and mean and standard deviation (SD) values were calculated.

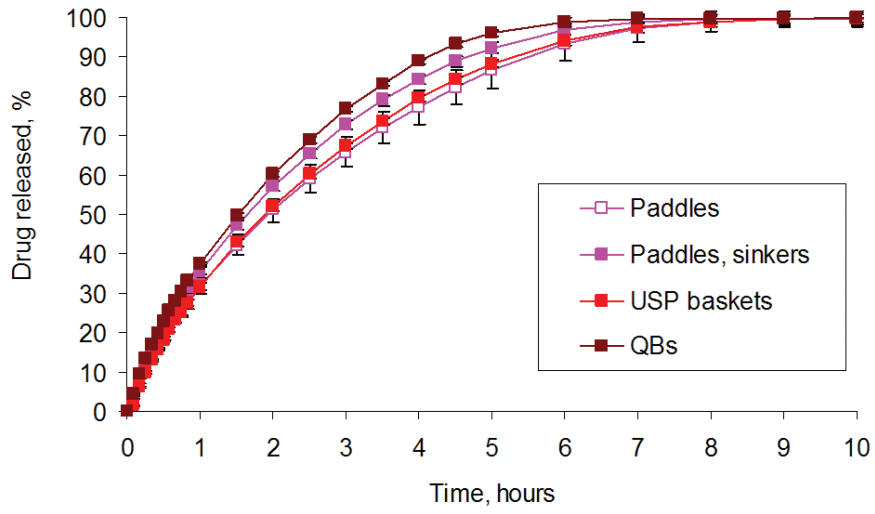
The dissolution results generated were compared using the *f2* factor.[7,8] An *f2* value between 50 and 100 indicates that the two dissolution profiles are similar.

TABLE 1

POLYOX™ NF Grades	Approximate Molecular Weight (Da)	Viscosity Range in Water at 25ºC (cP)		
		5% Solution	2% Solution	1% Solution
WSR-1105 LEO	900,000	8,800-17,600		
WSR N-12K	1,000,000		400-800	
WSR N-60K	2,000,000		2,000-4,000	
WSR-301 LEO	4,000,000			1,650-5,500
WSR Coagulant	5,000,000			5,500-7,500
WSR-303 LEO	7,000,000			7,500-10,000

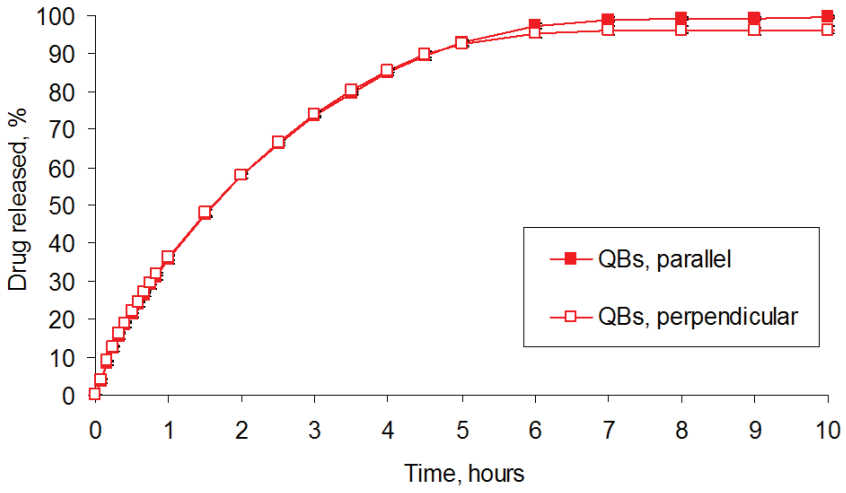
POLYOX™ Polymers Suitable for ER Matrix Applications (Courtesy of The Dow Chemical Company).

FIGURE 2



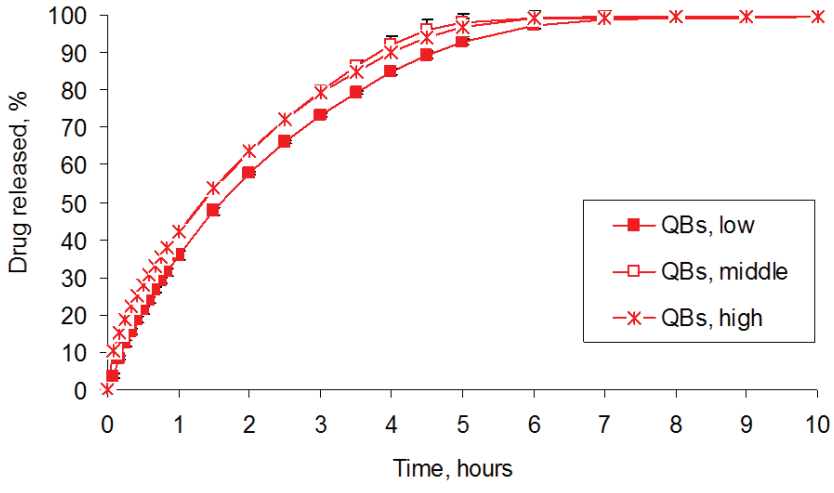
The influence of dissolution method on metformin HCl release from PEO ER matrices (100 rpm).

FIGURE 3



The influence of QBs position relative to the shaft of the paddle on metformin HCl release from PEO ER matrices (100 rpm).

FIGURE 4



The influence of QBs position above the paddle on metformin HCl release from PEO ER matrices (100 rpm).

RESULTS & DISCUSSION

Resulting tablets had a good breaking strength of 21.1 ± 2.0 kp and low friability values of 0.03%. Reproducible first-order drug-release profiles were obtained for all dissolution testing methods used in this study (Figure 2).

Figure 2 shows that metformin HCl release from PEO matrices was slightly, but not significantly, faster when QBs (*f2* = 57) or paddles with sinkers (*f2* = 62) were used, as compared to paddles without sinkers, all tested at 100 rpm. USP baskets produced a profile similar to the dissolution data obtained with USP II method (*f2* = 91).

The use of QBs resulted in the most reproducible results with SD values of less than 1.3%. The USP II (paddles) method resulted in the highest SD values of up to 7%. This can be explained by the fact that some PEO matrices were found to stick to the bottom of the dissolution chamber or float onto the surface of the dissolution medium, resulting in a variable drug release.

Figure 3 shows that the position of the QBs relative to the shaft of the paddle had no significant effect on drug release from PEO matrices (*f2* = 80). Additionally, positions of the QBs 3 cm or 5 cm above the paddle resulted in a slightly faster metformin HCl release compared to the lower position of 1 cm with *f2* values of 57 and 60, respectively (Figure 4). These results confirm one of the findings of McCarthy, et al., that an

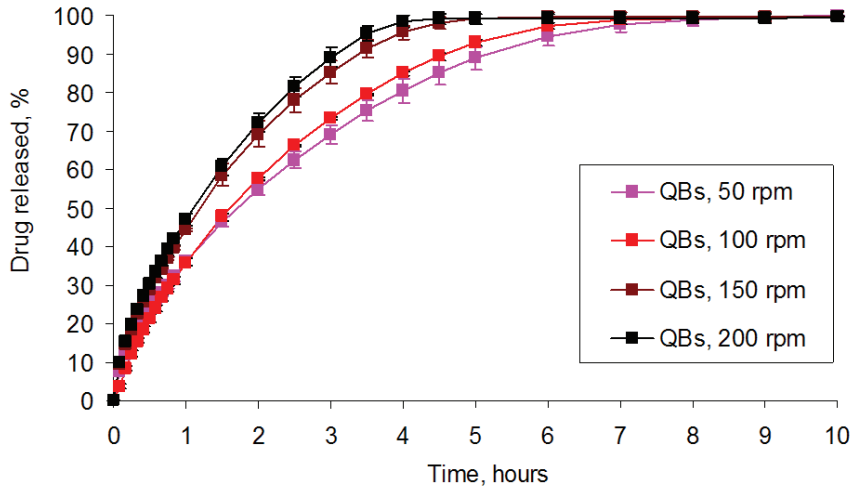
area of relatively low fluid velocity exists just above the paddle, resulting in a slightly slower drug release.[9]

Drug release from hydrophilic matrices is controlled by diffusion through the gel layer and erosion of the gel at the tablet surface. For metformin HCl, a freely soluble compound, the rate of release from the matrix is predominantly controlled by diffusion.[10] Drug release from such formulations is often independent of the hydrodynamic conditions within the dissolution vessel.

For the PEO ER matrices studied in this discussion, drug release was faster from matrices placed in QBs when higher paddle rotational speeds of 100 rpm (*f2* =72), 150 rpm (*f2* = 50), and 200 rpm (*f2* =46) were employed, compared to 50 rpm (Figure 5). This may be due to the formulation containing low molecular weight polymer (WSR-1105, MW = 900,000), and therefore, faster erosion may be expected under increased agitation intensity. When higher molecular weight polymers, WSR-301 (MW = 4,000,000) or WSR-303 (MW = 7,000,000), were used in this formulation, no significant effect of medium agitation rate on drug release was recorded.

At all rotational speeds, reproducible release profiles were obtained with standard deviations of less than 3% at all time points.

FIGURE 5



The influence of paddle speed on metformin HCl release from PEO ER matrices using quadrangular baskets.

CONCLUSIONS

The selection and development of a discriminatory dissolution methodology is an important tool to guide formulation development, assess stability on storage, and to use as a routine quality measure in production. The unique properties of polyethylene oxide in terms of high swelling and gelling can create challenges for the analytical method development, which requires careful consideration of the dissolution method used to assess product performance.

Reproducible first-order metformin HCl release profiles were obtained from POLYOX matrix tablets, for all dissolution testing methods used in this study. Metformin HCl release from PEO matrices was slightly, but not significantly, faster when QBs or paddles with sinkers were used, as compared to paddles without sinkers. USP baskets produced a profile similar to the dissolution data obtained with USP II method.

The position of the QBs relative to the shaft of the paddle had no significant effect on drug release from PEO matrices. Additionally, positions of the QBs 3 cm or 5 cm above the paddle resulted in a slightly faster metformin HCl release compared to the lower position of 1 cm.

Drug release was found to be faster from matrices placed in QBs at higher paddle rotational speeds.

The use of QBs resulted in the most reproducible dissolution results with SD values of less than 1.3%. Therefore, quadrangular baskets may be recommended wherever possible instead of USP I (baskets) and USP II (paddles). Alternatively, USP II with sinkers can be

utilized for in vitro drug dissolution testing of hydrophilic matrix tablets based on POLYOX.

This work demonstrates that quadrangular baskets easily fitted to the existing apparatus can provide a useful alternative to traditional testing methods for in vitro drug release, eliminating the variability associated with sticking of hydrated matrices to the bottom of the vessel or tablet floating onto the surface of the dissolution medium.

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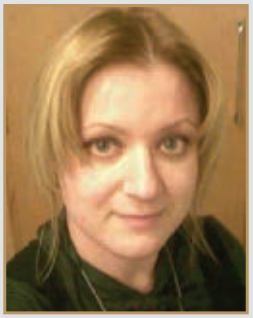
BIOGRAPHIES

Dr. Marina Levina is a Senior Manager within Product Development of Colorcon. She has 10 years of experience working with excipients, responsible for technical aspects of Colorcon's range of immediate- and modified-release products. Dr. Levina has published over 50 research abstracts and papers in the area of pharmaceutical technology and presented at various conferences and seminars.



Dasha Palmer is a Scientist within Product Development of Colorcon. She has 5 years of experience working with Colorcon's film-coating systems and excipients for immediate- and modified-release applications.

Dr. Ali Rajabi-Siahboomi is Senior Director of Scientific Affairs at Colorcon. He has held various academic positions in Nottingham and Liverpool JM Universities before joining Colorcon. His main research interests are focused in the areas of solid dosage form pharmaceutics and pharmaceutical technology with an emphasis on oral drug delivery systems. He has published over 150 articles, book chapters, abstracts, and patents.

ADVANCED DELIVERY DEVICES

A Compact, Controllable, Implantable Delivery Device Driven by Electro-Osmosis

By: Sai Bhavaraju, PhD; John Gordon, MS, MBA; and Ashok Joshi, PhD

MicroLin LLC has demonstrated feasibility of a compact, implantable, drug delivery device technology driven by electro-osmosis. Delivery rate is dependant on the resistance in a circuit and can thus be controlled electronically. The device may be started electronically, stopped, and delivery rate adjusted via wireless communication. The device is simple in design with a single moving component compared to the alternative mechanical- and gas-driven technologies, thus the pump enables size reduction compared to conventional, controllable, implantable pumps. Data is presented showing fast response time, and the technology has been demonstrated in vivo in rabbits at target rates of 1.4 microliters per hour over an 8-week period with excellent histopathology at the implantation site. Several examples of potential applications are described.

BACKGROUND & CURRENT TECHNOLOGY

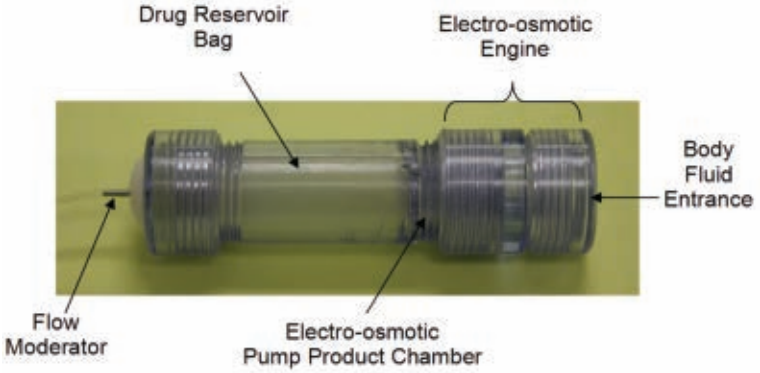
Feasibility has been demonstrated of a compact, implantable, drug delivery device technology that is driven by electro-osmosis that can be controlled electronically. To improve the effectiveness of a drug therapy, direct administration to a specific site within a patient's body may be preferred, especially when appropriate concentrations cannot reach the target site by systemic administration or when systemic dosing results in adverse side effects.[1] Representative examples of body sites that are difficult to treat using systemic administration include the eye, knee, and central nervous system. Certain cancers, such as breast cancer or meningiomas, where large doses of toxic chemotherapies (ie, rapamycin, bevacizumab, or irinotecan) are typically administered to the patient intravenously, may result in numerous undesired side effects outside the targeted area.[2]

Examples of drugs that can be delivered into targeted areas within the patient's body space include morphines, heparins, and similar drugs, protein therapeutics, small-molecule drugs, neurotrophic factors, anti-inflammatories, anti-angiogenics (eg, anti-vegf), anti-virals, anti-bacterials, and anti-neoplastics, anti-hypertensives, anti-atherosclerosis and anti-diabetics drugs. Other examples include immuno-suppressants to reduce rejection of transplanted organs, cytostatins for treatment of tumors, insulins, and the like. The drug may advantageously be delivered into an arterial vessel. Systemic drug administrations for treating the aforementioned conditions may have additional reactions. For example, oral medications can have systemic side effects; topical applications may sting and engender poor patient compliance; and injections generally require a medical visit, can be painful, and risk infection.

As an alternative to systemic administration of drugs, implantable pumps are now being used in patients who require the delivery of drugs to specific areas of their body.[3,4] Pumps are advantageous because a steady concentration at the site is achievable at the therapeutic concentration. Treating physicians widely recognize the benefits of utilizing an implantable pump.

Implantable drug delivery pumps may be either passive or active. Passive pumps can only provide a single dosage rate.

FIGURE 1



Microlin Electro-Osmotic Drug Delivery Device

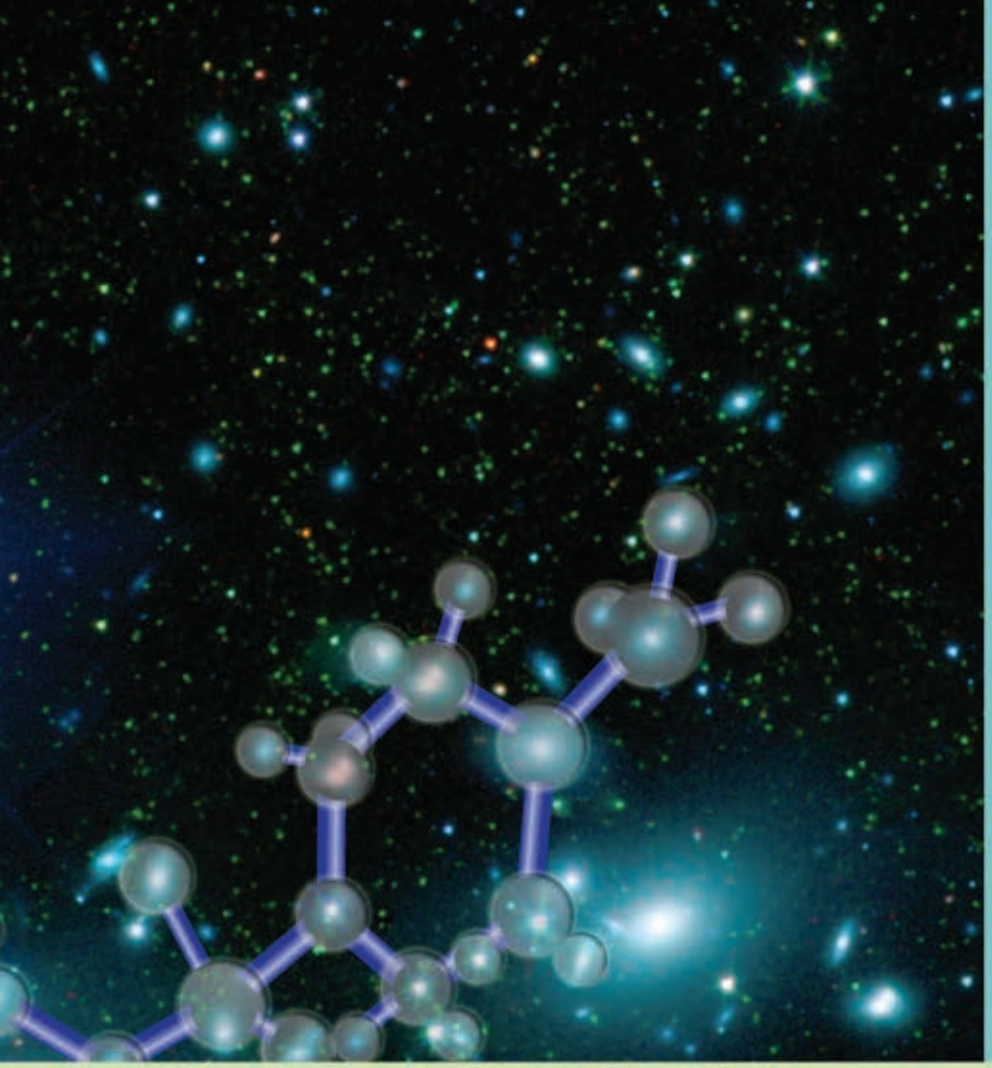


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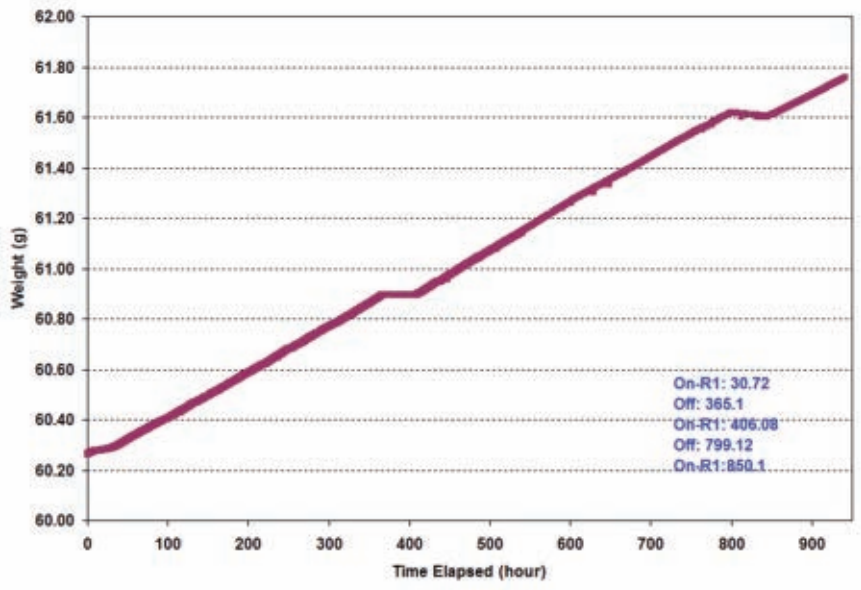
FIGURE 2



Weight Delivered Versus Time of the Microlin Electro-Osmotic Device

Passive drug delivery devices typically rely upon a pressurized drug reservoir to deliver the drug, which is then delivered to the patient using force provided by the pressurized reservoir. Passive drug delivery devices include erodible polymer-drug systems (eg, Oculex Pharmaceuticals, BDSI Inc., ULURU Inc.), porous membrane systems (eg, mPhase technologies, iM MED, Inc.), and osmotic pumps (Alzet). The passive devices must be removed after their supply is exhausted and offer only limited ability to change the dose in response to the clinical picture.

