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The Benefits of Magnetofection

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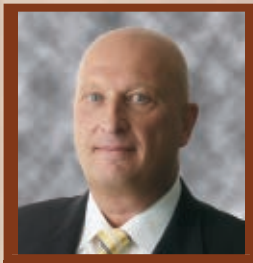

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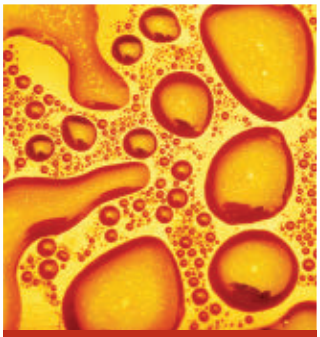

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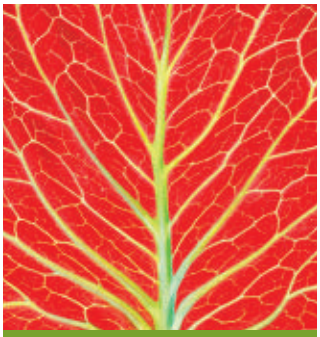

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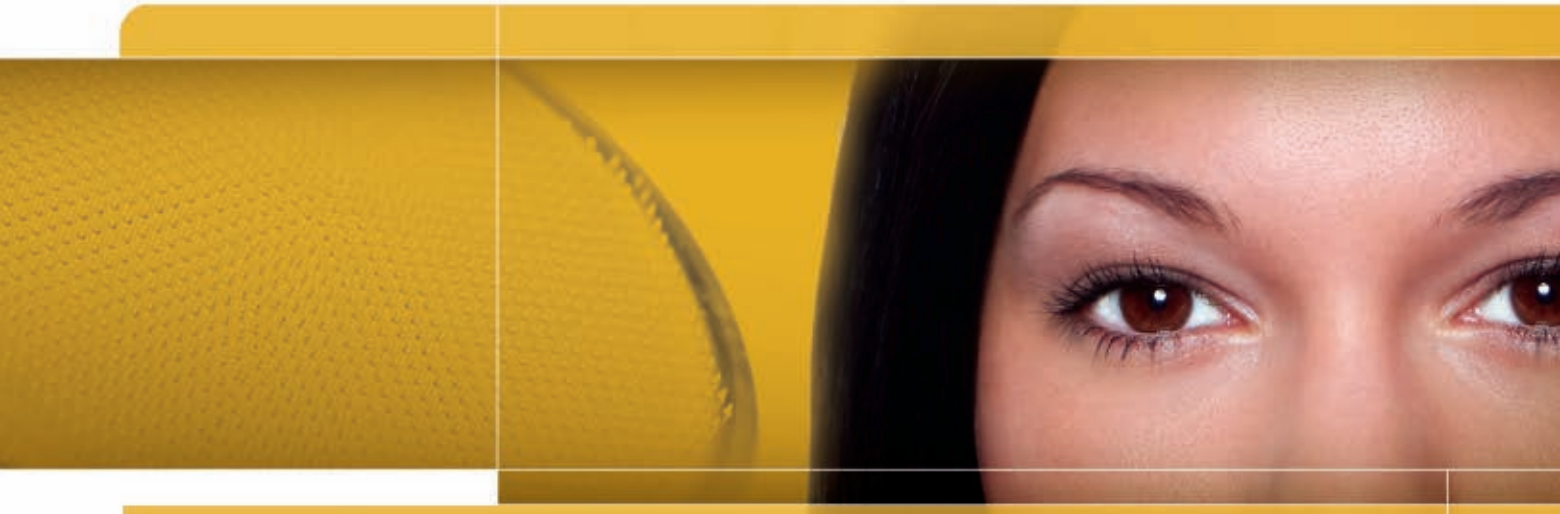

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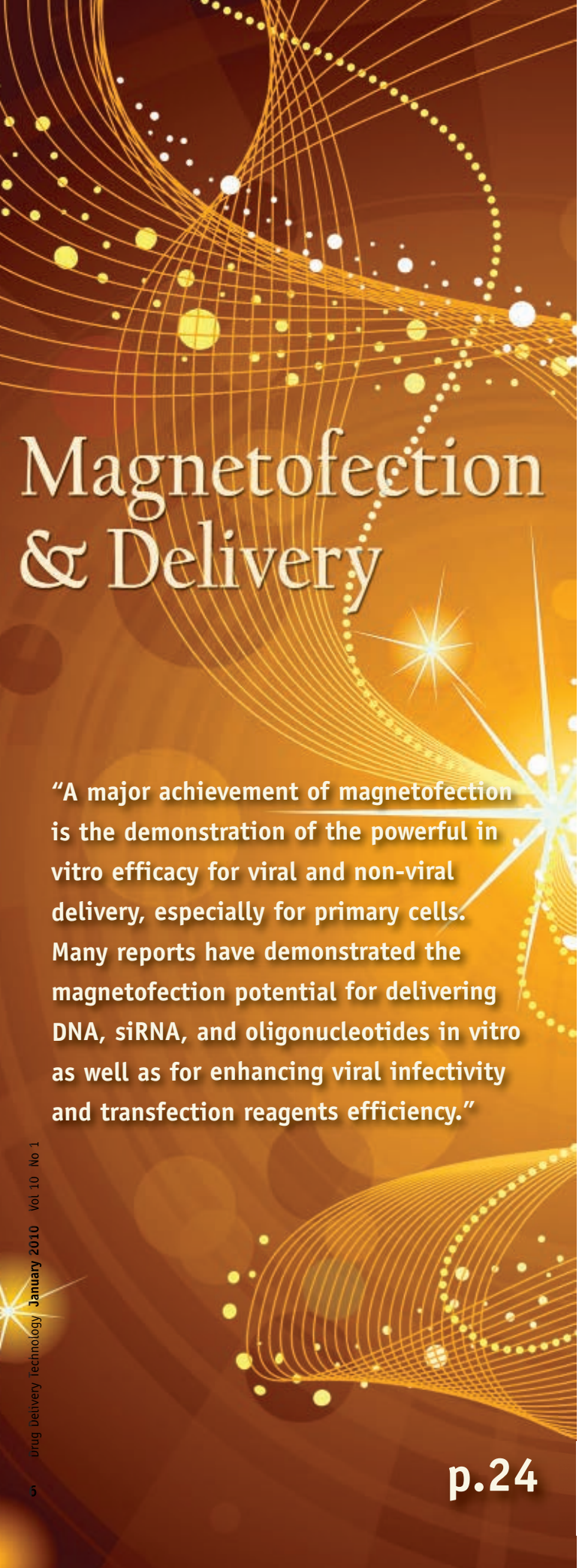

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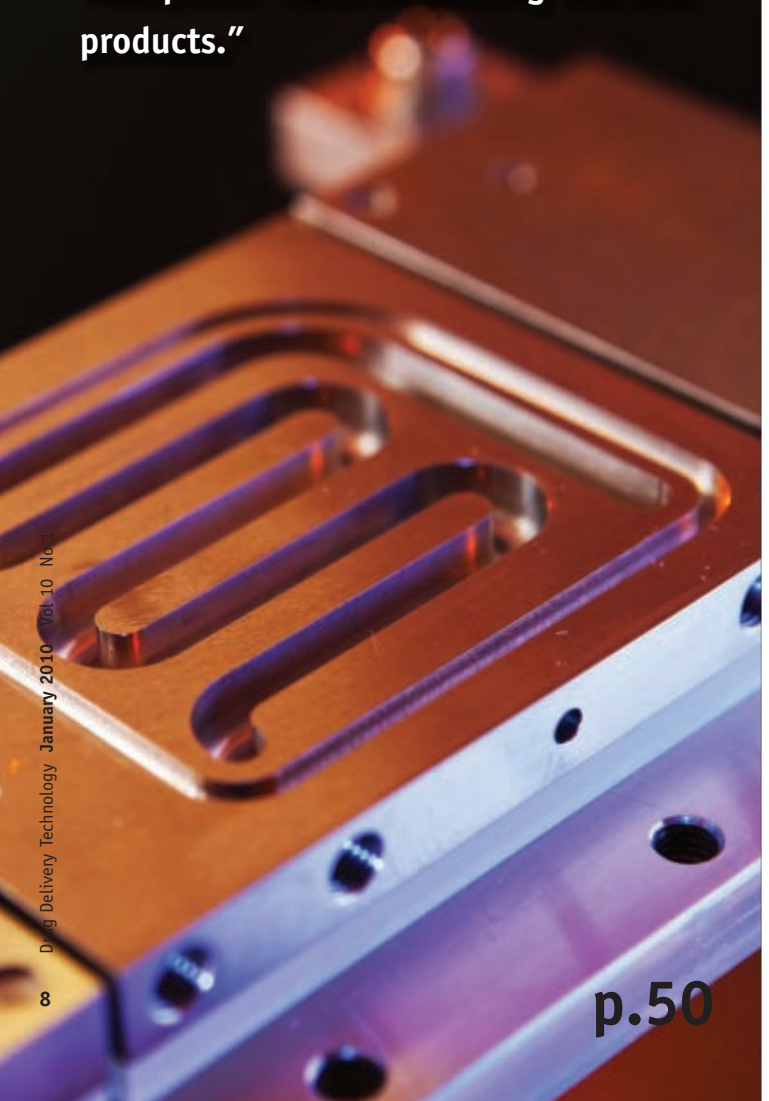

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Market News and Trends

MonoSol Rx & Strativa Pharmaceuticals Extend Strategic Relationship

MonoSol Rx, the developers of PharmFilm technology and a drug delivery company specializing in proprietary pharmaceutical film products, recently announced it has entered into a new licensing and development agreement that grants the option to develop three new products with Strativa Pharmaceuticals, the proprietary products division of a wholly owned subsidiary of Par Pharmaceutical Companies, Inc. Strativa has the option to license exclusive US commercialization rights for the three additional oral soluble film (OSF) products to be developed using MonoSol Rx's PharmFilm technology.

The new option agreements are an extension of the strategic relationship between MonoSol Rx and Strativa, initiated in June 2008 when Strativa acquired exclusive US commercialization rights to MonoSol Rx's ondansetron OSF, which will be marketed under the trade name Zuplenz. The NDA for Zuplenz was accepted for review by the US FDA in June 2009, and a response is expected in the first quarter of 2010 as mandated by the Prescription Drug User Fee Act (PDUFA) guidelines.

"The Strativa corporate strategy is an ideal fit with the MonoSol Rx partnering model, as demonstrated by our successful development and regulatory submission of Zuplenz OSF," said A. Mark Schobel, President and CEO of MonoSol Rx. "We welcome the opportunity to expand our relationship for the potential development and commercialization of three additional OSF products that leverage the MonoSol Rx PharmFilm technology. The Strativa team has been a valuable partner for us and recognizes that drug delivery via film may offer numerous benefits across the entire pharmaceutical spectrum, from improving onset of action and dosing accuracy to enhancing patient compliance to providing highly differentiated drug products that can extend the revenue life cycle of soon-to-be-expired or expired blockbuster compounds."

Terms of the new agreements provide the option to license and develop three additional OSF products under a similar structure to the companies' ondansetron OSF exclusive licensing agreement, which entitles MonoSol Rx to pre-commercialization and sales-based milestone payments, as well as payments for the purchase of product supply and royalties on net sales.

"These new agreements with Strativa represent a direct endorsement, from a current partner, that MonoSol Rx has the capabilities and technology necessary to address the needs of the pharmaceutical industry," added Keith J. Kendall, Executive Vice President and CFO of MonoSol Rx. "Our strategy is to leverage film drug delivery to create new partnership opportunities. These relationships generate incremental streams of revenue for MonoSol Rx while providing an effective, differentiated dosage form that potentially allows our partners to preserve revenue life cycles or compete more effectively in crowded therapeutic markets. The success of our revenue-sharing business model has led to the doubling of our revenue growth in each of the past 2 years, and is anticipated to create similar returns in 2010 and beyond."

Dicerna Signs Deal With Kyowa Hakko to Develop RNAi Cancer Treatments

Dicerna Pharmaceuticals, Inc., a second-generation RNA interference (RNAi) company developing novel therapeutics utilizing its proprietary Dicer Substrate Technology and Dicer Substrate siRNA (DsiRNA) molecules, and Kyowa Hakko Kirin Co., Ltd., one of Japan's leading biopharmaceutical companies, recently announced the two companies have entered into a research collaboration and license agreement for the research, development, and commercialization of drug delivery systems and DsiRNA pharmaceuticals for therapeutic targets in oncology.

Under the terms of the collaboration, Dicerna will receive $4 million in up-front cash payments including research funding, and up to $120 million in additional research funding, development and commercial milestones for exclusive rights to one target in the field of oncology. According to the progress of the research collaboration, Kyowa Hakko Kirin and Dicerna may expand the scope of the collaboration by adding approximately up to 10 targets under similar terms and may broaden the therapeutic focus of the partnership. Dicerna is entitled to royalty payments on sales from products for these targets. Dicerna also has an option to equally co-promote and profit-share (50:50) in the US for the initial target.

Alnylam & MIT Collaborators Report New Preclinical Research on Systemic Delivery of RNAi Therapeutics

Alnylam Pharmaceuticals, Inc., a leading RNAi therapeutics company, and collaborators from the David H. Koch Institute for Integrative Research at the Massachusetts Institute of Technology (MIT) recently announced the publication of new data describing further advancements in discovery and development of novel lipidoid formulations for the systemic delivery of RNAi therapeutics. Lipidoids are lipid-like materials discovered for the delivery of RNAi therapeutics, and were originally described by Alnylam and MIT collaborators in Nature Biotechnology. In particular, the new research findings demonstrate the discovery of new lipidoid materials that facilitate significantly improved in vivo potency for RNAi therapeutics.

"We are very encouraged with the substantial progress we and our collaborators have made with lipid nanoparticles (LNPs) based on novel lipid-like materials, such as lipidoids," said Victor Kotelianski, MD, PhD, DSc, Senior Vice President, Distinguished Alnylam Fellow. "To our knowledge, these new LNP formulations facilitate endogenous liver gene silencing at doses that are orders-of-magnitude lower than those required by previously described siRNA delivery approaches, thereby setting a new standard in potency for the systemic delivery of RNAi therapeutics. In addition, the current study is the first to report on the simultaneous and highly specific RNAi-mediated silencing of as many as five liver targets in vivo, serving as proof-of-principle that multiple genes involved in similar or divergent biological pathways can be silenced with a single administration of a single drug product. From a therapeutic standpoint, this could enable novel pharmaceutical strategies, where silencing of multiple targets could achieve an enhanced level of efficacy."

The new preclinical data describe a formulation based on a lipidoid known as C12-200 that was shown to enable gene silencing in vivo in rodents at doses below 0.01 mg/kg; demonstrate complete, rapid, and durable gene silencing in rodents as soon as 24 hours with protein levels returning to baseline within 20 to 35 days; specifically inhibit expression of as many as five target genes simultaneously after a single injection of an LNP formulation in rodents; and demonstrate potent and selective silencing of the clinically relevant gene transthyretin (TTR) at doses as low as 0.03 mg/kg in non-human primates.

"We are excited by the delivery performance of these new formulations," said Daniel Anderson, PhD of the David H. Koch Institute for Integrative Cancer Research at MIT. "This work demonstrates that doses measured in micrograms per kilogram can provide potent gene silencing with RNAi in several species including primates. This greatly improved efficacy allows us to significantly decrease the dose levels of LNPs, thereby widening the therapeutic index, and also opens the door to formulations that can simultaneously inhibit multiple genes or pathways."