Active drug delivery devices are variable rate devices and usually include a metering pump system to deliver the drug. Pumps of this type provide variable flow rates, typically through the use of a solenoid pump or a peristaltic pump. A benefit of a variable flow rate pump is that rate can be adjusted to the clinical need. In the solenoid pump, the flow rate of medication fluid can be controlled by changing the stroke rate of the pump. In the peristaltic pump, the flow rate can be controlled by changing the roller velocity of the pump. However, both of these types of programmable pumps require intricate designs with many moving parts and complicated controlling mechanisms. The devices are electrically powered and include a battery for operating the pump, the electronic circuitry used to control flow rate of the pump, and to communicate through telemetry to an external device to allow programming of the pump.

Active devices range from electronically controlled rate dispensers to fully programmable infusers. Examples of commercial pumps of this type include Synchromed™ manufactured by Medtronic and MIP™ manufactured by Minimed.[5] These devices offer sophisticated control and are effective for regional drug delivery, but typically, they require bulky outer housings for accommodating the drug, propellant chambers, and other mechanical parts. These exemplary systems require pumps of a size that may be too large for implantation in cramped sites, such as the brain, eye, or ear. They are typically implanted in subcutaneous tissue in the torso. Although clearly beneficial to patients and doctors that utilize them, one area in which active implantable pumps can be improved is in size reduction and volume efficiency. As such, it would be more desirable to utilize pumps having designs similar to the aforementioned passive constant flow pumps, but with the capabilities of active pumps.

To address this need, Microlin developed an implantable pump that enables size reduction, has an uncomplicated design (especially for constant flow rate), and can be designed easily for variable flow rates or semi-continuous flow rates. Microlin's drug delivery device is based on electro-osmotic pumping principle, which has the advantage of being volume efficient and simple like an osmotic device, but the delivery rate is a function of the current flowing through a circuit connecting two electrodes within the device.

PROOF-OF-PRINCIPLE

A photo of the "breadboard" Microlin drug delivery device tested is shown in Figure 1. This device had a 2-cc volume drug reservoir and was about 4 cc overall in size but will be trimmed down to 2.5 to 3 cc in a more refined design. As the Figure shows, the drug delivery device comprises a drug reservoir contained within a displaceable member, an electro-osmotic pump product chamber, an electro-osmotic pump, and

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housing. The reservoir contains the drug, which is delivered upon displacement of the displaceable member. The drug could be in the form of a liquid, gel, paste, or other semi-solid material that is capable of being delivered out of the reservoir. The reservoir is fabricated out of biocompatible material, such as polycarbonate or titanium. The displaceable member may be a bladder, a diaphragm, a bellows, or a plunger.

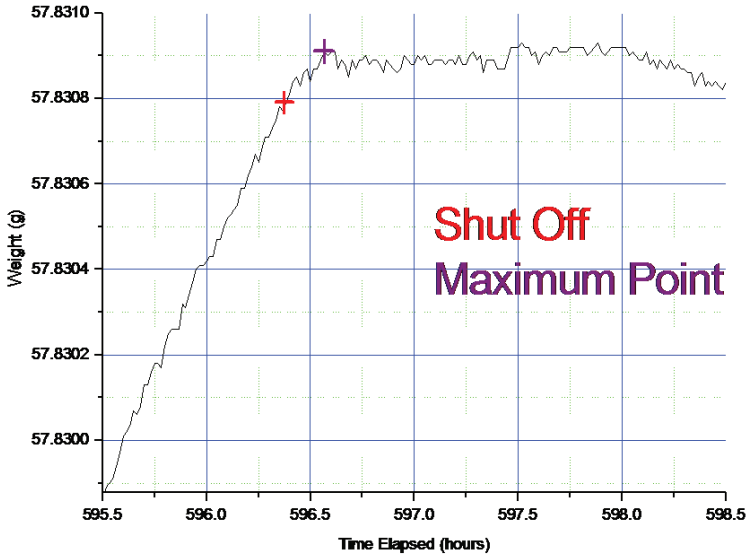
The electro-osmotic pump product chamber is positioned between the displaceable member and the electro-osmotic pump, and is capable of containing water that is controllably generated during operation of the electro-osmotic pump.

The electro-osmotic pump includes an external electrode, an ion exchange membrane, a membrane support member (that provides mechanical rigidity to the membrane), and an internal electrode. The internal electrode is positioned within the electro-osmotic pump product chamber. The ion-exchange membrane separates the electro-chemical pump product chamber containing the internal electrode from the surrounding body fluid. The external electrode may be positioned inside the device or can be positioned entirely away from the housing or on the outside wall of the device, in which case the ion exchange membrane has more direct access to the body fluid. A porous separator can be placed directly adjacent to the ion exchange membrane to prevent biofouling of the membrane.

PRINCIPLE OF OPERATION

After considering several types of electrode types and configurations, a system using a zinc external electrode (anode), silver chloride internal electrode (cathode), and a cationic ion exchange membrane was found to be best suited for an implantable application. The electro-osmotic pump is operated by simply connecting the two electrodes with a resistor in the circuit, resulting in electrical current passing between the two electrodes galvanically. The word galvanically is used because no external power source is required.[6,7]

FIGURE 3



Shut-Off Behavior of the Microlin Electro-Osmotic Pump

At the Anode

The external electrode, zinc, is oxidized according to the following reaction:

$Zn \rightarrow Zn^{2+} + 2e^-$ (Reaction 1). Sodium (Na^+) ions present in body fluid migrate under an electrical potential through the membrane into the electro-osmotic pump product chamber toward the silver chloride electrode. As sodium ions transport through the membrane, neutral water molecules associated with the ions are drawn across the membrane, increasing the liquid mass in the electro-osmotic pump product chamber. This water transport is known as electro-osmotic drag.

At the Cathode

The internal electrode, silver chloride (AgCl cathode), is reduced to metallic silver-releasing chloride ions into solution according to the equation: $2AgCl + 2e^- \rightarrow 2Ag + 2Cl^-$ (Reaction 2). As a result of chloride ion released from the cathode and sodium ion entering through the membrane, the sodium chloride concentration in the pump product chamber typically is greater than in body fluid, thus there is an additional osmotic driving force for water transport across the membrane. Transport across the membrane results in pressure within the electro-chemical pump product chamber that, in turn, imparts a force upon the displaceable member (the only movable component), which controllably expels drug from the reservoir through a catheter until it is delivered to the target site.

The aforementioned device and process enables a controlled delivery of a drug over an extended period of time at a precise and accurate rate in as much as the water transported is proportional to the current,

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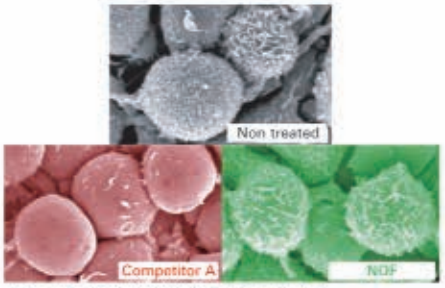

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which in turn depends on the value of the resistor.

A controller can be connected to the electrodes to vary the delivery rate of the device and can be positioned within, external or remote from the body. In simple form, the controller can be a resistor, but may also be a more complex circuit, variable resistor, multi-position switch, wave-form generator/processor, or switch that uses electro-magnetic induction, RF signaling, infrared, magnetism, mechanics, or transduction for communication. The controller may or may not contain a battery. An activation switch is connected to the controller and can be of the electronic, ionic, or mechanical type and capable of being controlled remotely via the controller.

IN VITRO PERFORMANCE CHARACTERISTICS

In vitro experiments were performed at 37°C in electrolyte-simulating body fluid. The experiments involved complete immersion of the device; liquid in the drug reservoir flowed to a precision balance where the liquid weight dispensed was measured over time. The circuit between electrodes included a resistor and an on/off switch.

The major performance highlights of the Microlin device from in vitro testing include the following:

- Up to 2 months continuous operation is demonstrated. Figure 2 shows a typical dispense curve of 2 cc. Microlin device in simulated body fluid with 2 shut-offs and restarts. Figure 2 shows the device consistently delivered reservoir contents at a rate of 1.85 microliters/hour.
- Linearity of the delivery rate with current demonstrated over a range of 0.6 to 4.4 microliters/hour/cm^2.
- Device performance is independent of orientation.
- Both piston type and bag designs demonstrated steady delivery.
- Operational pressure of up to 325 psi has been demonstrated in a piston-type device.
- The typical shut-off response time (time for the device to stop delivering once the current is shut off) is typically less than 15 minutes. An example of a pump shut-off is shown in Figure 3. Figure 3 shows that after shut-off (red plus) it takes less than 10 minutes before the device stops pumping (purple plus).
- The volume of the electro-osmotic pump to the overall device volume is less than 33%.
- Best cationic ion exchange membrane selected to obtain the lowest pump-to-device volume ratio and best switch-on and shut-off response times.

IN VIVO PERFORMANCE CHARACTERISTICS

Three animal studies have been conducted to determine which of the various component choices and structure configurations are best suited for in vivo operation. Each of these studies involved subcutaneous implantation except for a few that were implanted intra-peritoneally.

Devices where found to deliver at a steady rate of about 1.4 microliters/hour for 8 weeks, the final time point of the study. After 8 weeks of operation, there was no adverse reaction between the device and the tissue. According to the histopathologist who examined surrounding tissue and who witnessed the explantation, the reaction to the device from the body was similar to what would be observed from the implantation of any inert material.

SUMMARY

In summary, the Microlin drug delivery device has many beneficial features. It can deliver drugs in a continuous or intermittent mode with precise dosing within the therapeutic range, resulting in lower overall dosages, decreased exposure of the target site to the drug, and decreased distribution to non-target tissues. The present device is an adjustable rate device in which delivery rates less than 1 microliter/hour are achievable, including the delivery of concentrated or viscous drug formulations that may require elevated pressure. The device is simple in construction with one moving part (reservoir wall), and the overall dimensions are compact and volume efficient. The device shape can be adapted to the delivery region or for the specific intended use.

An example application of the Microlin device is for implantable drug delivery, where limitations associated with absorption of drugs through the gastro-intestinal tract or limitations in crossing the brain-blood-barrier are overcome. The device is constructed of sterilizable, biocompatible materials and lends itself to be integrated with a sensor and controller, allowing rate variation in response

to a bioresponse variable. Future versions may be designed to have a refillable drug reservoir. ◆

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BIOGRAPHIES

Dr. Sai Bhavaraju is a Senior Scientist at Microlin LLC and at Ceramatec, Inc. He joined the company in 2001 as a scientist working on the development of the Electro-osmotic Pump Drug Delivery Device and was involved in the designing, assembly, and testing of the breadboard prototype devices in vivo in rabbits. Dr. Bhavaraju has also contributed toward development of a wound closure device and wound delivery device that are presently at later stages of commercialization. He is lead researcher on industrial applications of sodium ion conducting membranes and has actively worked with researchers from many corporations, such as DuPont, P& G, Kobe Steel, and ADM on these projects. Dr. Bhavaraju earned his PhD at the University of Houston in Inorganic Electrochemistry.

John Gordon is Product Development Manager of Microlin LLC. He has been developing electro-chemical technologies, filing over 60 patents. Beginning in 1992, he began developing electro-chemical gas generators for applications, including drug delivery, later medical oxygen sensors, and more recently, developing implantable electro-osmotic pumps and wound-healing technologies. Mr. Gordon was Engineering Manager of Ceramatec Analytical that manufactured and sold devices for medical applications in compliance with Good Manufacturing Practices (GMP), Food and Drug Administration (FDA), and International Standards Organization (ISO) requirements. He earned his MS at Columbia University and his MBA at University of Utah.

Dr. Ashok Joshi is President of Microlin LLC and is a well-recognized innovator and high-technology entrepreneur for the past 25 years. Dr. Joshi has developed several technologies in the energy, environmental, and biotech fields; he is inventor of more than 75 issued US patents, and has over 40 pending US patents. He was responsible for commercializing 5 products, 2 for institutional use, 2 for medical use, and 1 for industrial use. Dr. Joshi founded 6 other companies of which he sold 3, and still runs with an active interest in 3. He earned his PhD from Northwestern University.

REFORMULATING SUCCESS

How to Choose a CRO

Part 3 of a 6-part series on business models & best practices for navigating the new normal.

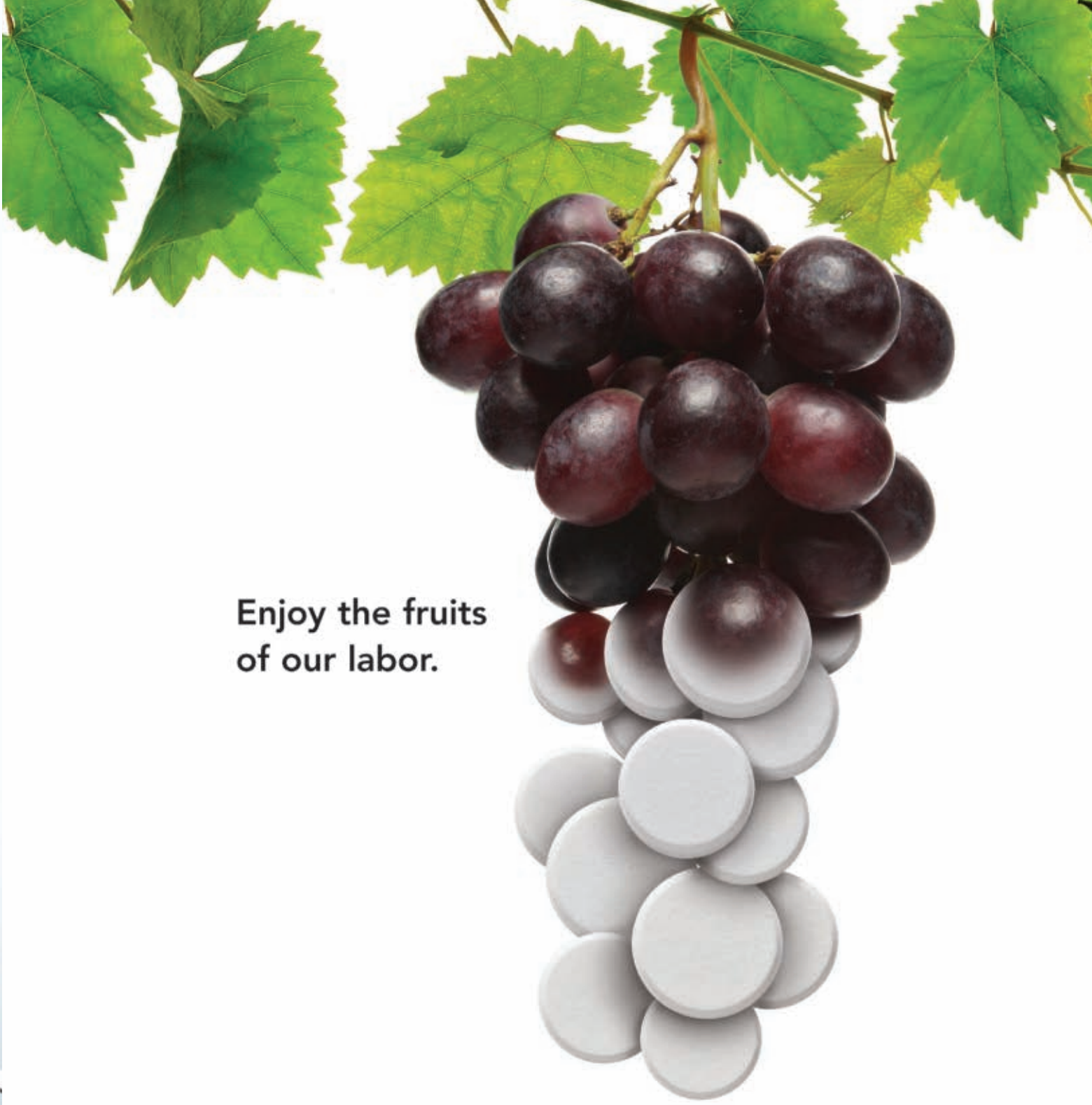
By: Derek Hennecke, President & CEO Xcelience LLC

A recovery by any other name - would it smell as sweet? The sights and sounds of recovery abound. Housing prices and sales are stabilizing, corporate revenues are up, and the stock market is looking healthier by the day. So why don't I feel happy yet? Because our industry, though like a phoenix reborn from the ashes, is still suffering growing pains.