Lipidoid formulations represent one of several approaches Alnylam is pursuing for systemic delivery of RNAi therapeutics. Additional approaches include other lipid nanoparticles formulations, mimetic lipoprotein particles (MLPs), siRNA conjugation strategies, and single-stranded RNAi, among others. Alnylam is currently enrolling patients in a Phase I clinical program with its systemic RNAi therapeutic ALN-VSP for the treatment of liver cancers. In addition, Alnylam intends to initiate a Phase I trial in the first half of 2010 for an additional systemic RNAi therapeutic, ALN-TTR for the treatment of TTR-mediated amyloidosis. ALN-VSP and ALN-TTR both utilize a first- generation lipid nanoparticle formulation known as stable nucleic acid-lipid particles (SNALP), developed in collaboration with Tekmira Pharmaceuticals Corp.

Market News and Trends

to-BBB Technologies BV & Lundbeck Join Forces on Brain Delivery of Antibodies

to-BBB, the Dutch drug brain delivery company, and the pharmaceutical company H. Lundbeck A/S are entering into a research collaboration to evaluate delivery of antibodies to the brain for central nervous system (CNS) diseases. This research could provide the backbone of new emerging therapies for unserved brain diseases.

"We are very pleased to collaborate with Lundbeck," said Pieter Gaillard, CSO of to-BBB. "to-BBB's brain delivery technology combined with Lundbeck's strong knowledge in the area of CNS disorders should result in further progress to improve the lives of patients with devastating brain diseases."

Lundbeck is an international pharmaceutical company engaged in research to find new drugs for treatment of CNS disorders, including depression, schizophrenia, Alzheimer's disease, and Parkinson's disease. The collaboration with to-BBB could provide Lundbeck with an opportunity to improve the brain delivery of therapeutic antibodies addressing CNS diseases.

Thanks to the advances of biotechnology, therapeutic antibodies have become well-established treatment modalities to address many systemic diseases. The blood-brain barrier (BBB) is unfortunately a significant obstacle in the treatment of CNS disorders because it prevents delivery of many drug candidates to their disease target.

to-BBB's proprietary G-Technology is a safe technology for drug delivery to the brain and 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. The company has shown proof-of-concept in several model systems, including brain microdialysis, pain inhibition, viral encephalitis, and brain tumors, based on which Lundbeck will now evaluate the technology in their labs.

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. to-BBB is headquartered in The Netherlands at the Leiden Bio Science Park and has established a fully owned subsidiary, to-BBB Taiwan Ltd., in Taipei, Taiwan.

Evolva Enters Discovery Collaboration With Roche

Evolva Holding SA recently announced it has signed an agreement with Roche to create compounds with activity on targets in oncology and anti-infectives using Evolva's technology platform. Roche will pay Evolva an up-front technology access fee and ongoing research fees. Roche will have responsibility to take forward any compounds discovered during the collaboration and will potentially pay Evolva research and clinical milestone fees as well as royalties on any products that result from the collaboration. Evolva will have the first right to any compounds not taken forward, or subsequently deprioritised by Roche.

"The agreement with Roche represents another step forward in the development of our genetic chemistry technologies," said Neil Goldsmith, CEO & Managing Director of Evolva. "By exploring biosynthetic scaffolds that have many of the design features of nature we aim to build a pipeline of novel diverse compounds with anti-infective and anti-cancer effects. We are very pleased to have a leading player such as Roche expressing their confidence in our discovery platform."

Evolva's proprietary discovery technology platform uses a disruptive technological approach to the creation of novel small compounds that differs sharply from the prevailing synthetic chemistry and protein engineering approaches in the pharmaceutical industry today. Based on this technology, Evolva has a number of discovery and preclinical partnerships, which in 2008 generated revenues of about CHF 12 million. Evolva also has an attractive pipeline of compounds - one compound (for renal and cardiovascular diseases) entered Phase I at the beginning of 2009, and two others (an anti-fungal and an anti-viral) are expected to enter Phase I in 2010.

Bioject Establishes Strategic Alliance With MPI Research

Bioject Medical Technologies Inc., a leading developer of needle-free injection therapy systems, recently announced it has established a strategic alliance with MPI Research, a leading preclinical research organization with experience in the development of injectable therapeutics.

The strategic alliance creates a preferred partnership relationship that allows Bioject to gain access to a range of capabilities and resources needed for the company to explore its drug-plus-device opportunities, including access to pharmacologic, analytical, safety, and other preclinical testing resources available at MPI Research. The strategic alliance offers MPI Research the opportunity to provide Bioject's needle-free technology as an alternate delivery option to current drug/biologic manufacturers who may be interested in seeking a more highly competitive and differentiable drug-plus-device brand. This alliance also increases the possibility that Bioject and MPI Research may be able to secure government-sponsored grants or funding directed at improvements in drug-plus-device or vaccine-plus-device-based treatments, which could also lead to potential new drug-plus-device combinations.

"We look forward to our new strategic alliance with MPI Research, which adds the much needed resource capabilities that we have been seeking as a first step in advancing our new drug-plus-device business strategy," said Ralph Makar, Bioject's President and CEO. "This is a positive step forward for both organizations and allows each partner to leverage the strengths, resources, and technologies available that we believe will lead to additional new business opportunities for both companies. We are excited and enthusiastic about the potential for the future."

"Bioject and MPI Research share an innovative and entrepreneurial spirit that creates a synergy vital to our industry," added CEO and Chairman of MPI Research, Bill Parfet. "It is a pleasure to collaborate with a company that has such highly developed technological expertise and strategic vision."

Bioject Medical Technologies Inc., based in Portland, Oregon, is an innovative developer and manufacturer of needle-free injection therapy systems (NFITS). NFITS provide an empowering technology and works by forcing medication at high speed through a tiny orifice held against the skin. This creates a fine stream of high-pressure fluid penetrating the skin and depositing medication in the tissue beneath. The company is focused on developing mutually beneficial agreements with leading pharmaceutical, biotechnology, and veterinary companies.

EXCIPIENT UPDATE

A Competitive Comparison of an ODT Excipient System

By: John K. Tillotson, PhD

INTRODUCTION

In recent years, orally disintegrating tablets (ODTs) have increased in popularity due to the numerous advantages they offer over conventional, swallow tablets. These advantages include ease of administration, rapid onset of action, and the convenience of taking the medication without water. Furthermore, in the case of orally absorbed actives, increased bioavailability can be achieved.

Due to these advantages, various drugs are being developed and launched in ODT dosage form. Initially, ODTs were developed by lyophilization, a process which produced rapidly disintegrating tablets. However, the process had limitations, including specialized equipment requirements, costly processing, limited drug loading, and tablet durability. Subsequently, molded-tablet ODTs were developed. These tablets also disintegrated relatively rapidly; however, there were still limitations, including reduced manufacturing speeds, lack of tablet durability, and the need for getting the tablets manufactured by the ODT vendor. Most recently, focus has been on manufacturing ODTs by direct compression (DC) unit operations and giving customers the flexibility to manufacture internally or outsource it. The advantages of DC are speed of manufacture, low cost, and increased tablet durability. Disadvantages include prolonged disintegration times and inferior organoleptics. In order to reduce or eliminate the disadvantages associated with the DC manufacture of ODTs, numerous excipient systems have been marketed to the pharmaceutical industry. The current paper focuses on comparing one such system, Pharmaburst® 500, with two of its competitors. For purposes of the study, the competitors will be identified as Competitor L and Competitor F.

STUDY

The competitive analysis contemplated the following areas of performance: physical characteristics, flow, dilution capacity, placebo performance, speed sensitivity, and high-dose formulation performance.