The rumored collapse of Azopharma in Florida this past April was part of that suffering. The recovery is supposed to be well underway, and yet in April, we heard that hundreds of employees lost their jobs there. Many clients, similarly, were thrust into the situation of not knowing where their samples were and in what condition. No one would wish Azopharma's outcome on anyone, and yet, it is part of our rebirthing. We live in a New Normal, and some companies don't make the cut. In Azopharma's case, part of the reason can be traced to its own strategy. It grew too quickly. Marketing spending was inappropriate relative to its size and was probably indicative of other spending practices as well. I know first-hand the company had some very good scientists, but the science was married to a strategy reminiscent of the Dot Com era, which involved building as many visitors as possible as quickly as possible regardless of the resources required to support them.

But there's more to it than that. I believe part of the reason Azopharma has failed is that our industry's clients are being far, far choosier than ever before. And that can only do the whole industry good. There are and probably always will be many CROs, simply because there are low-entry barriers. The problem is that there are also high-exit barriers. That means for a certain percentage of start-ups, things go well, until they don't. Then they implode, the company disappears, and the client gets burnt.

What separates the good from the bad is often not good science.



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Good science is a given. Without it, word gets around and the CRO won't last a year. The CRO landscape is scattered with the corpses of companies set up by a handful of good scientists, and nothing else. What they lacked was a customer-driven strategy to guide the scientific process where the client wants it to be.

Clients for many years put up with a lot from these CRO start-ups. They put up with project delays, disruptions, quality issues, employee turnover/loss of project knowledge, and other inefficiencies. In the New Normal, they're not having it anymore. Clients are demanding not just good science at good prices, but also quality, speed, reliability, efficient business practices, and so much more. Enough of them have been burned that in choosing a CRO, they're looking deeper. It's no longer enough to ask if anyone knows a good CRO and go with the recommendation. I believe very strongly this new client is going to change the industry fundamentally and drive it to new and better heights.

The following are some of the fundamental criteria today's client is (and should be) looking for in a good, solid CRO that will be there until your project is completed and beyond.

SLOW & STEADY GROWTH

Hyper-growth is a red flag. I once worked at a company that sky-rocketed from 80 to 250 people in 2 years. It's extremely challenging for management to reign in a horse that's stampeding. Some months after I left, the horses went over the cliff. Current staff count is zero.

Similarly, watch for out-of-control M&A strategies. What is the quality of the pieces they are picking up? Are they overextending themselves? Can they control and integrate the bits?

NO SIGNIFICANT LAY-OFFS

Overzealous hiring may be a red flag, but so is overzealous firing. Letting a lot of people go can be the first sign of an imminent failure, throwing your project into a risky situation. Even if the CRO's financials seem solid enough, the lay-off is going to significantly reduce capacity, which means you should wonder if they will have the capacity for your project when they say they will - or will it be delayed? Will they make more lay-offs letting people with your project-knowledge go? Will they have to hire (more delays) and train staff to be able to take on your project?

LONGEVITY

There are undoubtedly some brand new companies out there that are very good, and have a bright future, so this is by no means a make-or-break thing. But in an industry with a high turnover rate, there is simply no substitute for a proven track-record.

LARGE-PHARMA FOLLOWING

The big companies vet extremely thoroughly, with their due diligences often spanning months or years. Pursuing these large pharma companies is not for the faint-hearted and requires a long-term orientation to dedicate sales people and equipment purchases. A CRO that consistently wins over the big guys is most likely the real thing.

SYSTEMS & UPKEEP

Does the service provider have an integrated IT architecture? Do all the HPLCs run off a common CDS system or are they all stand-alones? A commitment to investing back in the business is important. Is the company investing in new equipment and capabilities? Are those purchases paid for by leasing or from the company's cash reserves? Leasing is not necessarily bad, but too much puts more pressure on future sales to cover the monthly rent. Same goes for the building. What does the facility look like? Good upkeep and maintenance? Does the facility look like a rabbit warren? Growth comes in small stages, so it is natural to add space here and there. However, eventually the owner has to come back to the table and build a bigger, better location that has a good flow of people and materials. Also, look for clues like being in the same place. Employees who work on different floors of the same building interact 50% less than those on the same floor.

ASK YOUR FRIENDS, BUT…

Our industry relies heavily on word of mouth and checking with our friends for testimonials and references. In some cases, this is

useful, but in many cases, it isn't. In our industry, there's not a lot of feedback learning. When your child is learning to ride a bike, he or she falls a few times, learns from the mistake, gets back up, and keeps going. In the CRO industry, it can be 2 years after a project before you find out if something worked or not. That feedback is too little too late for learning. You also can't assume the CRO that worked for your friend will work for you. There are two reasons for this. One is that your project is probably different, using different science and equipment. The other is that the CRO environment itself isn't stable enough. Imagine your friend recommending Azopharma to you 3 months ago because they had successfully completed a project there. By all means, accept the suggestions of friends and colleagues as a starting point then conduct your own due diligence.

MEET THE MANAGEMENT

Always, always, meet management and look them in the eye. Listen to your gut. Remember though that you're not necessarily looking for the ultra-confident charismatic guy with the powerful story. This type of leader can be risky. While they can be associated with some pretty impressive home runs, the truth is, the majority of them are associated with volatile company performances. They take big risks in acquisitions, shift into new fields, and change strategies with the direction of the prevailing wind. Give me any day the type of manager I read about in an op-ed article titled The Humble Hound, by David Brooks. "The humble hound leader thinks less about her mental strengths than about her weaknesses," writes Brooks. "She knows her performance slips when she has to handle more than one problem at a time, so she turns off her phone and e-mail while making decisions. She knows she has a bias for caution, so she writes a memo advocating the more daring option before writing another advocating the most safe…

In short, she spends a lot of time on metacognition - thinking about her thinking - and then building external scaffolding devices to compensate for her weaknesses." Such a leader rarely seeks the glory or the loud applause, but navigates competently and carefully. She doesn't believe in radical shifts in behavior or perpetual restructuring. When I'm vetting a company - be it for a partnership, as a supplier, or what have you - I'd take this leader over the vain flashy type any day. I've seen too many of the other type fall. And I'd add one more caveat to Brooks' description - he or she should also exhibit integrity in every decision. Watch for messy backgrounds - persistent rumors of unethical behavior; rumors they don't pay all their bills, etc. Even rumors of unethical personal behavior are often indicative of character in general. If they don't treat others well, you won't be any different. Love the company that asks for feedback.

We have a standing joke in Xcelience that someone will thank a QA auditor for the free advice. Every new pair of eyes finds new things. It amazes me how many things can always be improved even after you have 1 to 2 client visits every week.

So go ahead dear reader - rake my company over the coals. Demand the most. Conduct a thorough due diligence. I'm ready to meet your discerning eye. I will do my utmost to live up to your increasing expectations. Together we will emerge from the ashes and make our industry stronger, more stable, and more efficient and reliable than ever. ◆

BIOGRAPHY

Derek G. Hennecke, MBA
President & CEO
Xcelience

Derek G. Hennecke is a founding member of Xcelience and its current CEO and President. He has a long history of growing strong businesses around the world. He balances a scientific and business background with nearly 2 decades of international experience in the healthcare industry and a track record as a highly successful international turn-around manager in the global drug development community. Xcelience is the first company Mr. Hennecke has managed as an owner, having launched a management buy-out from MDS Pharma Services in 2006. The newly formed company immediately embarked on a robust pattern of strong growth. This growth was recognized in May 2008, when Mr. Hennecke was selected as a finalist for the coveted *2008 Ernst & Young Florida Entrepreneur of the Year* award, a nomination based on the demonstration of extraordinary success in the areas of innovation, financial performance, personal commitment to community, and the company's perpetual growth since its official formation. Mr. Hennecke was also recognized as a finalist for the *Ultimate CEO* awards by the Tampa Business Journal in 2008. This is in addition to Xcelience's nomination for *Small Business of the Year* by the Greater Tampa Bay Chamber of Commerce, also this year. Before founding Xcelience, Mr. Hennecke managed the same Tampa-based business while also overseeing a Seattle and a Montreal-based plant as Vice President and General Manager, Pharmaceutics and Biopharmaceuticals. Prior to that, he spent more than 10 years abroad working for the Dutch-based conglomerate DSM. In Montreal, he was GM of a 250-staff Biologics plant for more than 2 years. In Cairo, Egypt, as GM, he oversaw a radical turn-around in an anti-infectives plant that was originally slated for closure. He also spent 2 years in Holland developing new Pharma intermediates, and two years in Mexico as Commercial Director covering Central and South America. He also worked for Roche, both in Canada and Germany. Mr. Hennecke earned his BSc in Microbiology from the University of Alberta in Canada and his MBA from the Erasmus University in Rotterdam, The Netherlands.

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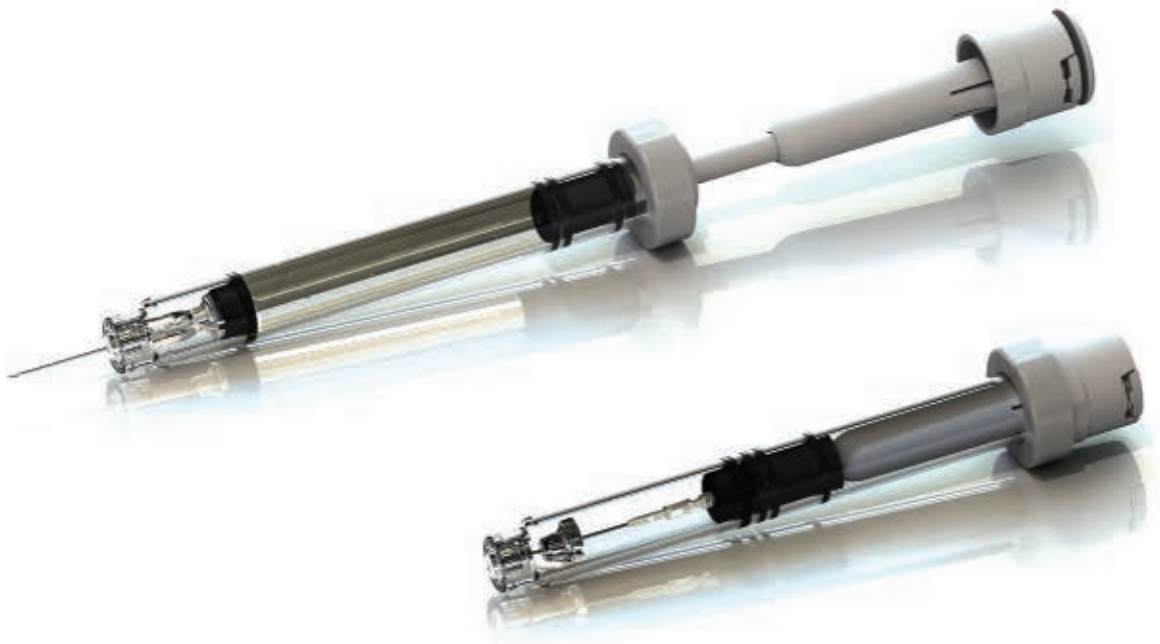

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SPECIAL FEATURE

Prefilled Syringes Gain Favor With Pharma, Caregivers & Patients

By: Cindy H. Dubin, Contributor

Prefilled syringes continue to gain attention in drug delivery because of the value they offer in improving administration, patient compliance, increased safety, and dosing accuracy. As a result, prefilled syringes are a growing alternative to vials for many of today's parenteral products. Pharmaceutical companies recognize the advantages of prefilled syringes with specific regard to preventing dose overfill (healthcare workers appreciate the convenience), and patients find reduced discomfort and ease of self-administration.

Prefilled syringes are used to package injectable drugs and vaccines. Some of the therapeutic drug classes in which drugs are packaged in prefilled syringes include antithrombotic agents, vaccines, blood stimulants, interferons, and rheumatoid arthritis medication. To date, there are more than 50 drugs and vaccines now available in a prefilled syringe format. It's estimated there will be 2.5 billion prefilled syringes used this year. With countless more pipeline drugs expected to be launched in a prefilled syringe, the market will continue to grow at rates well above 10% per year for the foreseeable future, says Tom Westbye, Director, Product Development, Unilife Corporation.

As the use of prefilled syringes continues to grow, the issue of prefilled syringe safety has received increased attention.[1] With the passage of the US Needlestick Safety and Prevention Act of 2000, prefilled syringe manufacturers began incorporating safety elements into the design of the device. These can reduce the risk of needle injuries. As more medications are self-administered at home, safety becomes an important driver. Additionally, prefilled syringes help eliminate dosing errors, as they contain the exact dose, according to a market analysis by Frost & Sullivan.[2]

Due to these technological advances in safety, dosing, and compliance, prefilled syringes are one of the fastest expanding growth opportunity areas and stand to make strong gains. The market for prefilled syringes has seen healthy growth in recent years. According to recent estimates, the market for prefilled systems is expected to top $2.4 billion by the end of this year, states the Parenteral Drug Association (PDA), which will sponsor The Universe of Prefilled Syringes and Injection Devices conference in October.

AKTIVAX–A PARADIGM SHIFT IN HYPODERMIC INJECTIONS

The AktiVax approach moves away from traditional methods that incorporate syringes and temperature-controlled vials and instead offers room-temperature stable, prefilled, unit-dose vaccine reconstitution and delivery devices.

FIGURE 1

According to Amir Genosar, Chief Technology Officer at AktiVax, the company has set itself apart from competitors by offering a prefilled syringe with both liquid and powder in a high-barrier film package that gets mixed right before injection. The company's leading reconstitution device, Immunoject™ (Figure 1), is a patent-pending unit-dose prefilled reconstitution and administration device.

"The market is moving to single-dose packaging," says Jim Searles, PhD, Head of Vaccine Formulation and Processing Technologies at AktiVax. "Multi-dose vials are open to contamination risks that single-dose packages are not."

It is Mr. Genosar's 11-year-old daughter, Romi, who actually designed Immunoject during "inventing time" with her dad. At the time, he was looking for a solution to meet industry demand for disposable, prefilled syringes and was not coming up with any successful solutions on his own, so he shared his thoughts with his daughter.

The Immunoject syringe looks like a matchbook. Where the matches would usually be attached, there is a blister that contains water, a barrier wall, and a very small, molded pouch that contains vaccine formulated as a dry powder. The other side of the Immunoject is a flat piece of plastic with instructions for the caregiver. The side is folded over to pop the blister and mix the dry powder with the water to make the vaccine solution.

Folding over the top of the Immunoject also exposes a small needle used to administer the vaccine. All caregivers need to do is insert the needle into a patient's arm and squeeze the Immunoject's two flaps together. When the vaccine is administered, the caregiver folds the top flap back in the opposite direction and the needle is destroyed and protected, avoiding accidental needlesticks.

Immunoject was developed for super high-volume rapid production, enabling vaccine-on-demand conversion of bulk stable powder vaccines into finished products ready for deployment. Immunoject is currently under development, but AktiVax is linking up with partners whose vaccines would be ideal for the device.

"We believe that Immunoject represents a true paradigm shift in hypodermic injections," says Mr. Genosar.

BD MEDICAL–SIMPLE POINT OF DELIVERY

One of the drivers for prefilled syringe adoption by end-users is simplicity, summizes Brian Lynch, Marketing Manager, BD Medical - Pharmaceutical Systems. "The whole idea is to deliver the best care option at the point of delivery, and this can be done by reducing risk and easing administration," he says. "The potential for deviations from best clinical practices is better managed through the use of prefilled syringes; consider that preparation for a traditional vial requires approximately 12 steps, while only 3 or 4 are required for a prefilled syringe."

Through consultative and scientific expertise coupled with extensive clinical knowledge, BD is able to provide a range of drug delivery options to meet specific market and customer requirements. BD provides a host of innovative solutions, including product technology offerings around the various syringe materials and system components depending on a drug or molecule. Additionally, BD offers comprehensive ergonomic and visual enhancements to address end-user needs, drug branding, and differentiation strategies.

FIGURE 2

BD Hypak SCF™: the worldwide standard for glass prefillable syringes.

BD offers both glass and plastic prefillable syringes to address the demands of the market and in response to end-user preferences. The BD Sterifill SCF™ plastic prefillable syringe is a crystal clear polymer (BD's proprietary cyclic olefin) syringe for use with drugs or in therapeutic classes with specific needs, such as contrast media. The BD Hypak SCF™ glass prefillable syringe is widely used throughout a variety of therapeutic classes (Figure 2).

Regarding plastic prefillable syringes, today they are an option being considered for niche applications based on specific and unique clinical and end-user requirements.

"The industry regulatory precedence and manufacturing/development infrastructure for injectable drugs and biologics is built today for, and around, glass. In any case, glass or plastic,

FIGURE 3

A range of prefilled syringe solutions available from Catalent.

vaccines or biologics, science should be the road map to ensure the highest degree of compatibility and lowest degree of risk," says Mr. Lynch.

BD is also investing in prefillable microdelivery systems and self-injection solutions for chronic therapies. The BD Soluvia™ injection system is a prefillable microinjection system integrated with a microneedle, enabling a drug or vaccine to be delivered intradermally. The dermal layer contains a dense network of lymphatic vessels feeding local lymph nodes, resulting in rapid and efficient therapeutic response. It also contains a high concentration of potent immune cells that plays a key role to initiate the immune response following vaccination.

This past April, BD Medical - Pharmaceutical Systems opened a new production facility in Tatabánya, Hungary, to meet the growing worldwide demand for the prefillable syringes that are sold to pharmaceutical and biotechnology firms whose injectable drugs are delivered using these devices.

"This plant increases our global manufacturing network and offers our pharma clients a multiple plant sourcing and capacity option," says Mr. Lynch.

CATALENT–FILLING & FINISHING PREFILLED SYRINGES

For Fill-and-Finish contractors, market proximity is an important competitive factor, and the past 12 months has seen major prefilled syringe CMOs expanding their operations in regional markets, particularly in North America. As a leading provider of prefilled syringe solutions (Figure 3), Catalent offers a range of services and technologies to support pharmaceutical product development, drug delivery, manufacturing, and packaging needs, says Sheila Dell, PhD, Vice President of Business Development for the Sterile Technologies business of Catalent Pharma Solutions.