PHYSICAL CHARACTERISTICS

All ODT excipient systems were tested on a Hosokawa Powder Tester (Hosokawa, Japan) for bulk density (BD), tapped density (TD), and angle of repose (AOR). For each excipient system, the Carr's Index (CI) was calculated using the BD and TD. Particle Size Distribution (PSD) for each excipient system was determined employing a Malvern Particle Size Analyzer (Malvern Instruments LTD, United Kingdom). Table 1 displays the physical characteristics of the respective ODT excipient systems, and Figure 1 displays the PSD of each excipient system.

FLOW

Of primary importance in DC tableting is the flow of formulations out of the hopper, onto the press, and into the die cavity. It is often the flow characteristics, or lack thereof, that determines the uniformity of tablet weight. Additionally, the ability of an excipient system to continue to flow well even when diluted with poorly flowing actives is a desirable attribute.

In order to comparatively evaluate the ODT excipient systems with regard to flow, the systems were tested as pure blends and as binary blends in conjunction with Crospovidone XL (angle of repose = 46º, CI = 31.3), which was employed as a model for a poorly flowing active pharmaceutical ingredient (Model API). The pure blends were tested through a restrictive aperture of 0.25" diameter, while the binary blends Model API at concentrations of 15%, 25%, and 50% were tested through a restrictive aperture of 0.6693". 60 mL of each powder was allowed to gravity flow to completion. Time was recorded at start and completion. Powders that did not flow or bridged prior to completion were considered to exhibit no flow through the aperture. Results for the binary blend flow testing are displayed in Figure 2.

Analysis by paired t-test demonstrated no significant difference in flow properties

TABLE 1

ODT Excipient System	BD (g/mL)	TD (g/mL)	AOR (º)	Carr's Index
Pharmaburst 500	0.411	0.485	33.1	15.3
Competitor L	0.509	0.657	39.6	22.5
Competitor F	0.531	0.654	35.4	18.8

Physical Characteristics of Study ODT Excipient Systems


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of excipients between Competitor L (P = 0.980) or Competitor F (P = 0.672).

At 10% dilution of Model API in the blend, both Pharmaburst 500 and Competitor F flowed significantly better than Competitor L (p = 0.0003, p = 0.0002, respectively). Pharmaburst 500 and Competitor F did not exhibit a significant difference in flow velocity at the 10% dilution (p = 0.552). At 25% dilution of Model API in the blend, Pharmaburst 500 flows significantly better than both Competitor L and Competitor F (p = 0.0190, p = 0.0332, respectively). At 40% dilution of Model API in the blend, Pharmaburst 500 exhibited superior flow to both Competitor L and Competitor F (p < 0.0001, p = 0.0448, respectively).

DILUTION CAPACITY

Each excipient system was diluted with acetaminophen non-DC powder at levels of 10%, 25%, and 50%. Compressions of the powder systems took place on an instrumented Lloyd's press (Lloyd Instruments LTD, United Kingdom) outfitted with a 15-mm FF punch (Natoli Engineering, St. Charles, MO). Compression to limit was performed at 15, 20, and 25 kN at a speed of 10 mm/min. Hardness (kP) served as the response. Results for the dilution capacity study are displayed in Figure 3.

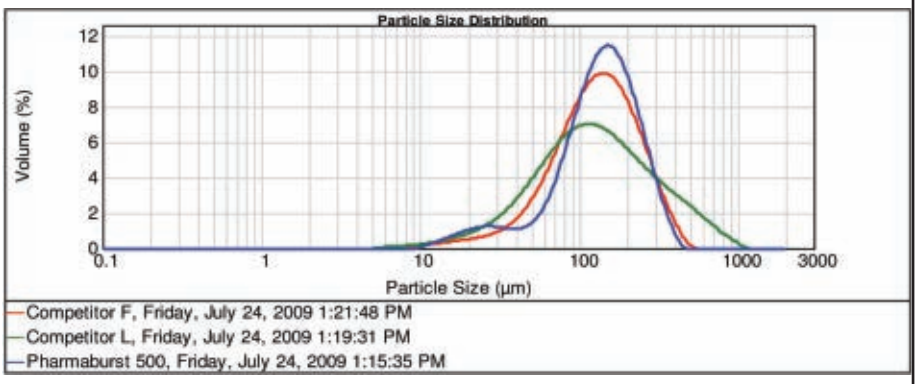
Looking at Figure 3, it is apparent that Pharmaburst 500 offers greater dilution capacity, even with poorly compressible non DC APIs, than Competitor L or Competitor F at all dilution and compression force levels.

PLACEBO PERFORMANCE

To comparatively evaluate the placebo performance of the respective excipient systems, each was blended for 5 minutes with 2.5% of Lubripharm™ SSF, sodium stearyl fumarate (SPI Pharma - Wilmington, DE). Subsequently, 400-mg of each blend were compressed on a GP-8 instrumented tablet press (Globe Pharma, New Brunswick, NJ) outfitted with 0.4375" FFBE "D" tooling (Natoli Engineering). Hardness, friability, and USP/EP disintegration time were measured as responses.

The data indicate that placebos compressed from Pharmaburst 500 disintegrate more rapidly than placebos of Competitor L or Competitor F at all hardness levels. Moreover, it is worth noting that

FIGURE 1



PSD of ODT Excipient Systems

Pharmaburst 500 achieves high hardness at much lower compression force compared to competitors. For example, at 15 kN, Pharmaburst 500 placebo reaches 17 kP vs. competitor's below 10 kP.

SPEED SENSITIVITY

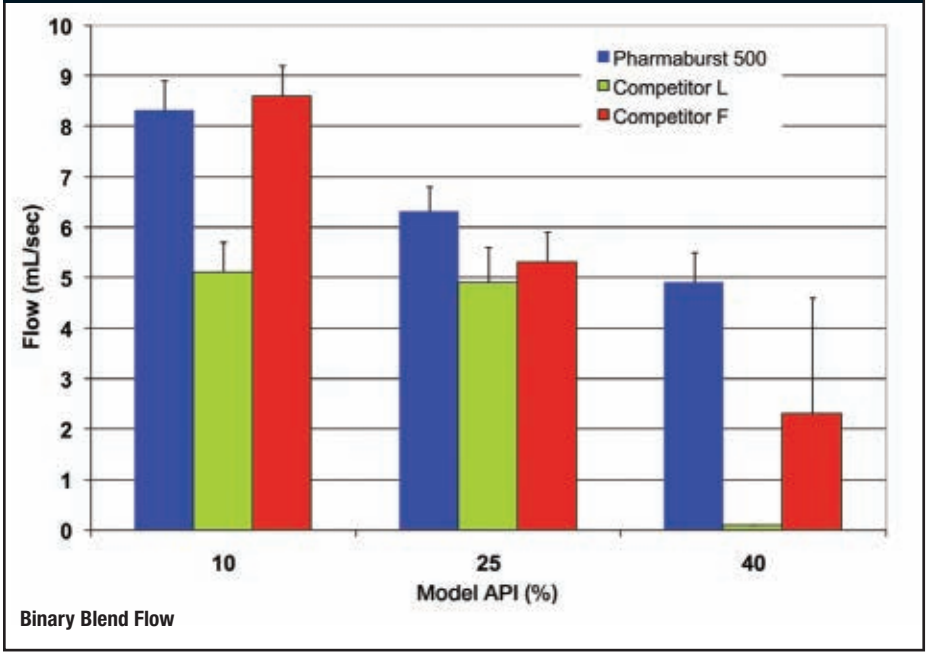
To compare speed sensitivity, each system was blended with 2.5% Lubripharm SSF and compressed on an instrumented Manesty Beta Press (Oystar Manesty, United Kingdom) outfitted with 0.625" FFBE "B" tooling at speeds of 40, 60, and 80 rpm at a compression force of 20 kN. Hardness was considered as the response. All three ODT excipient systems are relatively insensitive to increases in press speed, even at relatively low dwell times.

HIGH DOSE FORMULATION PERFORMANCE

In order to compare high-dose performance, each ODT excipient system was blended with 50% taste-masked Acetaminophen (93%) and 2.5% Lubripharm SSF. 1000-mg tablets were compressed at 10, 15, 20, and 25 kN with 1 kN of pre-compression on an instrumented GP-8 tablet press outfitted with 0.625" FFBE "D" tooling at 25 rpm. Tablet hardness, friability, and disintegration time were measured as responses. Tablet disintegration vs. hardness is displayed in Figure 4. Tablet friability is displayed in Table 2.

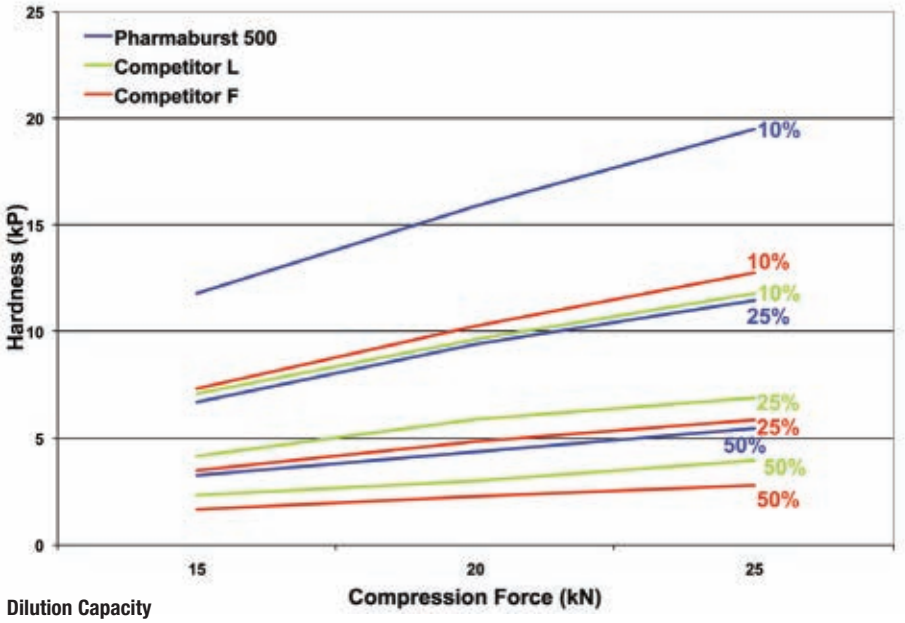
Pharmaburst 500 provides for harder, more rapidly disintegrating high-dose tablets than Competitor L and Competitor F.

FIGURE 2



Binary Blend Flow

FIGURE 3



Dilution Capacity

Additionally, high dose ODTs made with Pharmaburst 500 exhibit lower friability than Competitor L and Competitor F at all compression forces.

CONCLUSION

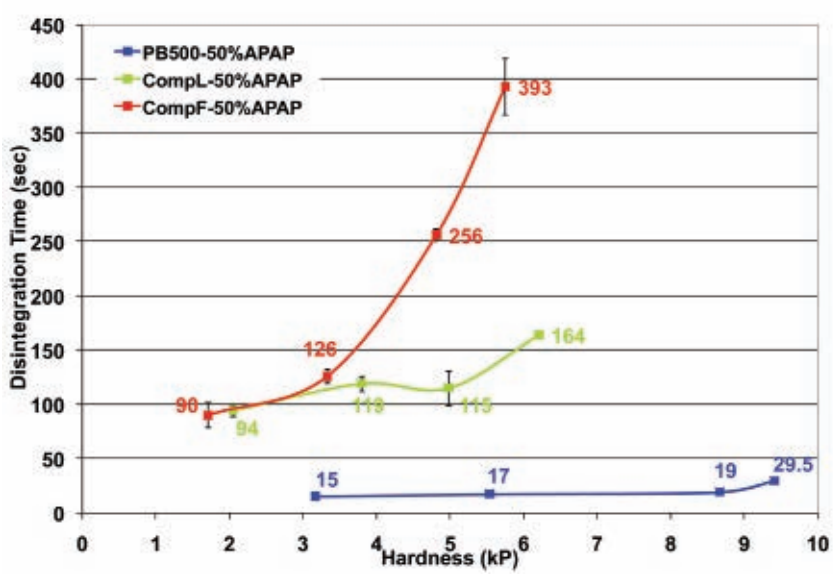
Pharmaburst 500 significantly outperformed Competitor L and Competitor F with regard to flow, dilution capacity, overall placebo performance, and overall high-dose performance. With regard to speed sensitivity, all three excipient systems performed equally well. In addition, internal and external taste panels have shown the superior organoleptic attributes of Pharmaburst 500. The results demonstrate that Pharmaburst 500, which is a fully optimized, "use-as-received" excipient system, delivers optimum performance in terms of tablet robustness, high drug loading capacity and distintegratoin time; all of which are critical for a successful ODT launch.

TABLE 2

ODT Excipient System	10 kN	15 kN	20 kN	25 kN
Pharmaburst 500	1.44	0.252	0.030	0.050
Competitor L	100	4.732	0.670	0.410
Competitor F	100	100	0.307	0.218

Friability Per Compression Force (%)

FIGURE 4



USP/EP Disintegration Time vs. Hardness

BIOGRAPHY

Dr. John K. Tillotson is a Senior Scientist in the ARTS Department (Applications Research & Technical Services) at SPI Pharma, a global company focussed on excipients, antacids and drug delivery/ development services. Dr. Tillotson earned his BS in Pharmacy from Ferris State University, Big Rapids, MI, and his PhD in Industrial Pharmacy from the University of Cincinnati, Cincinnati, OH, where he trained under Dr. Adel Sakr. He has held industrial positions in Guatemala and the US. Dr. Tillotson's primary areas of interest are quick-dissolve tablet technologies, particularly directly compressible modalities. Additionally, he specializes in multiple-regression analysis and optimizations of quick-dissolve technologies, solutions, and systems. Previously, Dr. Tillotson was involved with the development and optimization of bumetanide sustained-release technologies through multiple-response optimization. He has developed several quick-dissolve systems for nutraceuticals, OTC, and prescription products. Additionally, he has participated in idiosyncratic ODT formulation development for various APIs. Dr. Tillotson has presented various original, workshop, invited symposium, and/or poster presentations at national and international meetings. He has published papers discussing the use of multiple-response optimization for the development of ER formulations, as well as papers discussing the benefits of various ODT excipient systems. He is a member of the Rho Chi Pharmaceutical Honor Society and of the AAPS.

Product Development, Expectations & the Real World

By: Josef Bossart, PhD

It's Christmas day, and you announce to your kids that the family will be going to Disney World for Spring Break. You and your spouse have checked your schedules and the family budget, and it should all work. A week later, you are at the office and when you ask your boss for that week off, you get the news that the contract the company had bid on was won and you will need to be in South America that week. You feel as though you have shot yourself in the foot. There will be other chances to go to Disney World, but your credibility with the kids has just taken a big hit. Only a little more planning could have avoided the problem. Your kids would have been just as happy to visit Disney World this summer, but you promised Spring Break.

It's much easier to establish expectations than it is to deliver on them. It's human nature to want to please people by providing optimistic timelines. In your personal life, failing to meet expectations is often limited to embarrassment, in business, it can be much more costly. Failing to meet business expectations damages credibility that can lead to lost opportunities, lost funding, and in worst case situations, a failed business. Establishing stretch expectations that can be met on time and on budget is one of the most important responsibilities of a leader.

MANAGING EXPECTATIONS

How do you set internal and external expectations for the development of your drug delivery-enabled product? If your team has never developed a product with this technology or for this indication, you'll need to depend on your team's best estimate based on a detailed project plan. This project plan is often based on a core clinical development plan, which usually defines the minimal program required to secure approval. But development programs we know often require more than the basic minimum program to secure approval, and when implemented, programs are subject to unexpected and uncontrollable external delays.