For instance, the ASI autoinjector is a single-use device designed to provide patients with an easy-to-use injection. Audible and visual signals indicate when the injection is complete. A retractable needle prevents needlesticks. The ASI can be used for a range of prefilled syringe applications, including highly viscous formulations, and offers variable and fixed dosing options.

The US Needlestick Safety and Prevention Act of 2000 mandated that safety shields must be present on prefilled syringes. The Protector Safety Shield System™ can be used with almost any type of prefilled syringe, completely encases the needle when not in use, and can be drawn back for injection. After use, the system slides back to shield and lock the needle into place, preventing needlestick injury. The needle can then be removed with the shield in place for disposal.

Catalent has begun various stability studies of water for injection (WFI) and saline solutions in prefilled syringes in response to the recent availability of modern connection devices between freeze-dried product and the prefilled syringe containing diluent.

Dr. Dell indicates Catalent is focused on the interaction of prefilled syringes with drugs as it relates to stability. Catalent is working to eliminate any interaction between drugs and packaging materials as regulating bodies will scrutinize processing and quality control issues. She says glass syringes have typically been used in prefilled syringes because of their high chemical resistance and low moisture permeability.

For new biotechnology drugs, however, glass contains trace amounts of alkali ions, which can leach out, according to Frost & Sullivan. Cycloolefin-copolymers (COCs) are challenging glass in the prefilled syringe market because of its potential interaction with the biotech class of drugs. COCs are a glass-clear amorphous copolymers based on cyclic and linear olefins. These materials form a family of engineering resins that exhibit a unique combination of properties, including high transparency, low density, excellent moisture barrier capabilities, and resistance to aqueous and polar organic media.

UNILIFE CORP.–SAFETY IN THE BARREL

Unilife is preparing to launch what it claims will be the world's first prefilled syringe with automatic safety features that are fully integrated inside the glass barrel. For pharmaceutical companies, the Unifill™ syringe (Figure 4) can be

integrated into the same filling and packaging systems currently used with standard prefilled syringes. As a primary drug container, it is virtually the same size as a standard prefilled syringe, eliminating the need to purchase and attach bulky ancillary safety devices, explains Mr. Westbye of Unilife.

"It is intuitive for use by either healthcare workers or patients who self-administer prescription medication, with its compact size making it easy to handle and convenient to dispose. Most of all however, it allows operators to control the speed of automatic needle retraction directly into the barrel to virtually eliminate the risk of infection from needlestick injury or aerosol. All of this makes it an ideal device for pharmaceutical companies seeking to enhance customer care, strengthen brand differentiation, and extend product lifecycles," he adds.

Many once saw the full integration of safety features within the glass barrel of a prefilled syringe as an impossible task. As a primary container, it was thought that the additional components would conflict with fundamental device requirements, such as material compatibility and sterility.

"Our proprietary technology is uniquely positioned to satisfactorily address such issues," explains Mr. Westbye. "We are building strong relationships with many established suppliers of proven formulations of key materials, such as glass and rubber. And we've hired a world-class team with the pharmaceutical and medical device knowledge to successfully co-ordinate the design, development, and validation of the product."

Unilife has recently agreed to a list of therapeutic classes, including vaccines and antithrombotic agents, of which sanofi-aventis has the exclusive right to negotiate to purchase the Unifill syringe until June 2014.

FIGURE 4

Unifill™ ready-to-fill safety syringe before and after use.

"With both the first Unifill assembly line and our new state-of-the art and custom-designed facility scheduled to be ready by the end of 2010, we are now in a position to strengthen relationships with a number of other interested pharmaceutical parties seeking access to our products," he says.

The transition of global healthcare markets to the mandatory use of safety syringes continues to gain pace. Pharmaceutical companies increasingly recognize the need to comply with needlestick prevention laws across North America, Europe, and parts of the Asia-Pacific.

"Some have traditionally seen the need to comply with needlestick prevention laws as something of an inconvenience, as the attachment of current ancillary safety products onto standard prefilled syringes can increase packaging, transport, and storage costs by up to 70%. The Unifill syringe gives them an opportunity to turn compliance into a real business opportunity. They can improve industrial efficiencies, enhance customer care, and deliver powerful differentiation for their brands. That's a winning drug-device combination, with the Unifill syringe in a class of its own. There are no other prefilled syringes with automatic safety features that are fully integrated within the glass barrel and suitable for integration into standard fill finish systems. We see the current usage of ancillary safety products that must be attached onto standard prefilled syringes as a temporary stop-gap measure. The future of this industry is the seamless integration of safety into the fill-finish systems of pharmaceutical manufacturers."

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Technology Showcase

Licensing Opportunities

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

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Technology Showcase

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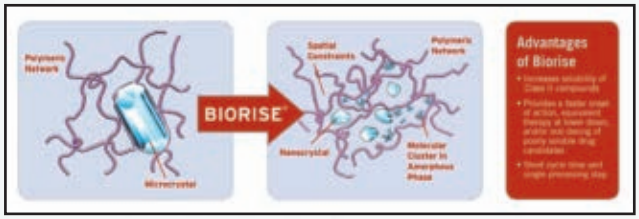
Technology Showcase

Bioavailability Enhancement



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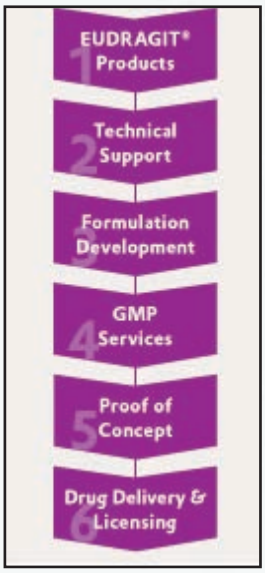

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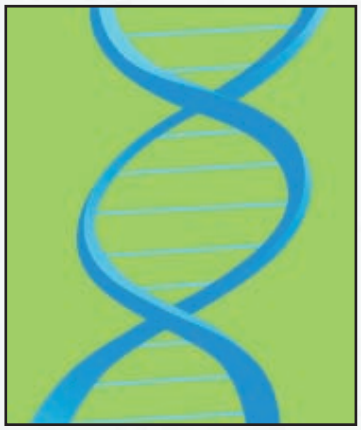
Oligonucleotide-Based Therapeutics Tools



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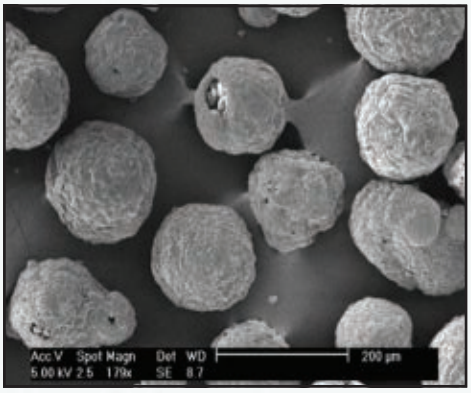

Mallinckrodt Baker's PanExcea™ MC200G performance excipient for Oral Disintegrating Tablet (ODT) applications combines two ingredients for rapid tablet disintegration and dispersion with good taste and texture. Designed for more flexibility at a lower cost, PanExcea MC200G performance excipients enable more API loading capacity while reducing tableting, licensing, and equipment expenses. For more information, contact Mallinckrodt Baker at (800) 943-4747 or visit **www.mallbaker.com/panexcea** to request a free sample.

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Technology Showcase

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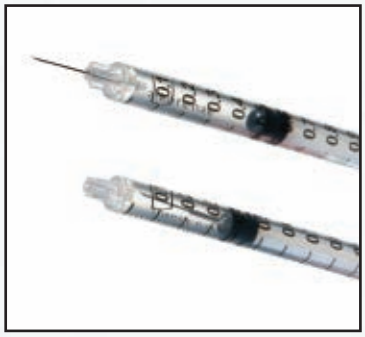
Prefilled/Clinical Safety Syringes



Unilife Medical Solutions has a range of prefilled and clinical safety syringes suitable for pharmaceutical companies, healthcare facilities, and patients who self-administer prescription medication. Our products incorporate passive and fully integrated safety features that can help customers comply with needlestick prevention laws and encourage single-use and safe disposal practices outside of healthcare settings. The products feature a passive (automated) needle retraction mechanism allowing operators to control the speed of needle retraction directly from the body into the barrel of the syringe. The Unilife Ready-to-Fill Syringe features a glass barrel and is compatible with the manufacturing procedures used to fill standard prefilled syringes. The Unitract 1-mL Insulin Syringe is FDA certified and now being manufactured in the PA facility. For more information, contact Unilife at (717) 938-9323 or visit **www.unilife.com**.

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For more information on growth opportunities in the Drug Delivery market, please contact Johanna Haynes at johanna.haynes@frost.com.

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Formulation & Evaluation of Time-Controlled Pulsatile-Release Propranolol HCl Pellets Prepared by a Suspension/Solution-Layering Process Using a Fluid Bed System

By: Himanshu K. Solanki, Bhupendra G. Prajapati, MPharm, and Girish N. Patel, PhD

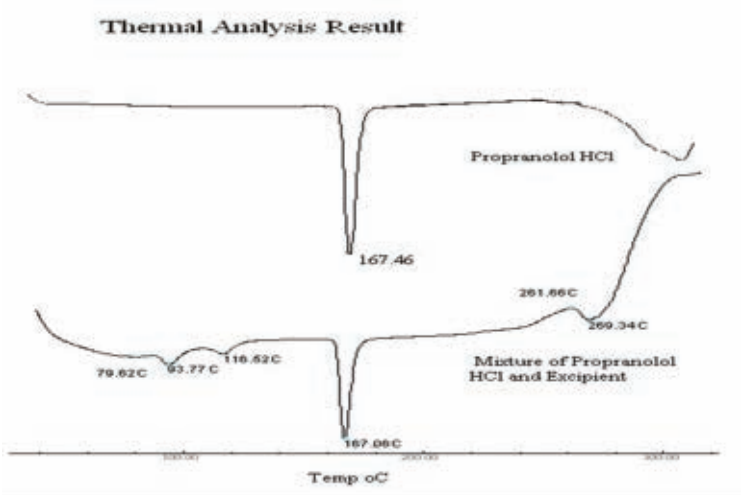
ABSTRACT

The objective of the present study was to prepare time-controlled pulsatile- release propranolol hydrochloride (HCl) pellets for early morning hypertension. Propranolol HCl pellets were prepared using two different viscosity grades of hydroxypropyl methylcellulose (HPMC 5 cps and HPMC K4M) as binders using a solution/suspension layering process. In this process, a layering drug binder solution was placed onto non-pareil beads using a fluid bed coater. The drug-loaded pellets were then coated with an aqueous dispersion of ethyl cellulose (Aquacoat ECD) at different processing times using a fluid bed coater that retards the drug release in the physiological environment of the stomach and 1 to 2 hrs in the intestine. The resultant pellets were evaluated for physico-chemical characteristics properties, such as drug-to-excipient compatibility by differential scanning calorimetry (DSC) analysis, mean diameter, bulk density, tapped density, hausnors ratio, angle of repose, percent weight gain, drug content, and in vitro drug release. It can be concluded that increasing the viscosity grade and processing time for the coating of Aquacoat ECD results in extended drug release.

INTRODUCTION

Propranolol HCl is a non-selective beta-adrenergic blocking agent widely used in the treatment of hypertension, angina pectoris, and other cardiovascular disorders. It is almost completely absorbed following oral administration, but its bioavailability has been limited due to extensive first-pass metabolism. The short biological half-life (3 to 6 hrs) and high frequency of administration initiated the need to develop a once-a-day controlled-release formulation.[1] Therefore, propranolol HCl was used as a model drug. Propranolol HCl is currently available as extended-release capsules (BetacapTR, Sun Pharmaceuticals). In the present study, two different viscosity grades of the hydrophilic polymer hydroxypropyl methylcellulose (HPMC 5 cps and HPMC K4M) were used as binding agents, and the hydrophobic polymer ethyl cellulose (EC) was used as a coating polymer to provide time-controlled release of propranolol HCl. Ethyl cellulose is a well-known water-insoluble polymer that has long been used as a rate-controlling membrane in medication dosage forms to regulate drug release, whereas HPMC, a commonly used hydrophilic polymer in

FIGURE 1



DSC Spectra of Propranolol HCl & Mixture of Excipients With Drug

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drug delivery systems, is a mixed alkyl hydroxyalkyl cellulose ether containing methoxyl and hydroxypropyl.[2] The hydration rate of HPMC depends on the nature of these substituents. Specifically, the hydration rate of HPMC increases with an increase in the hydroxypropyl content. The solubility of HPMC is pH-independent.[3] In the present study, HPMC 5 cps and HPMC K4M were used as hydrophilic binding agents because they form a strong viscous gel upon contact with aqueous media, which may be useful in controlled delivery of highly water-soluble drugs.

The objective of the study was to formulate time-controlled pulsatile-release propranolol HCl pellets using two different viscosity grades of hydroxypropyl methylcellulose (HPMC 5 cps and HPMC K4M) using a solution/suspension layering process, and then coating the drug-loaded pellets with an aqueous dispersion of EC using a fluid bed system to elucidate the release kinetics of propranolol HCl from the pellets.[4-6]

MATERIALS

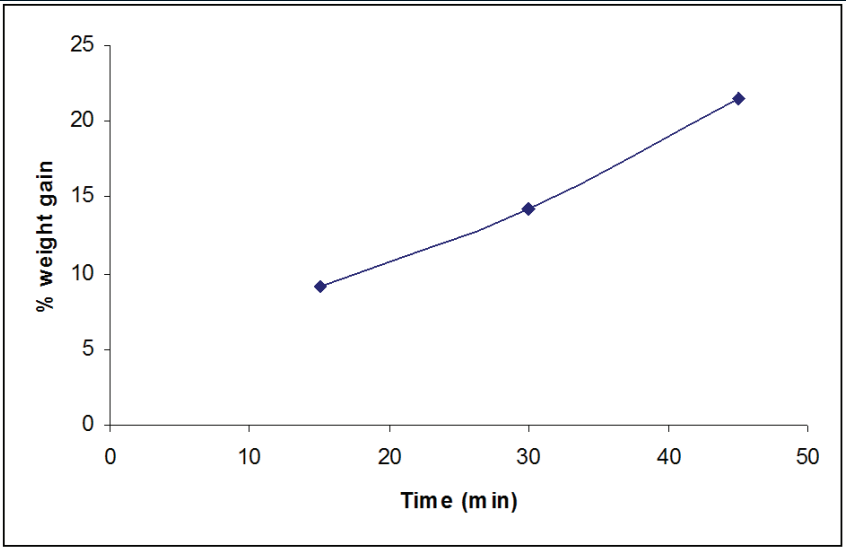
Propranolol HCl was obtained as a gift sample from IPCA Laboratory Ltd. (Silvassa, India). Two different viscosity grades of hydroxypropyl methylcellulose (HPMC 5 cps and HPMC K4M) as well as PEG-4000 were procured from S.D Fine Chemicals (Mumbai, India). Non-pareils & Aquacoat ECD (aqueous dispersion of ethyl cellulose) were obtained as gift samples from Corel Pharmachem Ltd. (Ahmedabad, India).

METHODS

Preparation of Drug-Loaded Pellets

In formulations P1, P2, and P3, propranolol HCl (1 g) were dissolved or dispersed in an ethanol/water (60:40 w/w) mixture containing 5% (w/v) HPMC 5 cps (Methocel® E5) and 5% w/v Ac-di-sol. In formulations P4, P5, and P6, propranolol HCl (1 g) were dissolved or dispersed in an ethanol/water (60:40 w/w) mixture containing

FIGURE 2



Weight Gain of Coating Formulation at Different Time Intervals

TABLE 1

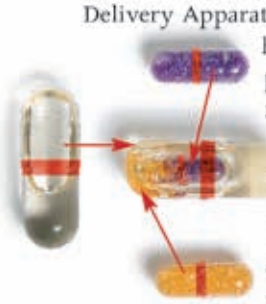
Formulation Code	P1	P2	P3	P4	P5	P6
Drug Layering on Non-pareil Beads						
Propranolol HCl (g)	1	1	1	1	1	1
HPMC 5 cps (g)	5	5	5			
HPMC K4M (g)				1.5	1.5	1.5
Ac-di-sol (g)	5	5	5	5	5	5
Ethanol:Water (60:40) ml	100	100	100	100	100	100
Coating of Drug Loaded Pellets						
Aquacoat ECD (ml)	10	10	10	10	10	10
PEG 4000 (g)	1.25	1.25	1.25	1.25	1.25	1.25
Ethanol (96%) ml	100	100	100	100	100	100
Coating Time (min)	10	20	30	10	20	30

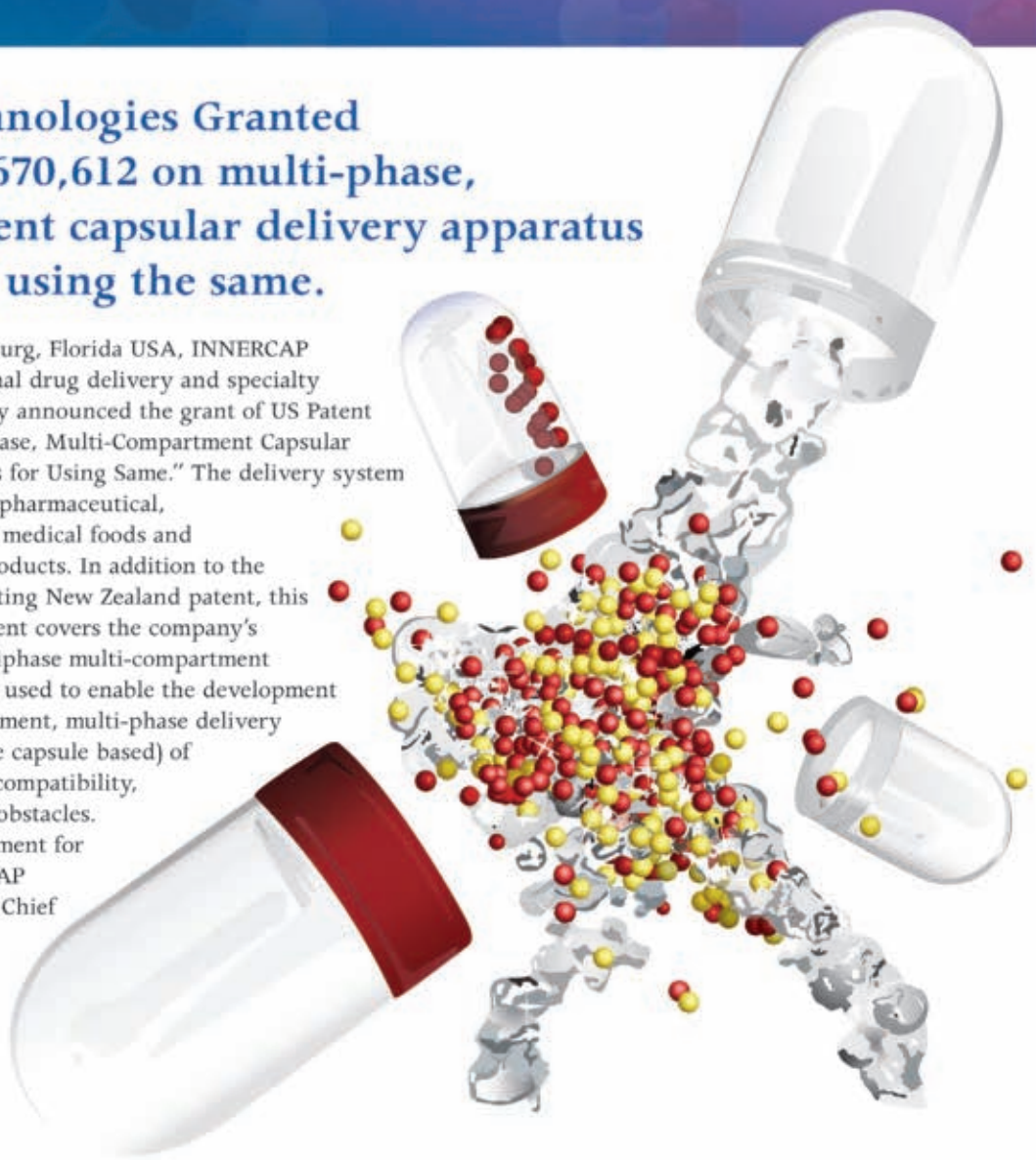
Composition of Coated Pellets

THE ADVANTAGES

OF MULTI-PHASE, MULTI-COMPARTMENT CAPSULES ARE CLEAR

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





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

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

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

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

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

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

INNERCAP™ TECHNOLOGIES, INC

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

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TABLE 2

Formulation	Mean Diameter (µm)	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Hausner Ratio	Angle of Repose(θ)	Flow Rate(g/s)
P1	928	0.769	0.8	1.04	22.45	4.285
P2	958	0.8	0.816	1.02	23.27	2.727
P3	960	0.8	0.833	1.041	23.27	3.333
P4	969	0.8	0.833	1.041	22.45	3.33
P5	991	0.784	0.833	1.062	24.45	3.333
P6	972	0.782	0.8	1.053	24.21	3.23

Characteristics Properties of Coated Pellets

1.5 % (w/v) HPMC K4M (Methocel® K4M) and 5% w/v Ac-di-sol. Propranolol hydrochloride-loaded pellets were prepared by layering the drug binder solution onto non-pareil beads in a fluidized bed coater (Cronimach Machinery, Ahmedabad, India). The layering conditions were as follows: batch size 40 g, inlet air temperature 60°C, atomizing air pressure 1.25 kg/cm^2, and spray rate 5 ml/min. The processing time was kept constant at 20 mins for drug layering on the non-pareil pellets.

Coating of Drug-Loaded Pellets

Pellets were coated with a 4% (w/v) EC solution in 96% (v/v) ethanol, plasticized with 5% PEG 4000 (w/w) based on weight of coating polymer in a fluidized bed coater under the following conditions: batch size 40 g, inlet air temperature 60°C, outlet temperature 40°C, atomizing air pressure 1.25 kg/cm^2, and spray rate 5 ml/min.[6] The coating was done under a different processing (coating) time, such as 15, 30, and 45 mins. The composition of coated pellets are shown in Table 1.

EVALUATION

Drug-Excipient Compatibility Study (Thermal Analysis)

DSC scans were taken of powdered samples of propranolol HCl and the mixtures of excipients with drug. DSC analyses of powders were recorded using a DSC-Shimadzu 60 with TDA trend line software. The pans were positioned on a sample pan holder of a DSC 60. The thermal traces were obtained by heating from 50°C to 300°C at a heating rate of 10°C. Thermograms were obtained by the DSC 60 thermal analyzer program and recorded at a chart speed of 1 inch/min. The thermogram, transion temperature range, onset of peak transition, and maximum peak of transition were recorded.

Characteristics of Coated Pellets

BULK & TAPPED DENSITY: Bulk and tapped densities of coated pellets were run with a 10-g sample of each formulation in a Tap density test apparatus.

HAUSNER RATIO & FLOWABILITY: Hausner ratio (HR) is the ratio between tapped (ρt) and bulk densities (ρb). Hausner ratio = tapped density (ρt)/bulk density (ρb). The closer the ratio is to 1, the better the flow characteristics. Particles with poor flow generally have a Hausner ratio greater than 1.25. The flow rate and angle of repose were also investigated on the coated pellets.

Viscosity of Coating Solution

A Brookfield digital viscometer (spindle No. S18) was used to measure the viscosity of the 4% EC coating solution, which was 40 to 45 cps.

Determination of Coating Level (% Weight Gain)

Percentage weight gain was calculated using the following equation: Percentage Weight Gain = $[(W_t-W_o)/ W_o] \times 100$. Where W_t = weight of non-pareil beads after coating, and W_o = initial weight of non-pareil beads.

Drug Content

The propranolol HCl pellets were tested for their drug content. Accurately weighed 250-mg pellets were finely powdered; quantities of the powder equivalent to 40 mg of propranolol HCl were accurately weighed and transferred to a 100-ml volumetric flask. The flask was filled with distilled water and mixed thoroughly. The solution was made up to volume and filtered. 1 ml of the resulting solution was diluted to 100 ml with distilled water, and the absorbance of the resulting solution at the maximum 290 nm was measured using a UV/Vis double beam spectrophotometer. The linearity equation obtained from the calibration curve as described previously was used for estimating the propranolol HCl in the pellet formulations.

In Vitro Dissolution Study

In vitro drug-release studies were conducted for all formulations using a dissolution test apparatus (Veego UDA-8D

USP standard). Drug-release studies were carried out using a USP XXIII dissolution rate test apparatus (Apparatus 2, 50 rpm, 37.5°C) for 2 hrs in 0.1 M HCl (900 ml) as the average gastric emptying time is about 2 hrs. The dissolution medium was then replaced with a pH 6.8 phosphate buffer (900 ml) and tested for drug release. At the end of each time period, 10 ml of the samples were taken and analyzed for their propranolol HCl content. A 10-ml volume of fresh and filtered dissolution medium was added to achieve the appropriate volume after each sample withdrawal. The samples were analyzed using a UV spectrophotometer at 290 nm.

Kinetic Modelling & Mechanism of Drug Release

Data obtained from in vitro drug-release studies were fitted to various kinetic equations. The kinetic models used included zero-order, first-order, Higuchi, Hixson Crowell, and Korsmeyer pappas equations. The following plots were made for the appropriate models:

- QV_st (zero-order kinetic models)
- Log $(Q_o - Q_t) V_st$ (first-order kinetic model)
- $Q_tV_s\sqrt{t}$ (Higuchi model)
- $\sqrt[3]{Q_o} - \sqrt[3]{Q_t} = {}^kHC \times t$ (Hixson Crowell model)
- $M_t / M_\infty = Kt^n$ (Korsmeyer pappas model)

Where Q_t is the amount of propranolol HCl released at time t, and Q_o is the initial amount of propranolol HCl in dosage form. To investigate the mechanism of in vitro drug release and compare the release profile differences among these matrix formulations, the percent drug released versus time profiles were used.

TABLE 3

Model/Formulation	P1	P2	P3	P4	P5	P6
Zero	0.9486	0.974	0.9431	0.9845	0.9685	0.9619
First	0.9045	0.8855	0.8025	0.8417	0.8921	0.9001
Higuchi	0.8828	0.8161	0.811	0.9228	0.8581	0.8299
Hixson	0.9354	0.9075	0.9237	0.9569	0.9572	0.9482
Korsmeyer (n)	1.93	1.99	1.94	1.54	1.71	1.71

Result of Drug-Release Kinetics Study

Comparison of Dissolution Profiles

The similarity factor (f_2) has been adopted by the CDER (FDA) and by the EMEA (European Agency for the Evaluation Unit of Medicinal Product) as a criterion for the assessment of the similarity between two in vitro profiles and is included in the SUPAC guideline. The similarity factor fits the result between 0 and 100. It is 100 when the test and references are identical and tends to 0 as the dissimilarity increases. This similarity factor is calculated using the following equation:

Equation 1.

$$f_2 = 50 \times \log\left\{\left[1 + \left(\frac{1}{n}\right)\sum_{j=1}^{n} |R_j - T_j|^2\right]^{-0.5} \times 100\right\}$$

Where n is the number of dissolution time, and R_j and T_j are the reference and test dissolution values at time t. Two dissolution profiles are considered similar when the f_2 value is 50 to 100. As per the FDA and EMEA guidelines, two dissolution profiles are declared similar if f_2 is between 50 and 100.

RESULTS & DISCUSSION

In the present investigation, the attempt was made to prepare bilayered non-pareils of propranolol HCl using a fluid bed coating method. Two different viscosity grades of HPMC 5 cps (low viscosity grade) and HPMC K4M (high viscosity grade) were used as binding solutions in which propranolol HCl was dissolved or dispersed and then layered on non-pareil pellets. Here, drug was dispersed or dissolved within the coating solution, and layering executed on non-pareil pellets. Thus, drug was released from the surface of the non-pareils when it came into contact with the dissolution medium, and the problem of dose dumping could be avoided. Drug-loaded pellets were then coated with EC at different processing times, such as 15, 30, and 45 mins for optimization of a suitable processing time and to achieve extended drug release. EC has a high glass transition temperature of approximately 130°C. Here, PEG 4000 was used as a plasticizer for the coating formulation, which is hydrophilic, so the coating layer would get easily wetted.

Differential Scanning Calorimetry Analysis

Differential scanning calorimetry (DSC) enables the quantitative detection of all

processes in which energy is required or produced (ie, endothermic or exothermic phase transformations). The thermograms of propranolol HCl and mixture of excipients with drug are shown in Figure 1. The melting point of propranolol HCl is between 163°C and 167°C. In DSC Spectra, the propranolol HCl melting peak was 167.46°C, and in the physical mixture, it was near 167.06°C. This confirmed the physicochemical compatibility of drug with the formulation excipients used in the study.

Characteristic Properties of Coated Pellets

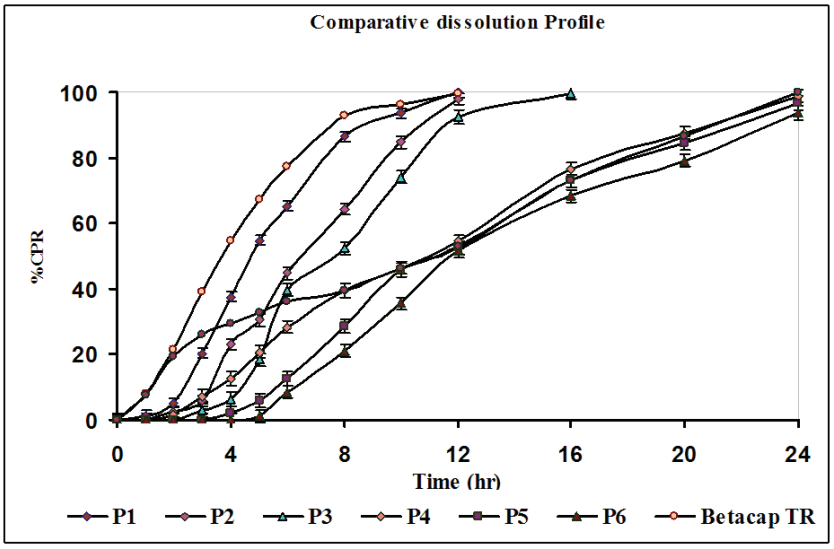
All coated pellets showed good spherical geometry. As shown in Table 2, the average diameter of 928 to 991 micrometers was obtained depending on the amount of binding agent and coating level. Notably, the amount of binding agent affected the mean particle size. As the amount of binding agent increased, significant increases in particle sizes of F3 to F5 formulations were observed (Table 2).

Also shown in Table 2, all angles of repose values were below 30°, and the angle of repose was not significantly affected by the particle size of the pellets. According to flow rates, angle of repose and Hausner ratio values of all the pellet formulations have good free flowing nature. Drug content in drug-loaded pellets was found to be approximately 23%. As processing time increase, so does the percent weight gain in coated pellets (Figure 2).

In Vitro Dissolution Study

In vitro release studies were carried out for the formulations in both acidic and basic media to simulate in vivo conditions. The release studies were carried out at pH 1.2 (HCl buffer) (simulated gastric fluid) for 2 hrs, to mimic the acidic conditions prevailing in the stomach, and for the following remaining hrs in basic medium, ie, pH 6.8 (phosphate buffer), to mimic the environment in the small intestine.

FIGURE 3



Comparison of Dissolution Profiles

Figure 3 shows the comparison between batches P1 to P6 and market preparation Betacap TR. According to market preparation, an oral time-controlled release formulation of propranolol HCl should provide release of 7.81% in 1 hr, 21.3% in 2 hrs, 56.74% in 4 hrs, 77.21% in 6 hrs, 96.11% in 10 hrs, and 99.53% in 12 hrs. When a similarity factor was applied to the bilayer coated pellets and market preparation of propranolol HCl, Formulation P1 and P2 pellets resulted in a drug-release profile close to that of market preparation needed for propranolol HCl. However, Formulation P1 showed the highest similarity factor compared to formulation P2. So, the similarity factor values indicate the similarity of the in vitro release rate of the market preparation and Formulation P1.

Kinetic Modelling & Mechanism of Drug-Release Study

The release data of tablets were fitted into various mathematical models (zero-order, first-order, Higuchi's square root, Hixson-Crowell cube root law, and Peppas equation to evaluate the kinetics and mechanism of drug release from the tablets. The model that best fits the release data is selected based on the correlation coefficient (r) value in various models. The model that results in a high r value is considered the best fit of the release data. The release constant was calculated from the slope of the appropriate plots, and the regression coefficient (r^2) was determined.

It was found that the in vitro drug release of batch P1 was best explained by zero-order as the plot showed highest linearity ($r^2 = 0.9486$). In the case of batch P2, it was found that the in vitro drug release was best explained by zero-order as its plot showed highest linearity ($r^2 = 0.974$); therefore, the drug release was also found to be close to zero-order kinetics, indicating that the concentration was nearly independent of drug

release. In the case of batch P3, it was found that in vitro drug release was best explained by zero-order as its plot showed highest linearity (r^2 = 0.9441). In the case of batch P4, it was found that in vitro drug release was best explain by zero-order as the plot showed highest linearity (r^2 = 0.9844) followed by Higuchi's equation (r^2 = 0.9228). For batch P5, it was found that in vitro drug release was best explained by zero-order as its plot showed highest linearity (r^2 = 0.968). Batch P6's in vitro drug release was best explained by zero-order with a plot showing highest linearity (r^2 = 0.9619) followed by first-order (r^2 = 0.9005).

The Hixson Crowell cube root model indicated that drug release from pellets changed with a change in surface area and diameter of the pellets. In the case of the Korsmeyer Peppas equation, the value of diffusion exponent for all batches lies between 1.54 and 1.93, indicating drug release from pellets was by super case-II transport or typical zero-order drug release mechanism.

CONCLUSION

From the results and discussion, it can be concluded that an increase in the viscosity grade of HPMC and processing time for coating of Aquacoat ECD shows extended drug release. The batch P1 preparation showed similarity with the market product Betacap TR, indicating the formulation is able to provide the desired product attributes. In addition, batch P1 shows good linearity (r^2 = 0.9486) for the zero-order model, indicating the formulation is able to provide the desired product attributes.

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FORCED DEGRADATION STUDIES

Forced Degradation as an Integral Part of HPLC Stability-Indicating Method Development

By: George Ngwa, PhD

INTRODUCTION

High performance liquid chromatography (HPLC) is an integral analytical tool in assessing drug product stability. HPLC methods should be able to separate, detect, and quantify the various drug-related degradants that can form on storage or manufacturing, plus detect and quantify any drug-related impurities that may be introduced during synthesis. Forced degradation studies (chemical and physical stress testing) of new chemical entities and drug products are essential to help develop and demonstrate the specificity of such stability-indicating methods. In addition to demonstrating specificity, forced degradation studies can be used to determine the degradation pathways and degradation products of the APIs that could form during storage, and facilitate formulation development, manufacturing, and packaging. Procedures for the preparation of specific degradation products needed for method validation often emerge from these studies. For marketing applications, current FDA and ICH guidance recommends inclusion of the results, including chromatograms of stressed samples, demonstration of the stability-indicating nature of the analytical procedures, and the degradation pathways of the API in solid state, solution, and drug product. The chemical structures of significant degradation products and the associated procedures for their isolation and/or characterization are also expected to be included in the filing. The experimental protocol for performing forced degradation studies will depend on the active ingredients and formulation involved because the chemistry of each compound is different. In general, a target of approximately 10% degradation of the API during forced degradation, or exposure to energy in slight excess of what is typically used in accelerated storage is recommended. In this way, the "worst-case" degradation products can be studied. The following will provide some suggestions for performing forced degradation studies based upon available guidance from the ICH and FDA.

STABILITY-INDICATING METHOD (SIM)

According to an FDA guidance document, a stability-indicating method is "a validated quantitative analytical procedure that can detect the changes with time in the pertinent properties of the drug substance and drug product. A stability-indicating method accurately measures the active ingredients, without interference from degradation products, process impurities, excipients, or other potential impurities."[1]

Implicit in the aforementioned definition are the following: a SIM must be validated (demonstrate that it is suitable for its intended use), specific (resolution of active from related substances, peak purity), reproducible, quantitative, and able to monitor a change in the chemical, physical, and microbiological properties of drug product over time. The demonstration of specificity and the ability of the method to monitor a change in the chemical properties of the drug over time, invariably calls for a forced degradation (stress testing) study to be done on the drug substance and drug product.