Looking to other companies' experiences with products using similar technologies and addressing similar indications can help us understand what we might reasonably expect. Looking at the performance of other companies doesn't tell us what they hoped to achieve; it tells us what they actually achieved in the real world. These products almost certainly had much more optimistic timelines than were actually realized.

If your internal plan has you getting through development and approval in 4 years, and similar products have taken 6 years, you may want to rethink your plan and what you communicate to the outside world. Unless you have a very definite idea of how and why you will beat the industry benchmarks, you may want to reconsider the expectations you are setting internally and externally. That single Phase III pivotal trial with 400 patients your clinical team says is all that's required for approval may well turn out to be two trials with a total of 600 patients. And it's hard to do two trials with 50% more patients in the same amount of time, or with the same budget.

The best advice in setting expectations is to blend your internal plan with real-world benchmarks and avoid the temptation to put forward your most optimistic scenario.

DRUG DELIVERY-ENABLED PRODUCT DEVELOPMENT PARAMETERS

We should be pretty familiar with the development times and success rates for

TABLE 1

Product Type	Mean Development & Approval Time	Average Success Rate
Pharma Products	8.0 Years[1]	16%[2]

1 – Extrapolated from Tufts data for products in development between 1997-2007.
2 – For Phase I products in development 1993-2004.

Pharma Product Clinical Development & Approval Times & Success Rates (Tufts Center for Drug Development, Reports and Press Releases)

pharmaceutical products in general. These figures have been available for more than 10 years thanks to the work of Dr. Joseph DiMasi and his colleagues at the Tufts Center for Drug Development. In addition to the much-publicized $1-billion plus estimate for the cost of developing a pharmaceutical product to approval (including product failures and the investment cost of money), this group has provided benchmarks for clinical development and approval times and success rates. This group's most recent figures are summarized in Table 1.

These numbers aren't directly applicable to the majority of drug delivery products as drug delivery-enabled products generally, but not always, incorporate previously used actives. This can significantly reduce the risk of development and hopefully improve the success rates for drug delivery-enabled products. At the same time, starting with approved actives should also reduce clinical development and regulatory review times because overall efficacy and safety parameters have already been defined.

Too often we like to look to the Tufts figures with a sense that they don't apply to drug delivery-enabled products. Drug delivery products of course have shorter development times and higher success rates when compared with new molecular entity products. But exactly how much shorter and how much higher? Top line figures for drug delivery-enabled products from the Bionumbers DD09 report are presented in Table 2.

Interesting numbers to be sure, and perhaps not quite what you expected. (Note: the development times and success rates in Table 2 relate only to the clinical development and regulatory review process. All preclinical and formulation work would be in addition to the aforementioned.). The extrapolated numbers in Table 2 offer a more realistic estimate of current (2010) success rates and times. There has been a consistent drop in success rate and a lengthening of development times throughout the past 15 years. The lengthening development and approval times is not an issue of lengthening FDA review times; these figures have remained remarkably consistent for more than a decade.

TABLE 2

Product Type	Mean Average Development & Approval Time	Average Success Rate	Mean Average Development & Approval Time	Average Success Rate
	Current (Extrapolated)		Historical (1993-2008)	
All DD-Enabled Products	6.5 Years	24%	5.8 Years	34%
DD-Enabled Products, New Molecular Entity Actives	8.5 Years	23%	7.6 Years	34%
DD-Enabled Products, Previously Approved Actives	6.2 Years	24%	5.5 Years	33%

Drug Delivery-Enabled Product Clinical Development & Approval Times & Success Rates (DD09 Report - Bionumbers, September 2009)

MANAGING EXPECTATIONS, REGRESSION TO THE MEAN

How do these numbers fit with the current expectations for your own pipeline of drug delivery-enabled products? Are you planning on putting four or five candidates into the clinic in hopes of getting one through to approval? Or are you expecting that you'll beat the odds and hit on your first and/or second product?

Well, there is good news for you optimists; it's possible to do better than one in four if you have selected the right targets, indications, benefits, and/or delivery platforms. Some classes of drug delivery-enabled products have success rates greater than 50%. But there are also classes of products with success rates of less than 20%.

In the same way, there are product classes that get through the clinic and to approval in less than 6.5 years; sometimes in much less time. And there are classes that take longer. Do you know where your products fit?

We'd all like to believe that we, our children, and our portfolio products are in one way or another exceptional and not subject to averages. If your development team forecasts clinical development to take 3 years and regulatory approval to take another year (the FDA permitting), do you budget accordingly? Or do you look at the experience of others and budget for the average, with the full intention to beat these benchmarks?

With a natural tendency to regress to the mean, it's hard to recommend budgeting and setting expectations for exceptional outcomes. This doesn't mean exceptional performances aren't possible; it's just that exceptional performances are, well, exceptional. Planning or budgeting on the

basis of exceptional performance is a formula for disappointment. Setting expectations internally and externally that your product can be approved in 2 years less than experience has shown for similar products can lead to big problems. If your product is approved according to your optimistic expectations, you're a winner, you've met expectations. But if your performance is in line with the average, you'll be considered a failure because of the expectations you have set. This can lead to finger-pointing, revised budgets, and further delays. Is it perhaps better to set real-world expectations, work toward exceptional performance, and reap the associated rewards of exceeding expectations?

REFLECTIONS

Our industry has reached a point at which drug delivery-enabled therapeutics are no longer one-off projects. Products are less an artisanal project, subject to the skill and technology of the artist/scientist and more a mainstream process for which we have considerable experience to estimate outcomes in terms of development and approval times, success rates, and costs. We should not be taken by surprise when results are more consistent with the means and medians rather than our best estimates.

The following are three Pharmanumbers Rules for estimating the costs and timelines for drug delivery-enabled products:

1. Expect to take 4 or 5 products into the clinic if you want to have one reach approval.

2. Plan on taking 6 or more years to develop a product from the start of clinicals through to approval if the development program demands anything more than simple bioequivalence trials.

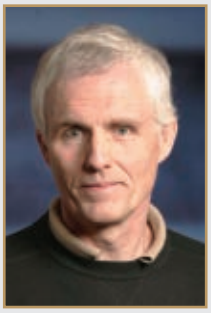
3. Budget no less than $160 million (2009 Dollars) in direct costs to get one product approved. It doesn't cost $160 million to develop one product, but three out of four or four out of five products are not going to make it.

The good news is that drug delivery-enabled products are still faster and cheaper to develop than traditional pharmaceutical products. The bad news is that these products are perhaps not as quick and easy to develop as you may have thought and budgeted. But knowing what the numbers are can give you a significant edge in setting expectations that help you to manage and beat the product development odds.

Taking your kids to Disney World, Yellowstone National Park, or on an African safari can be a truly enriching experience for the family. Just be sure you have a good idea of what it entails and that it's possible before you tell the kids. Children, like investors and analysts, don't respond well to blown expectations, even if you acted in good faith.

If you'd like a more in-depth understanding of the parameters and numbers that define the development performance of drug delivery products, please contact us, and we'll send you a complimentary copy of the executive summary from our latest report DD09 - Drug Delivery Product Success Rates, Development Times, Costs and Marketing Exclusivity. This report covers more than 600 products in development between 1993 and early 2009. Our contact information is available at www.bionumbers.com. ◆

BIOGRAPHY



Dr. Josef Bossart is Managing Director of Pharmanumbers LLC, a boutique research and consulting group providing the biopharmaceutical industry with analysis and insights that improves business outcomes. In addition to issuing industry reports, such as DD09 - Drug Delivery Product Success Rates, Development Times, Costs and Marketing Exclusivity under its Bionumbers division, Pharmanumbers provides strategy consulting and forecasting support for emerging and commercial-stage biopharma companies. Dr. Bossart has more than 3 decades of experience in the biopharmaceutical sector, including senior sales, marketing, business development, and management positions with Enzon Pharmaceuticals, GeneMedicine, US Ethicals, and Rhône-Poulenc Rorer. Dr. Bossart earned his PhD in Medicinal Chemistry from The Ohio State University, College of Pharmacy.