Forced degradation on the drug substance and product will (in addition to establishing specificity) also provide the following

FIGURE 1

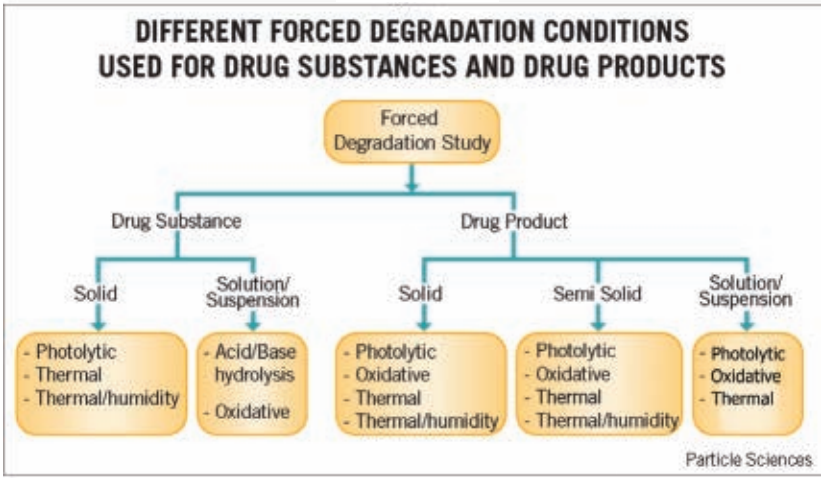

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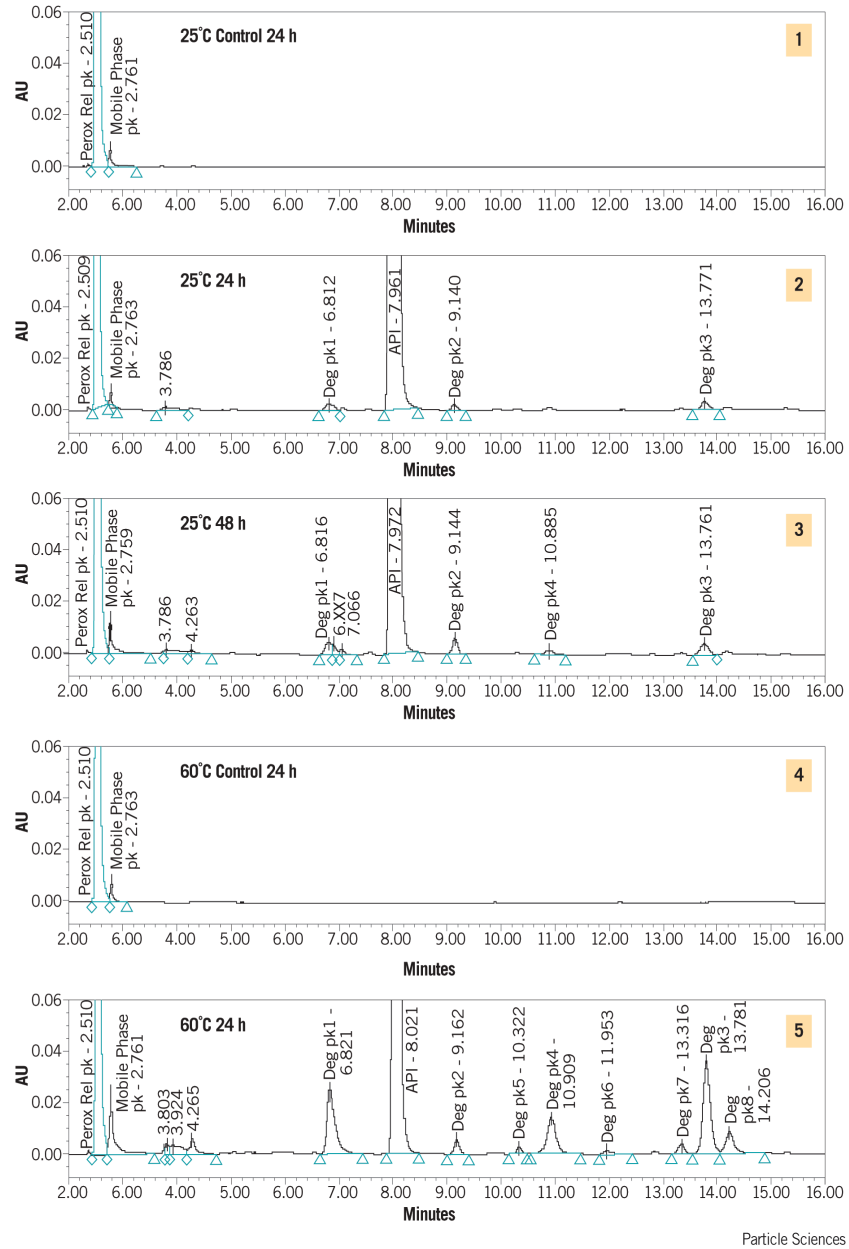
FIGURE 2

HPLC CHROMATOGRAPHIC SET

A sample HPLC chromatographic set showing the degradants generated on oxidative stress of an API using 3% peroxide at different temperatures and sampling times.



information: (1) determination of degradation pathways of drug substances and drug products; (2) discernment of degradation products in formulations that are related to drug substances versus those that are related to non-drug substances (eg, excipients); (3) structure elucidation of degradation products; (4) determination of the intrinsic stability of a drug substance molecule in solution and solid state; and (5) reveal the thermolytic, hydrolytic, oxidative, and photolytic degradation mechanism of the drug substance and drug product.[2,3]

From the foregoing, it is obvious that forced degradation plays a key role not just in the development of stability-indicating methods, but also in providing useful information about the degradation pathways and degradation products that could form during storage. The information thus obtained will facilitate pharmaceutical development in areas such as formulation development, manufacturing, and packaging, where knowledge of chemical behavior can be used to improve the quality of drug product.

Despite the importance of forced degradation in pharmaceutical development, the current regulatory guidance documents governing forced degradation studies are very general.[1,2] One of the guidance documents, *Q1A (R2) – Stability Testing of New Drug Substances and Products*, states: "Stress testing is likely to be carried out on a single batch of the drug substance. The testing should include the effect of temperatures (in 10°C increments (ie, 50°C, 60°C) above that for accelerated testing), humidity (ie, 75% relative humidity or greater) where appropriate, oxidation, and photolysis on the drug substance. The testing should also evaluate the susceptibility of the drug substance to hydrolysis across a wide range of pH values when in solution or suspension."

This quotation demonstrates just how broad and unspecific these guidelines are. There are few practical instructions. For example, the guidance does not specify pH, temperature ranges, specific oxidizing agents, or conditions to use, the number of freeze-thaw cycles, and so on. Furthermore, the question of how much stress is adequate as well as when to begin stress testing is left up to the

FORCED DEGRADATION STUDIES

TABLE 1

CONDITIONS GENERALLY EMPLOYED FOR FORCED DEGRADATION

Degradation Type	Experimental Condition	Storage Condition	Sampling Time
Hydrolysis	Control API (no acid or base)	40 °C, 60 °C	1, 3, 5 days
	0.1N HCl	40 °C, 60 °C	1, 3, 5 days
	0.1N NaOH	40 °C, 60 °C	1, 3, 5 days
	Acid Control (no API)	40 °C, 60 °C	1, 3, 5 days
	Base Control (no API)	40 °C, 60 °C	1, 3, 5 days
	pH: 2, 4, 6, 8	40 °C, 60 °C	1, 3, 5 days
Oxidative	3% H_2O_2	25 °C, 40 °C	1, 3, 5 days
	Peroxide Control	25 °C, 40 °C	1, 3, 5 days
	Azobisisobutyronitrile (AIBN)	40 °C, 60 °C	1, 3, 5 days
	AIBN Control	40 °C, 60 °C	1, 3, 5 days
Photolytic	Light, 1 X ICH	NA	1, 3, 5 days
	Light, 3 X ICH	NA	1, 3, 5 days
	Light control	NA	1, 3, 5 days
Thermal	Heat Chamber	60 °C	1, 3, 5 days
	Heat Chamber	60 °C / 75% RH	1, 3, 5 days
	Heat Chamber	80 °C	1, 3, 5 days
	Heat Chamber	80 °C / 75% RH	1, 3, 5 days
	Heat Control	Room Temp.	1, 3, 5 days

Particle Sciences

Conditions generally employed for forced degradation.

judgment of the pharmaceutical researcher. The following will provide some suggestions for performing forced degradation studies based upon available guidance from the ICH and FDA, thus narrowing these guidance generalities to practicalities.

APPROPRIATE TIMING

"If not performed earlier, stress studies should be conducted during Phase III to demonstrate the inherent stability of the drug substance, potential degradation pathways, and the capability and suitability of the proposed analytical procedures. The stress studies should assess the stability of the drug substance in different pH solutions, in the presence of oxygen and light, and at elevated temperatures and humidity levels. These one-time stress studies on a single batch are not considered part of the formal stability program. The results should be summarized and submitted in an annual report."[4]

The aforementioned quotation from the regulatory guidance document suggests that forced degradation studies could be delayed as late as Phase III clinical trials of the regulatory submission process. However, given the predictive nature of forced degradation studies, these studies are most beneficial if done initially in early development, ie, during the preclinical development or Phase I clinical trials. A forced degradation study on the drug substance at this stage will provide timely recommendations for improvements in the manufacturing process, ensure proper selection of stability-indicating analytical techniques, and ensure there is sufficient time for degradation product identification, degradation pathways elucidation, and optimization of stress conditions.[5] Such a proactive approach will help avert any surprises later in the development process.

HOW MUCH IS ENOUGH?

The question of how much stressing is enough has been the subject of much discussion amongst pharmaceutical scientists. In general, values anywhere between 5% to 20% degradation of the drug substance have been considered as reasonable and acceptable for validation of chromatographic assays.[6,7] However, for small pharmaceutical molecules for which acceptable stability limits of 90% of label claim is common, pharmaceutical scientists have agreed that approximately 10% degradation is optimal for use in analytical validation.[8] In the event that the experimental conditions generate little or no degradants due to the exceptional stability of the molecule, an evaluation should be made to verify if the drug substance has been exposed to energy in excess of the energy provided by accelerated storage (ie, 40°C for 6 months). If the answer is yes, then the experiment can be stopped and a note of the stability of the drug substance can be made. Unduly overstressing the drug substance may produce aberrant results.

EXPERIMENTAL DESIGN

In designing forced degradation studies, it must be remembered that more strenuous conditions than those used for accelerated studies (25°C/60% RH or 40°C/75% RH) should be used. At a minimum, the following conditions should be investigated: (1) acid and base hydrolysis, (2) hydrolysis at various pH, (3) thermal degradation, (4) photolysis, and (5) oxidation. For the drug substance and drug product, the scheme shown in Figure 1 could be used as a guide.[3]

The initial experiments should be focused on determining the conditions that degrade the drug by approximately 10%. The conditions generally employed for forced degradation are summarized in Table 1. However, some scientists have found it practical to begin at extreme conditions (80°C or even higher, 0.5N NaOH, 0.5N HCl, 3% H_2O_2)

FORCED DEGRADATION STUDIES

and testing at shorter (2, 5, 8, and 24 hrs, etc) multiple time points, thus allowing for a rough evaluation of rates of degradation.[9] Testing at early time points may permit distinction between primary degradants and their secondary degradation products. This strategy allows for better degradation pathway determination. It must be noted that a forced degradation study is a "living process" and should be done along the developmental time line as long as changes in the stability-indicating methods, manufacturing processes, or formulation changes are ongoing. Forced degradation is only considered complete after the manufacturing process is finalized, formulations established, and test procedures developed and qualified.

The conditions listed in Table 1 are by no means exhaustive and should be adjusted by the researcher as needed to generate ~10% degradation of the API. The nature (inherent stability/instability) of the particular drug substance will determine in which direction to adjust the stress conditions. Also, the aforementioned conditions could be used to stress the drug substance or drug product either in the solid or liquid/suspension form as applicable. The flow chart of Figure 1 should be followed as a guide.

As an example, sample chromatograms showing the degradants generated for an API using 3% peroxide at different temperatures and sampling times is shown in Figure 2. This was a scouting experiment to select the appropriate conditions for which a ~10% degradation will be generated. Chomatograms 2, 3, and 5 generated degradants totaling 5%, 11%, and 30% respectively. Therefore, the conditions for chromatogram 3 (3% peroxide at 25°C, for 48 hrs) were deemed suitable and were used for further method optimization.

For oxidative degradation with H_2O_2, at least one of the storage conditions should be at room temperature. Heating H_2O_2 solution increases the homolytic cleavage of the HO-OH bond to form the alkoxy radical (2HO•). The alkoxy radical is very reactive and may come to dominate the observed degradation pathway. Adding a small quantity of methanol in a confirmatory stress experiment quenches the alkoxy radical and rules out species produced by this more aggressive oxidizing agent. Also, the formation of peroxycarboxymidic acid has been observed when acetonitrile is used as a cosolvent in H_2O_2 stress studies (in basic conditions). The peroxycarboximidic acid has activated hydroxylation reactivity, which is not representative of H_2O_2. To circumvent these problems, some research scientists always perform a parallel or alternative oxidative study using azobisisobutyronitrile (AIBN), which is a less reactive oxidant and has been shown to produce more representative degradants.

SUMMARY

Forced degradation studies are indispensable in the development of stability-indicating and degradant-monitoring methods as part of a validation protocol. Forced degradation studies also provide invaluable insight in investigating degradation products and pathways of drug substances and products. Even though the ICH and FDA guidance documents only call for the inclusion of these studies in Phase III of the regulatory submission process, it is strongly recommended these studies be started as early as possible to be able to provide valuable information that can be used to assess the inherent stability of a drug, and to improve formulations and the manufacturing process.

Given that no specific set of conditions will be applicable to all drug substances and products, the pharmaceutical scientist should ensure the stress conditions are consistent with product decomposition under normal manufacturing, storage, and intended use conditions. Recommended stress factors include high and low pH, elevated temperature, photolysis, and oxidation. Care should be taken to avoid under-stressing or unduly over-stressing the drug substance or product, for this may lead to aberrant and non-representative results. A degradation level of approximately 10% of the drug substance should be optimal for method optimization.

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BIOGRAPHY

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RAMAN CHEMICAL IMAGING

Raman Chemical Imaging as a Tool for Measuring Layer Thickness in Sustained-Release Beads

By: Oksana Klueva, PhD, Ryan J.Priore, PhD, and Brian K. Jensen

ABSTRACT

Site-specific delivery and controlled release of active pharmaceutical ingredients (APIs) have resulted in a high demand for modified-release products. Sustained-release beads can deliver stable levels of drugs, which result in less-frequent dosing. For consistent drug delivery, it is imperative for the bead coating to be uniformly applied. In this study, Raman Chemical Imaging (RCI) coupled with optical microscopy was applied to investigate API and polymer coating thicknesses in commercial sustained-release beads. This approach was compared to scanning electron microscopy (SEM) and dissolution data obtained for the same batch.

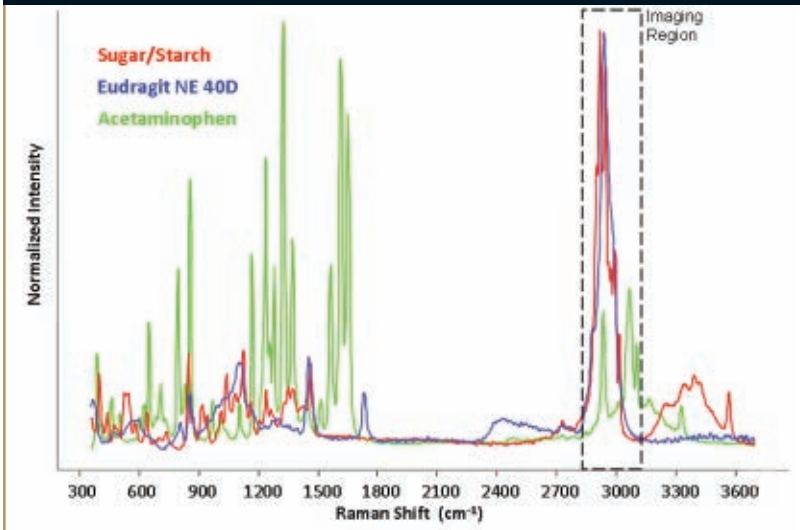
INTRODUCTION

Demand for modified-release products has grown in recent years due to favorable therapeutic qualities resulting from site-specific delivery and controlled release of an API. A modified-release mechanism ensures stable levels of the drug delivery and, therefore, lesser dosage frequency compared with instant-release formulations. These products include delayed-release and extended- (controlled, sustained) release products. Typical sustained-release systems use small beads encapsulating the drug in the core particle with a polymer coating or sandwiching the drug between an inert core and one or more polymer layers. In both cases, it is critical for consistent drug delivery that the bead coating is uniformly applied.

The validation of the coating process is generally achieved by surface analysis of coated bead cross-sections by SEM, which employs secondary or back-scattered electrons to produce nanometer-resolved surface images.[1] Because the analysis is carried out in vacuum, an SEM specimen should be dry and conductive in order to achieve high-quality imagery. Image artifacts may result from the charging of nonconductive specimens during electron beam scanning, therefore, most non-metal samples are coated with an ultra-thin layer of gold. One must distinguish coating layers by inherent morphology (or lack thereof), as the elemental composition of organic compounds is similar.

Matrix-assisted laser desorption/ionization with a time-of-flight mass analyzer (MALDI-TOF) is commonly used in tissue imaging and can also be used to analyze bead cross-sections.[2,3] It should be noted that image spatial resolution for MALDI-TOF is relatively low, about 20 micrometers, and is not always suitable for controlled-release beads. Both aforementioned analytical methods require special sample preparation and may not be sensitive to physico-chemical changes in the sample, such as hydration or polymorphism.

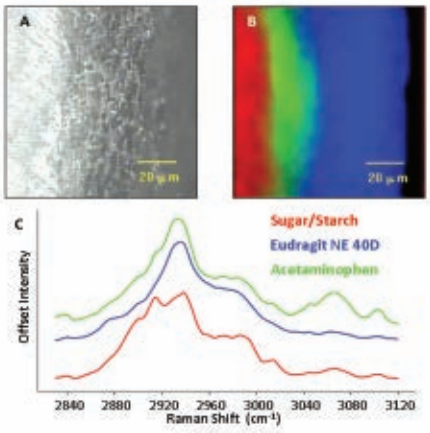
FIGURE 1



Raman dispersive spectra of pure components.

RAMAN CHEMICAL IMAGING

FIGURE 2



A typical optical and processed Raman chemical image of bead exterior at 20x magnification: (A) Optical microscopy image; (B) Processed Raman chemical image; and (C) Raman spectra of bead ingredients.