NUCLEIC ACID DELIVERY

Magnetofection: Magnetically Assisted & Targeted Nucleic Acids Delivery

By: Cédric Sapet, PhD; Loïc Le Gourrierec, PhD; Ulrike Schillinger, PhD; Olga Mykhaylyk, PhD; Séverine Augier, Christian Plank, PhD; and Olivier Zelphati, PhD

INTRODUCTION

The idea to treat genetic or acquired diseases by delivering the appropriate nucleic acids into cells to regulate the dysfunction, the lack, or the mutation of genes brings new perspectives for the medicine of tomorrow. However, even if clinical trials started in the 90s with the success of ADA-SCID treatment and recent success with gene therapy approaches, there is still a need for finding improved systems for delivering biological compounds in safe and efficient ways.[1]

Viruses constitute the most developed delivery systems and are the tools of choice in more than 70% of clinical trials.[2] They naturally own intrinsic properties to evade the reticuloendothelial system, bind specific cells, and deliver their genetic material into the nucleus. But the packaging capacity is relatively restricted for some viral species, and large-scale production has limitations. Furthermore, the immune response and the random integration of some viral species into the host genome often lead to non-desired effects.

The non-viral approach comprises essentially two categories, namely the use of synthetic chemical compounds for delivering nucleic acids and physical systems. The latter including electroporation, sonoporation, and laser irradiation, have been widely used.[3] Even though electroporation can be quite toxic when applied in cell culture, it is the most frequently used and efficient physical gene delivery system yielding positive results also in vivo (muscle, liver, tumors). The synthetic vectors commonly used for in vitro nucleic acid delivery are cationic lipids and polymers, which form complexes with nucleic acids called lipo- or polyplexes. These synthetic vectors are designed to optimize DNA complexation/condensation, specific binding, membrane fusion, endosomal release, or nuclear targeting. Although novel efficient in vitro systems for DNA/RNA delivery have been developed, these chemicals still show in vivo limitations, especially in terms of bioavailability at target sites.

MAGNETOFECTION: PRINCIPLE & MECHANISMS[4,5]

One of the fundamental barriers to drug delivery is the poor concentration of biomolecules at the target cells/tissues due to insufficient specificity (lack of specific cell tropism), rapid inactivation, and/or clearance from target sites. Magnetofection, which is based on magnetic drug targeting, can overcome this barrier by using both advantages of physical methods and synthetic vectors. Magnetofection is defined as nucleic acid delivery under the influence of a magnetic field acting on nucleic acid vectors that are associated with magnetic nanoparticles.[6]

In this way, the magnetic force exerted upon gene vectors allows for a rapid concentration of the applied vector dose on cells/organs and promotes cellular uptake. This allows decreasing the required process time of delivery to a few minutes. These factors are crucial for improvement of in vitro and in vivo nucleic acid delivery. The benefits of magnetofection are: (1) it can potentiate the efficacy of a given vector; (2) it overcomes the limited diffusion of gene vectors toward target cells; (3) it reduces vector inactivation during the delivery process; (4) it saves time and materials due to rapid kinetics and favorable dose-response profiles; (5) it allows localized delivery by magnetic force and minimized vector spread to non-target sites.

Formation of Magnetic Nanoparticles/Nucleic Acids Vector Complexes[7]

One advantage of this approach is the inherent flexibility and universality of the assembly process. Magnetic nanoparticles can be used to self-assemble with either "naked" nucleic acids (DNA, RNA, oligonucleotides) or lipo- or polyplexes (nucleic acids already packaged with transfection reagents) or viruses. Magnetic particles commonly used are iron oxide crystallites with around a 10-nm core size

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coated with polycations or polyanions. In aqueous media, they have hydrodynamic diameters of 100 to 250 nm, which is compatible with cellular uptake and intracellular processing. The association with gene vectors (nucleic acids, lipoplexes, and virus) is mainly achieved by salt-induced aggregation and electrostatic interactions. In some circumstances, formation of complexes can be due to hydrophobic and Van der Waals interactions.

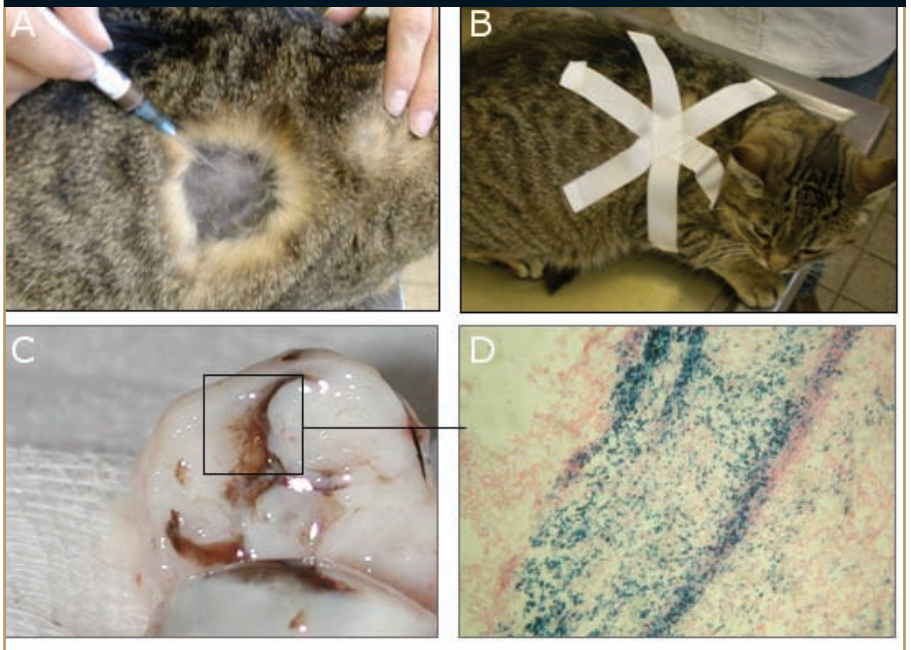
Concentration of Magnetic Vectors Onto the Target Cells/Tissues

The aforementioned formed complexes are then concentrated on cells/tissues by the influence of an external magnetic field generated by specific permanent electromagnets. Particles used in magnetofection are in general terms magnetically responsive solid phases that become magnetized in an external magnetic field but lose this magnetization when the field is removed. This is a feature of superparamagnetism. The particles, together with their payload, will migrate toward the highest density of magnetic field lines (inhomogeneous gradient magnetic field). The pattern of assembly depends on the geometry of the source. Regardless, the magnetic force acting on such particles in a liquid suspension is proportional to the particle size, the magnetic flux density, and the magnetic field gradient.

Cellular Uptake & Nucleic Acids Cytoplasmic Release[8]

Once concentrated onto cells/tissues, the cellular uptake of the nucleic acids is accomplished by two natural biological processes: endocytosis (clathrin-coated or caveolae) and/or macropinocytosis, depending on the cells. According to recent findings, magnetic field influence does not pull the particles directly across the plasma membrane.[9] Consequently, membrane architecture and structure stay intact in contrast to other physical methods. The nucleic acids are then released into cells by different mechanisms, depending upon the nanoparticle formulations used. Mechanisms that can be exploited include the "proton sponge effect" caused by the coated cationic polymers present in vector formulations (promoting osmotic swelling and disruption of the endosomal membrane) or endosome destabilization by cationic lipids present in the formulation that release the nucleic acid into cells by a flip-flop of cell negative lipids and charged neutralization. In magnetofection with viral vectors, the intrinsic biological properties underlying viral infectivity are exploited for delivery.