Raman spectroscopy is a laser-based vibrational spectroscopy technique that provides high specificity for determining the chemical composition and requires minimal or no sample preparation. Confocal Raman microscopy has been successfully applied to evaluate coating uniformity, thickness of the API layer, and drug-release mechanism.[4,5] Confocal Raman microscopy requires point-by-point mapping to construct an image and usually takes significant time to cover an appropriate area for layer thickness determination.

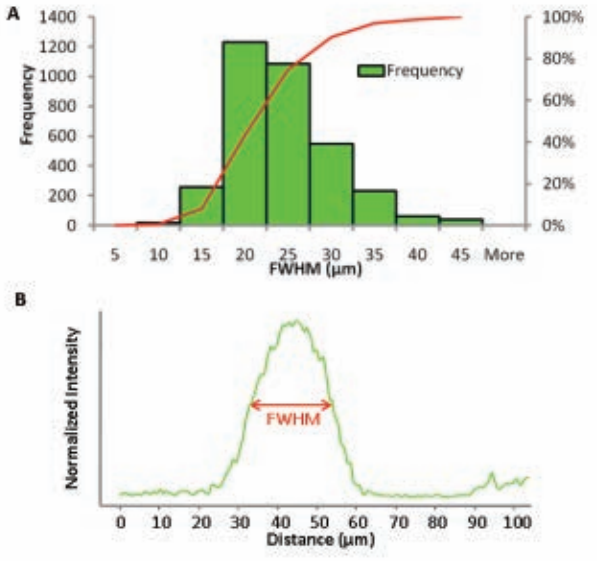
Wide-field RCI is a hyperspectral imaging method based on liquid crystal tunable filter technology that transmits spatially resolved wavelength frames to a Charge Coupled Device (CCD) detector. Wide-field RCI determines the chemical identity of individual components of a heterogeneous sample by combining the objectivity of Raman spectroscopy with the visual perception of digital imaging. It provides exceptional value for a variety of applications, including pharmaceutical research and development.[6] A full or partial Raman spectrum is captured for each pixel in the chemical image corresponding to a spatial location on a sample. Thus, a resulting data set, or hypercube, contains two spatial dimensions as well as a wavelength dimension. Each chemical entity in the field of view (FOV) can be identified by its distinctive spectral profile and correlated with an associated optical image. Specific Raman spectral planes are used for identification, placement, and sizing purposes. Advanced chemometric techniques may be used to isolate unique Raman signatures and separate multiple ingredients in complex systems or matrices.

In this study, RCI coupled with optical microscopy was applied to investigate API layer thickness in sustained-release beads. This method was compared to both SEM and dissolution data obtained for the same batch.

MATERIALS & METHODS

Sustained-release beads with acetaminophen (APAP) as an API were prepared by Vector Corporation. Sugar spheres (3 kg, 30-35 mesh) were loaded into a Vector Granurex GXR-35 Conical Rotor Processor (Vector Corporation) equipped with a K-Tron KT-20 precision powder feeder. Micronized Acetaminophen (Mallincrodt) was fed via the KT-20 into the GXR-35 dry and layered onto the spheres to a level of 15% w/w, using a 5% aqueous solution of PVP K-30 in water as a binder. The drug-layered beads were then functionally coated in the

FIGURE 3



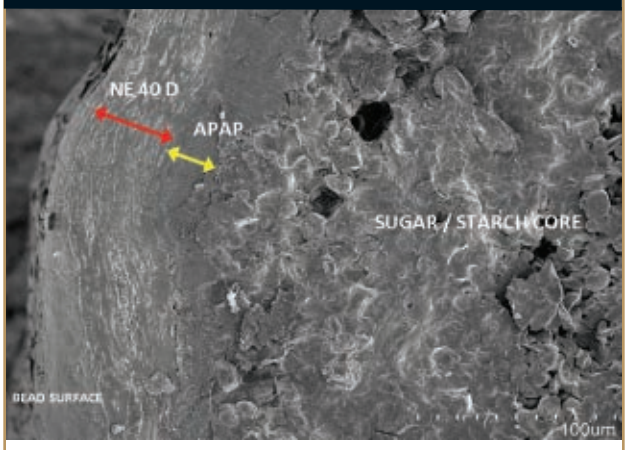
C

Category	Value
Average (μm)	21.8
Std. Dev. (μm)	5.8
Measurements	3475
D10 (μm)	15.5
D50 (μm)	20.7
D90 (μm)	29.9

Distribution of measured API layer thickness based on 29 individual beads and SNR ≥ 10σ: (A) Acetaminophen layer thickness distribution based on FWHM; (B) Example calculation of FWHM of the API layer; (C) Acetaminophen layer thickness summary statistics.

RAMAN CHEMICAL IMAGING

FIGURE 4



Representative SEM image of a cross-sectioned NE 40 D-coated APAP bead.

GX-35 rotor processor with the sustained-release polymer Eudragit® NE 40D, an aqueous dispersion of ethyl acrylate and methyl methacrylate copolymer (Evonik Industries) using the precision powder feeder to add minute amounts of talc to prevent blocking of the NE 40D-coated beads. The beads were coated to a target polymer content of 25% w/w at 300 rpm and 40°C air temperature. Produced beads looked smooth and uniform with better than 98% coating efficiency.

Dissolution testing was carried out using a Hewlett Packard 8452AUV-VIS photo-diode spectrophotometer using Method 06029 (University of Iowa, College of Pharmacy) for sustained-release APAP beads.

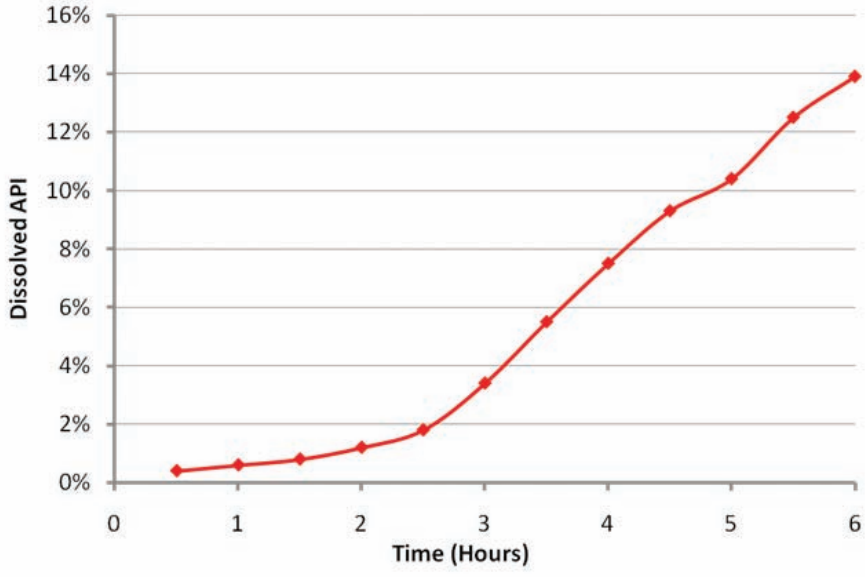
The surface and cross-sectional morphology of the 20 coated beads were observed via SEM images collected using a Hitachi S-4800 SEM. Beads were cross-sectioned to expose the core and inner layers for the RCI study. A total of 29 beads were investigated. All data was collected using a FALCON II™ Wide-Field Raman Chemical Imaging System (ChemImage Corporation) with 532-nm laser excitation. Brightfield reflectance and Raman chemical images were collected in an automated mode at 20x magnification across the right side for 29 individual beads. At 20x magnification, an FOV of 100 x 100 micrometer is interrogated. The following experimental conditions were employed. The laser power was set to 250 mW at the laser head. Each FOV was photobleached for 20 seconds before starting the acquisition. The C-H region was scanned from 2830 to 3120 cm^{-1} at a 5 cm^{-1} interval. Each frame was integrated for 1.5 seconds and 3 averages. All imaging data was processed and analyzed using the ChemImage Xpert™ software package.

RESULTS & DISCUSSION

Raman spectra of the pure component materials were acquired to construct a Raman spectral signature library as shown in Figure 1. Based on the Raman library of pure components, the imaging spectral range for efficient discrimination of each constituent was selected in the C-H spectral region (2700-3200 cm^{-1}).

The FALCON II microscope was focused on the edge of each bead to include all three layers. The RCI processing steps included cosmic ray removal, baseline correction, and vector normalization. For final ingredient discrimination, a spectral unmixing algorithm called Spectral Mixture Resolution (SMR) was applied to the RCI data. SMR evaluates each pixel spectrum using a linear combination of the pure component spectra to achieve an overall spectral contribution. The result is presented as a spatial distribution of each

FIGURE 5



Dissolution profile for NE 40 D-coated APAP beads.

ingredient. A representative data set comparing optical microscopy and RCI is shown in Figure 2. The RCI-derived ingredient images can be used to objectively measure the thickness of individual coating layers. The frame corresponding to the API was isolated and smoothed using a convolution filter with three averages, and an intensity profile for each row of pixels (128 in each frame) was generated. Intensity profiles (IP) with signal-to-noise ratio below 10 standard deviations were discarded. The thickness value was measured as the Full Width at Half Maximum (FWHM) of the IP trace. The average thickness value then was calculated based on 3475 measurements for 29 samples. A representative IP trace and API layer thickness distribution is shown in Figure 3. The APAP layer is 21.8 ± 5.8 micrometers thick (n = 29), D10 = 15.5 micrometers, D50 = 20.7 micrometers, and D90 = 29.9 micrometers. A consistent distribution of the drug layer within the sampled bead population was observed.

SEM results from 20 beads from the same batch revealed the API thickness was 15-20 micrometers. A representative SEM image of the cross-sectioned bead is shown in Figure 4. SEM data correlates well with the RCI results. Differences in the RCI-measured thicknesses can result from several factors such as the larger sample population, nonlinear dependence of Raman signal on sample volume, and FWHM metric for layer thickness determination.

Dissolution testing was carried out to evaluate sustained-release properties of the polymer-coated bead. The dissolution results showed a fairly linear zero-order release after 2 hours in 0.1N HCl media as shown in Figure 5. Due to the relatively large polymer coat, the dissolution was retarded to a greater extent than a typical formulation but was suitable for this investigation. At 6 hours, just under 14% of the drug had been released with a standard deviation of 0.7 (N = 6).

CONCLUSIONS

API layer coating thickness has been measured using wide-field RCI to characterize multilayered beads used for sustained-release drug delivery. Rich spectral and spatial information contained within the RCI data cube can provide valuable feedback during formulation and manufacturing processes and help correlate coating thickness with drug dissolution profiles. RCI technology is especially valuable for multilayer beads or for troubleshooting manufacturing processes.

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BIOGRAPHIES

Dr. Oksana Klueva started at ChemImage in 2004 as a Senior Scientist. After providing technical support for Air Quality and Biothreat applications on government projects, she moved to developing new applications and supporting marketing. After graduating from Boston University in 2002, she worked as an Application Scientist for Horiba Jobin Yvon, Optical Spectroscopy Division. Her responsibilities were to provide technical support for customers and during the sales process. Dr. Klueva earned her PhD in Physical Chemistry from Boston University and her MS in Organic Chemistry, Moscow State University.

Dr. Ryan J. Priore joined ChemImage Corporation in 2008 as a Senior Scientist and is the operational leader of the applications group, where he is responsible for exploring and developing pharmaceutical chemical imaging applications as well as delivering high-quality chemical imaging contract services. He earned his BS in Chemistry from the University of Pittsburgh and his PhD in Analytical Chemistry from the University of South Carolina for his development of real-time, optical computing technology. Dr. Priore then joined Ometric Corporation, where he led the application development of optical computing based, in-line process measurement instrumentation for the pharmaceutical, food, beverage, and pet nutrition industries. He is also the author of a dozen publications and patents on spectroscopic applications and instrumentation.

Brian K. Jensen has been with Vector Corporation for 25 years, previously as Senior Scientist, Process Development, and as Laboratory Manager since 2005. He is a graduate of Iowa State University and has been involved with a large number of Vector Corporation's customers, providing product and process development as well as providing guidance for product line improvements and equipment modifications. He holds several patents associated with Vector's fluid bed line and is a member of AAPS and CRS.

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Banner Pharmacaps Inc.

"Banner helps companies gain maximum productivity and product value from their pipeline. Big pharma and companies of all sizes choose Banner to distinguish their products, expand product life cycles, and most importantly, improve patient outcomes."

Banner is a leading global gelatin-based drug delivery and specialty pharmaceutical company that has developed a broad range of breakthrough softgel products. The company is a widely recognized market leader in soft gelatin capsule technology. Banner researches, develops, and produces innovative, proprietary drug delivery technologies and products for its own portfolio. The company also partners with pharmaceutical and biotech companies worldwide to find solutions to their formulation, processing, and product life-cycle challenges, and help them expand and improve their product pipelines. Drug Delivery Technology recently interviewed Roger E. Gordon, PhD, President and CEO of Banner, to discuss the company's proprietary technologies and expertise, and the future direction of the oral drug delivery industry.

Q: Can you please discuss Banner's drug delivery technologies and services?

A: Banner specializes in controlling the absorption and enhancing the bioavailability of insoluble and lipid-soluble compounds. Our focus is on improving the delivery of existing molecules to increase efficacy and reduce side effects. We also utilize our proprietary technologies and expertise to reduce dosage frequency in order to lower drug costs and improve patient compliance, as well as to target drug delivery and speed the onset of action.

Through our commitment to innovation and meeting marketplace needs, Banner has created a line of softgel variants that offer clear advantages over other dosage forms and standard softgel technologies. Among our innovative, patent-pending technology platforms is EnteriCare®, the first and only uncoated enteric softgel for reduced reflux and gastric irritation. Our proprietary enteric technology eliminates the inherent challenges of coated enteric formulations, which can often crack and chip, potentially compromising the integrity of the functional coating. Additionally, EnteriCare technology results in clear, elegant capsules that appeal to consumers.

Other Banner technologies include Versatrol™ Controlled-Release Softgels, a highly versatile delivery vehicle suitable for lipophilic and hydrophilic drugs. In addition to tailoring the drug release to almost any desired rate and extent, Versatrol also has an application for abuse resistance. Our two chewable formulations, an appealing dosage form for pediatric and geriatric patients, are LiquiSoft™

Chewable Liquid-filled Softgels and Chewels® Chewable Softgels. Softlet® Gelcaps, tablets enrobed with gelatin that are easily print-coded, tamper-evident, odor- and taste-masking, are widely used in over-the-counter products. Banner's Solvatrol™ Enhanced Solubility technology provides enhanced bioavailability and lessens biovariability.

Q: Many companies focus on drug delivery technologies. What makes Banner unique?

A: Banner stands out among the softgel companies because of our strategic focus, not only on developing unique, proprietary technology platforms that add value to our clients' products and increase the productivity of their pipeline, but because we have successfully proven each technology with products utilizing these technologies in the marketplace. We protect our innovations through regulatory applications and patents. Banner has considerable expertise in gelatin-based drug delivery systems, our primary focus. Our R&D labs and manufacturing plants operate in several locations in North America, as well as Europe. We have been developing drugs for many of the leading pharmaceutical companies around the world for several decades, and have developed and manufactured billions of units of softgel and Soflet products that are distributed through our marketing partners.

Q: How does Banner help companies find solutions and bring value to the industry?

A: It all goes back to understanding the clients' needs for their products. For highly variable, narrow therapeutic compounds, for example, improving safety can possibly be achieved by increasing bioavailability and reducing inter- and intra-subject biovariability. Or improving onset of action by maximizing the rate of absorption. Or improving patient compliance by reducing the dosing frequency through our controlled-release technology.

As an example, Banner has an NDA for valproic acid delayed-release softgel capsules. The product is formulated with our advanced enteric technology, EnteriCare. This technology enables two significant benefits. First, rather than needing to modify the API into a crystalline solid and thereby increasing cost, with our technology, we can utilize the natural liquid form of valproic acid. Second, releasing the API in the small intestine reduces any possible gastric irritation and reflux the patient may experience. Our capsule is also 40% smaller than the tablet formulation, providing patients with the convenience of a small, easy-to-swallow softgel.

Banner helps companies gain maximum productivity and product value from their pipeline. Big pharma and companies of all sizes choose Banner to distinguish their products, expand product life cycles, and most importantly, improve patient outcomes.

Q: What makes Banner an ideal partner?

A: Soft gelatin technology is a niche system for oral drug delivery that naturally shields products from generic assault or erosion. As a recognized industry leader in softgel technology, Banner offers considerable expertise, fundamental scientific understanding, and unique technologies that make us an ideal partner for life-cycle management.

Banner applies innovation to encapsulation. Pharma companies can leverage Banner's technologies to gain a competitive advantage by enhancing the biological properties of their patented drugs. Our development work and technologies also provide popular line extensions for consumer products. For example, we were the originators behind naproxen sodium and cetirizine softgels, which we also manufacture for the national brands as line extensions.

Banner has a solid track-record of achieving our client's drug

delivery and product development goals in a collegial, yet time-sensitive manner that meets regulators' expectations. We understand our customers' challenges and work with them to provide solutions.

Banner's global R&D staff comprises more than 80 professionals, and we have a strong and experienced pharma management team. Our global manufacturing facilities are located in High Point, NC; Olds, Calgary, Canada; Mexico City, Mexico; and Tilburg, The Netherlands. We also have specialized facilities: an applications laboratory, FDA-approved cytotoxic facility, a potent compounding suite, CaCo-2 cell lines, and a DEA Schedule II vault and manufacturing line. In addition, we develop and transfer analytical methods and support stability studies to ICH guidelines.

Q: What are some of the key challenges facing a pharmaceutical formulator in oral dosage forms?

A: First, pharmaceutical formulators must understand the factors that control the absorption of the API, and determine the sensitivity of the API to temperature, moisture, and light. Formulators must also ensure the API is compatible with the excipients in the formulation, and that the drug product will remain stable through the shelf-life of the product.

The next essential step is determining the factors and parameters that are critical to the manufacturing process and the formulation. A proper design of experiment at the outset helps ensure product failure does not occur further down the development path after making significant investments in time and money. A quality-consistent manufacturing process and formulation design that is scalable, from lab bench-scale to commercialization, is critical to product success. Of course, all formulators face the challenge of balancing product development, cost, speed, quality, and time.

Q: What is Banner's growth strategy, and what impact do you see Banner's technologies having in the market?

A: Banner has differentiated itself from other softgel companies by adopting a strategic focus based on the value proposition of product leadership. As a specialty pharma company, we are utilizing our unique drug delivery technologies to build a strong product portfolio. We will expand our technology platforms, looking at new areas such as site-specific targeting, for example, colonic delivery, targeting the colon by adjusting the pH of the EnteriCare shell matrix. We are also looking beyond gelatin to other polymer-variant technologies that will provide a more robust capsule or a multitude of release profiles in vivo, regardless of the environmental conditions, for example, pH, ionic strength, and bile salts. As a scientist, I am tremendously excited by the studies being conducted on how genes influence the performance of drugs. I believe personalized medicine could open up amazing opportunities for our technologies.

Q: What do you see as the future direction of the oral drug delivery industry?

A: Personalized medicine and the need for many unique combination products of highly insoluble APIs. The softgel dosage form can be easily filled with solubilized or suspended API in an almost infinite array of volumes and strengths. Further, the softgel dosage form shell can function as an immediate-release, a delayed-release, or a controlled-release barrier, thereby allowing the scientist to engineer the most appropriate blood level profile for the patient because the key elements, such as safety and efficacy, have been factored in. ◆

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CRAMS Trends

Contract Research & Manufacturing Services: Best Practices, Investment Strategy & Deal-Making

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

Introduction

The contract research and manufacturing services market (CRAMS) is one of the fastest growing segments in the pharmaceutical and biotechnology industry. Despite the recent economic downturn, the market continues to grow at a rapid pace of about 10% to 12% year-on-year compared to growth projections of 14% to 15% in 2007-2008 before the slowdown. In the mid-to-long-term, growth rates are expected to pick up pace, although a higher base effect combined with greater penetration is likely to have an impact on the overall scale of growth.

The downturn has had a significant impact on small-to-mid-size sponsors that have been outsourcing a greater percentage of their research and manufacturing compared to larger companies. Smaller companies have had issues with funding, especially early stage projects, which have, in some cases, resulted in payment delays and even defaults.

However, larger sponsors are looking to lower their costs as well as improve productivity by spinning off or selling their non-core activities, such as research and manufacturing, which favors the service providers by enabling them to garner a greater share of the business, and also potentially expand their services by acquiring these business segments.

As a result of these restructuring exercises, we are likely to see a larger number of long-term strategic deals between sponsors and service providers like the landmark 2008 Covance-Eli Lilly deal.

CRO Market Landscape

The US CRO market, which is the largest CRO market globally with a share of over 55% of all global trials in 2009, grew from $7.44 billion in 2006 to $9.76 billion by 2008, at about 14.5% growth year-on-year. This rapid growth in the market was driven by a variety of factors that include the emergence of specialty pharmaceutical and biotechnology companies as an engine for R&D growth and clinical pipeline expansion.

Traditionally, in the 90s and early 2000, "big-pharma" companies were the most important growth driver for CROs. However, the lack of significant blockbuster products and a shift in the R&D landscape resulted in the emergence of these tier 2 and 3 companies that have been the key drivers for providing tier 1 companies with a clinical pipeline to work on and take to market. This change in business model and supply-chain landscape of R&D has benefited CROs

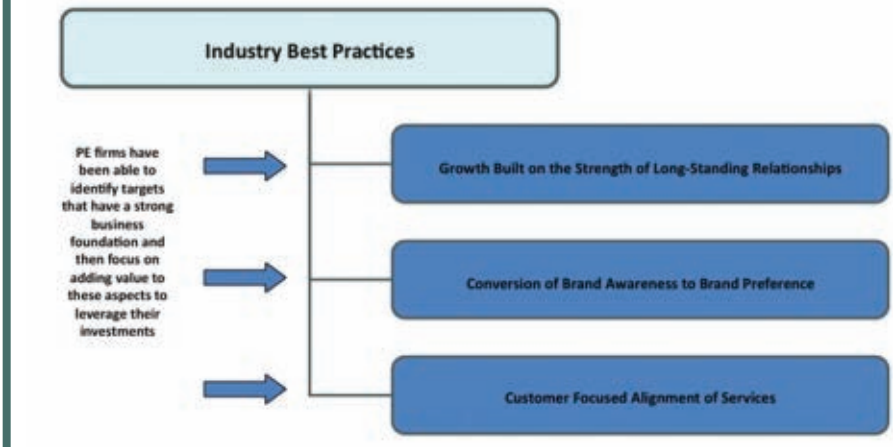

Figure 1. Industry Best Practices: Some of the Key Industry Best Practices in the US CRAMS Market in 2009-2010

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significantly, due to the lack of infrastructure and financial resources within these tier 2 and tier 3 developer companies to carry out and manage their trials.

Current assessments value the US CRO market to more than double its revenues from $10.9 billion in 2009 to $22.9 billion by 2016 at a compound annual growth rate (CAGR) of 11.1%.

CMO Market Landscape

The US pharmaceutical contract manufacturing markets, which include solid dosage, sterile and non-sterile semi-solids is forecast to grow from $9.3 billion in 2009 to $15.1 billion by 2014 at a CAGR of 10.1%.

In the short-term (2010), we expect some effects of the slowdown to affect the expansion activities of small-to-medium CMOs. This was also the expectation in 2009. The tight credit situation combined with recessionary effects has resulted in a slowdown of expansion activities. However, given the growth prospects for this segment, combined with the flurry of generic versions of major blockbuster drugs, the prospects for CMO growth continue to remain bullish.

Additionally, the average manufacturing plant utilization rate at pharmaceutical companies is less than 50%, resulting in several plant closures or sell-offs and increased outsourcing penetration.

Understanding some of the key industry best practices is vital to making intelligent investment decisions. Companies that are successful and sustainable in the long-term differentiate themselves from their competition through some key best practices discussed further.

1) Growth Built on the Strength of Long-Standing Relationships

The long-term success of top CMOs and CROs has been built on the back of strong long-standing relationships with major industry participants. Service providers that offer additional value-added, upstream and downstream services have tended to remain consistently successful over a longer term. Proprietary drug delivery platforms have also played an important role in ensuring the continued success of these mutually beneficial partnerships.

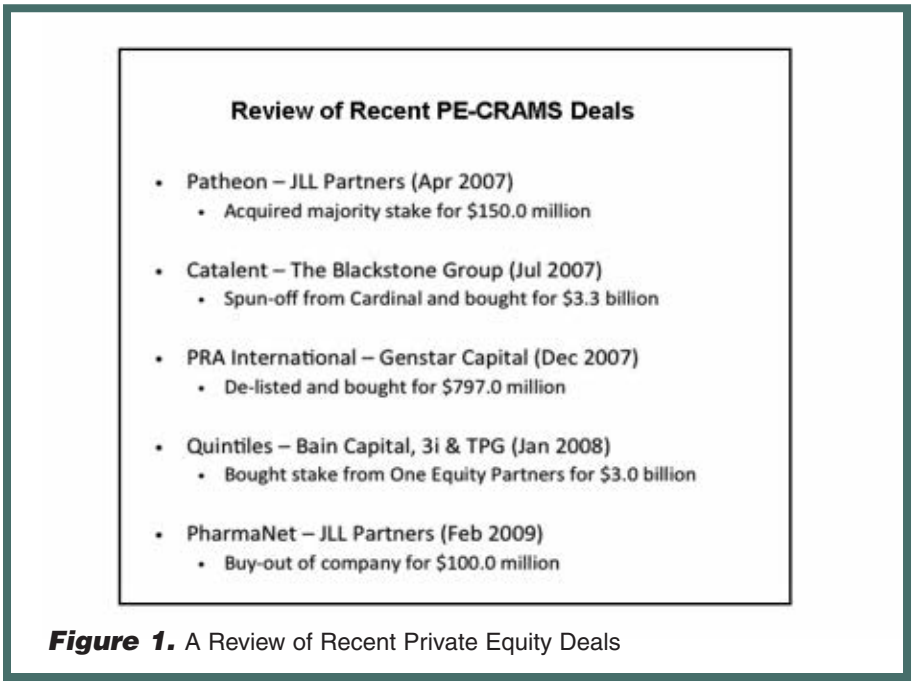

Figure 1. A Review of Recent Private Equity Deals

2) Conversion of Brand Awareness to Brand Preference

Top CMOs and CROs are renowned for their breadth of services, global reach, and the strength of their brand. In two surveys of pharmaceutical and biotechnology executives as a part of Frost & Sullivan Voice of the Customer Analysis of the US Pharmaceutical and Biotechnology CMO and CRO Markets, it was observed that there was a clear distinction between service providers that had a high brand awareness compared to those with a high brand preference.

The market leaders have been service providers with strong conversion rates and have stayed ahead of competition in the market by strategic initiatives and leveraging the strength of their brand.

3) Customer Focused Alignment of Services

CMOs and CROs not only need to adopt a highly customer-focused approach toward its clients but also constantly evaluate their needs and measuring their satisfaction against previous benchmarks on an ongoing basis to ensure quality services. By maintaining multiple channels of communication with its clients, service providers can ensure continuous engagement of its clients and smooth flow of information.

CMOs, for example, that are part of a larger pharmaceutical or biotechnology company, can draw expertise from the R&D division to help clients in addressing complex formulation challenges and improve productivity and efficiency of processes.

These are some of the industry best practices that have separated successful service providers from the rest of the industry. Private equity firms have been able to identify targets that have a strong business foundation and/or exhibit potential for these traits to then add value to the organization by focusing on these aspects and leveraging their investments.

Investment Strategy & Private Equity Deal-Making in CRAMS

Private equity firms typically target companies with strong cash flows, room for operational improvements, and short-to-mid-term stability. Mid-to-large-size pharmaceutical and biotechnology firms have fit this requirement well. However, these companies have remained out of the

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reach of private equity firms due to their large market capitalization and the tight credit situation.

Contract research and manufacturing firms, however, have continued to attract attention and investments from private equity firms for some time. In the recent past, this attention has increased considerably, as we've seen. The recent economic downturn has further lowered valuations of these firms and has put several companies within easy reach of private firms. CROs and CMOs provide these firms with good opportunities to improve efficiencies at these companies and then turnaround and sell them at a significant return on investment.

From an investment perspective, CROs and CMOs provide private equity firms with a strong access path to the pharmaceutical and biotechnology industry and perform core operations that are currently being increasingly outsourced. As big pharmaceutical companies are witnessing a shake up from major patent expiries and unfavorable cost structures, they are looking to increasingly outsource or sell off these core operations in a strategic manner to outsourcing partners.

Overview of Recent Private Equity Deals

A look at some of the recent private equity deals in the CRAMS sector reveals that most transactions have been in the top tier level of CMOs and CROs - these also represent a diverse range of types of transactions that include acquisitions, leveraged, secondary, and management buy-outs.

JLL Partners acquired a majority stake in Patheon for $150 million in 2007, at a time when Patheon was facing difficulties with integration of some earlier acquisitions, as well as establishing a stable financial foundation.

Catalent was created as a $3.3-billion spin-off from Cardinal Health by Blackstone group and has emerged as one of the top CMOs providing manufacturing, drug delivery, and development solutions.

PRA International was taken private through a buy-out by Genstar Capital in a deal valued at $797 million. It is interesting to note that Genstar previously held PRA International between 2001 and 2005 before divesting its investment through an IPO.

Bain Capital, 3i, and TPG Capital completed an approximately $3-billion secondary buy-out of Quintiles from One Equity Partners, the private equity firm that took Quintiles private in 2003 for $1.7 billion.

Finally, JLL Partners acquired PharmaNet in 2009 for $100 million buy-out. PharmaNet was facing difficulties with refinancing and a tight credit market, and it was an excellent opportunity for JLL to invest in a fast growing sector.

Summary

These transactions have virtually paved the way for further investment to flow into tier 2 companies as private equity firms uncover more opportunities. While the top tier CMOs and CROs represent a large market share opportunity and strong cash flows, the mid-tier service providers have traditionally experienced higher growth rates due to their niche focus. Additionally, private equity firms could also leverage their experience in improving operational efficiencies of their investments by combining the strengths of their investments across areas and further increase their growth potential. ◆

An in-depth report on this and other related topics can be obtained by contacting Frost & Sullivan at www.frost.com.

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

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Unethical Ethics

By: John A. Bermingham

I believe ethics is one of the most important and necessary assets a great CEO must possess. It can take years to gain this asset and a microsecond to lose it! Lately, it seems as though several of the Captains of Industry have been on shaky ground. The two most recent, following Bernie Madoff's Big Scam Adventure, are the Toyota and Goldman Sachs debacles.

Were the CEOs of these two companies caught leading their companies in an unethical manner or are the accusations against them bogus? Did Toyota's CEO Akio Toyoda know about the accelerator defects and hide it, and did Goldman Sachs' CEO Lloyd Blankfein know about the high risk to investors and the win/win for his company at the investors' expense on a questionable investment vehicle? Are they guilty of Unethical Ethics?

Let me tell you about a situation that I once faced. When I was a brand new CEO at Rolodex Corporation, one of the Senior Product Managers came into my office and asked if he could speak with me. I said sure, and he shut my door. He said there was something I needed to know, and information was purposely being held from me. He went on to say that most of our electronic organizer products had high defect rates, some models approaching 90%. We were shipping these products to our retailers, and most were coming back either from the retailer or directly from their customers.

When I asked why we were doing this, the answer was that the executives on the bonus plan wanted to hit their numbers to achieve their bonus compensation, so they kept on shipping known defective products. The product manager and I walked out to the warehouse so I could look at the defective products. There was about $3 million to $4 million in defective products I directed to be put into quarantine so we would not continue to ship them.

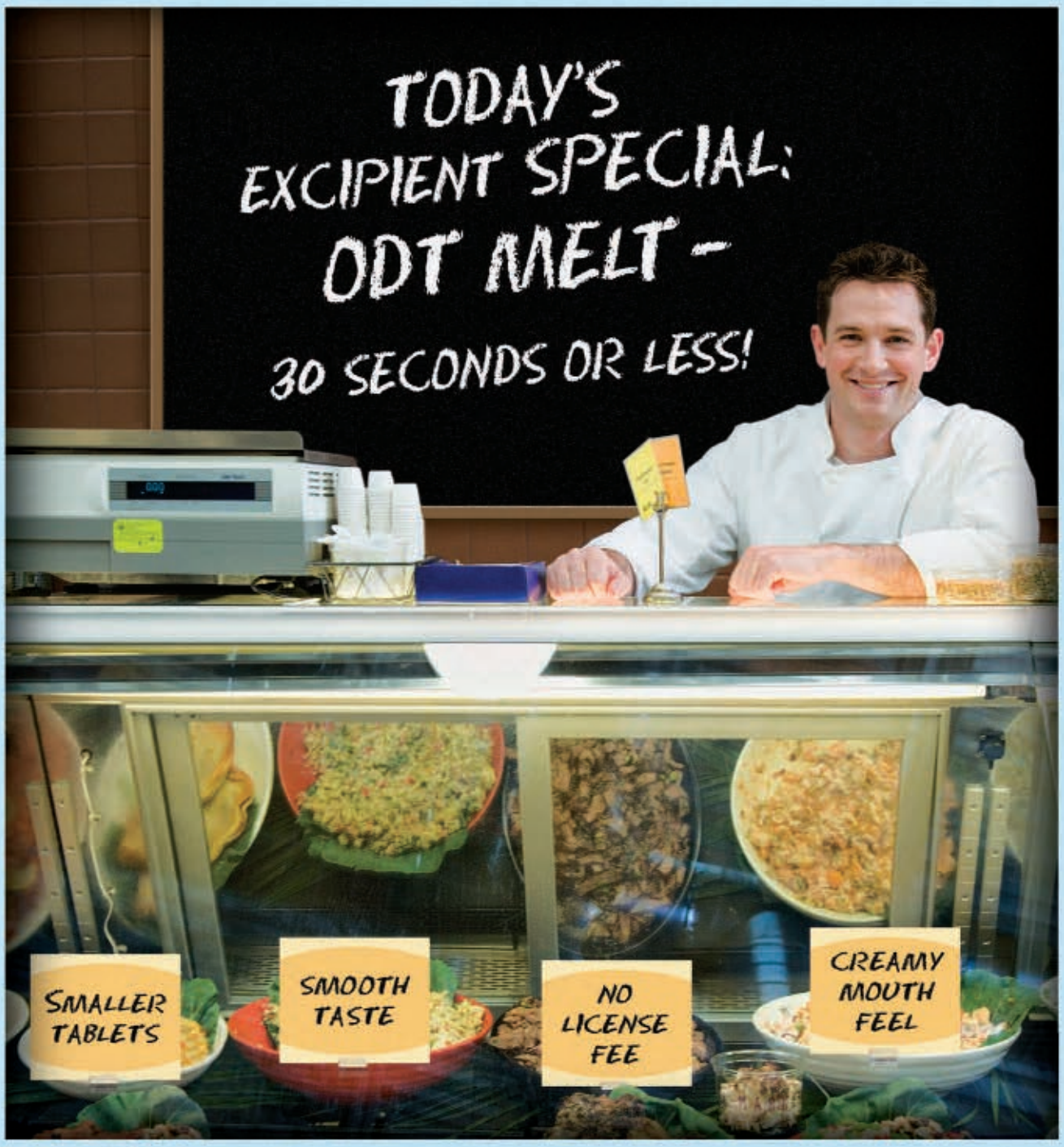
After dealing with the people who were guilty of knowingly shipping defective products, I contacted everyone of our retailers through telephone calls or e-mails and assured them we would support them on returns from their customers and make things right. I also gave direction that any retailer or customer who called regarding a defective product should be transferred to me. In addition, I met several customers in our lobby during this time and personally exchanged their defective products for new ones that had been individually quality control checked to ensure they worked properly. Plus, I added an additional product gift as a way of apologizing. Our quick action saved our retailers and appeased those customers who came directly to us for help. I had a choice to make in that situation; ignore the problem or do the right thing. For me, it was an easy choice. Do I join the Unethical Ethics gang or demonstrate I was a person of character?

In the case of the Toyota and Goldman Sachs CEOs, what if the CEOs had immediately come forward and announced Toyota has defective automobile accelerators, and Goldman Sachs has a very high-risk investment vehicle that will cost investors millions in losses while the company makes millions on the default and then proceeded to correct these situations? Even if the accusations are unfounded, these CEOs should not have let their respective situations get out of hand and to the point at which they are now.

I believe instead of going from neutral to a -10 in credibility as these companies have, they instead would have gone from neutral to a +10. Whether the accusations are true is not the point. These companies have taken a very hard hit in the market as a result of these CEO inactions. There is a Japanese saying I learned years ago. It says that *The fish always stinks from the head*! ◆

BIOGRAPHY

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



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