FIGURE 1



In vivo magnetofection as a treatment for feline fibrosarcoma with GM-CSF plasmid. After intratumoral injection of the plasmid-attached-nanoparticles (A), a magnetic field is applied directly onto the tumor for magnetic guidance of the magnetic beads-associated plasmid (B). Tumor biopsy (C) reveals a restricted targeting of the magnetic nanoparticles stained in blue. In (D), a magnification of the square zone in (C) confirms the efficiency of the delivery by cellular staining (image from Schillinger et al[5]).

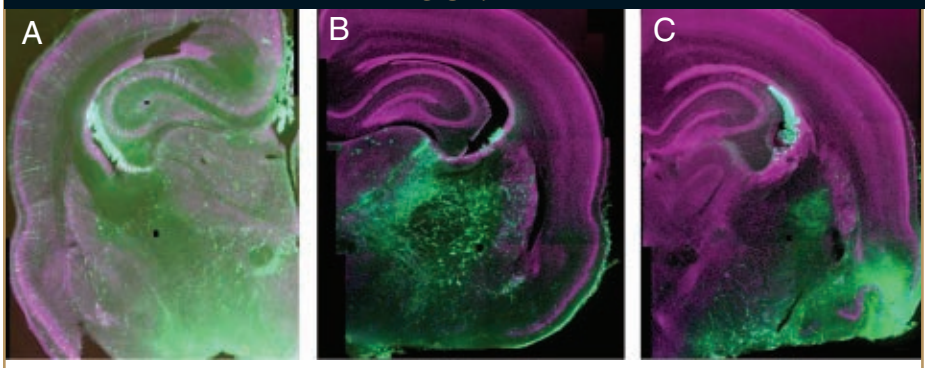
MAGNETOFECTION EFFICIENCY IN VITRO

A major achievement of magnetofection is the demonstration of the powerful in vitro efficacy for viral and non-viral delivery, especially for primary cells. Many reports have demonstrated the magnetofection potential for delivering DNA, siRNA, and oligonucleotides in vitro as well as for enhancing viral infectivity and transfection reagents efficiency.

Magnetofection to Control, Promote & Enhance Viral Transduction

The viral approach challenge would be avoiding potential side effects by systemic spread of delivery while maintaining or enhancing the action threshold and thus enlarging the therapeutic windows at a target site. It has been shown that coated magnetic nanoparticles can efficiently capture viral particles in suspension.[10] Furthermore, when this "viral magnetic system" is used in vitro, transgene expression is significantly higher in comparison to virus alone, especially when

FIGURE 2



In vivo GFP-lentivirus targeting mediated by ViroMag in the brains of rat embryos. Brain sections at 8 days after lateral ventricular injection of 10^9 particles of GFP-lentivirus into in utero rat embryos (E16) showed a diffuse GFP expression (anti-GFP antibodies in green) due to a widespread infection of neurons (A). The association of GFP-lentivirus with ViroMag (Oz Biosciences) induced a targeted local area as shown by the GFP expression in neurons lying under a magnet at the surface of the embryo skull (B). A more intense and restricted GFP-expression (C) was also observed when the magnet was positioned on the edge of the brain leading to an accumulation of viral particles and infected neurons in the focal area.

lower virus titers are used.[7] This is a real benefit particularly for retroviruses, which are known to be difficult for achieving high viral titers. Infectivity enhancement was demonstrated in several models especially with primary T cells.[11] Magnetofection allowed cells to be synchronously infected after the magnetization of viral particles. Synchronization is the key point when studying kinetics of viral infection as shown by Sacha et al. They demonstrated that early presentation of incoming virion-derived Gag epitopes was maximal at 6 hrs post-infection, while Gag epitopes presentation due to de novo synthesis occurred between 18 and 24 hrs. They also showed that penetration of virion-associated proteins into cytoplasm was sufficient to generate CD8+ T cell epitopes early after infection.[12] The use of magnetic nanoparticles also enhanced the effectiveness of cell fusion as demonstrated with the vector hemagglutinating virus of Japan envelope.[13] Efficient lentiviral-mediated transduction of airway epithelial cells is hampered by extracellular barriers and local confinement of viruses on the cell surface. Magnetofection increased infectivity as compared with virus alone in polarized bronchial cells and greatly enhanced transduction in "domes" (cells forming hemicysts containing fluid), which are resistant to lentiviral transduction.[14] Finally, it has also been demonstrated that magnetofection could enlarge the viral tropism by changing the receptor-dependent internalization mechanism to a simple cationic magnetic nanoparticle-mediated cell binding allowing transduction of non-permissive cells (particularly beneficial for adenovirus).[7,15]

Magnetofection for Transfecting Plasmid DNA

Magnetofection is a very effective way of transfecting plasmid DNA into a variety of primary cells. Indeed, primary mouse gastric gland epithelial, human umbilical vein endothelial cells, neurons, myoblasts, chondrocytes, and mouse embryonic stem cells have been successfully transfected.[16-21] For instance, in mature cultured neurons, magnetofection contributed to demonstrating the role of Debrin A in modulating glutamatergic and GABAergic synaptic activities.[22] A specific and detailed magnetofection protocol for cDNA and shRNA vectors transfection in hippocampal neurons cultured from several hours to 21 days in vitro has been published.[23] It also allows double-transfection and long-lasting DNA and shRNA constructs expression without interfering with neuronal differentiation. Because mature neurons are more sensitive to commercial lipid reagents exposure than immature neurons, the lipid exposure time for transfection (toxic for the neurons) can be reduced by magnetofection. Thus, Sbai et al, have associated a lipid reagent and magnetic particles for DNA transfection to point out the vesicular trafficking and secretion of MMP-2, -9, and TIMP-1 in neuronal cells.[18] Almost all kinds of neurons can be targeted via magnetofection; neurons from cerebellar granule, cortex, and dorsal root ganglions have also been successfully transfected.[24-27]

Magnetofection for Delivering siRNA

Magnetofection is a powerful method for gene silencing. McCaig et al have used magnetofection to deliver siRNA in primary human gastric myofibroblasts and deciphered the role of MMP-7 in redefining the gastric environment in response to bacteria.[28] This method of gene silencing is a valuable tool when dealing with primary endothelial cells and cell lines. For instance, siRNA delivery mediated by magnetofection in HUVEC contributed to demonstrate the critical role of a transcription factor in angiogenesis.[29] In the same way, magnetofection induced gene knockdown by siRNA in HMEC-1 allowed researchers to figure out the implication of ROCK-II in the formation of microparticles.[30] Comprehensive reviews of siRNA magnetofection have been published recently.[6,31,32]

Magnetofection for Delivering Oligonucleotides

Magnetofection is also suitable for the delivery of antisense oligonucleotides.[33] The

aim of the study by Krötz et al was to define the role of the p22phox subunit of endothelial NAD(P)-H-oxydase in primary endothelial cells by an antisense knock-out approach. The authors needed oligonucleotides to be delivered at low dose, rapidly, and with high efficiency because long-term incubation with commercial transfection reagents was quite toxic in the primary cells. This work showed that oligonucleotides, applied at low dose, became associated within minutes with the target cells, were rapidly internalized, and accumulated in the nuclei without the toxicity when magnetofection was used. In this manner, the authors were able to highlight the importance of SHP-2 for the formation of new blood vessels and to shed light on its role in angiogenic FGF-2-dependent endothelial cell signalling.[34]

MAGNETOFECTION EFFICIENCY IN VIVO

The utilization of iron oxide particles for in vivo diagnostics has been practiced for almost 40 years, and magnetic particles are now used routinely in the clinic as MRI contrast agents.[35] In the late 1960s, researchers proposed attaching drugs to magnetic particles to transport them to specific sites and to minimize systemic distribution of the administrated agents, while at the same time, ensuring the correct dose is delivered where it is needed. Therapeutic agents (drugs or genes) attached to magnetic nanoparticles can then be concentrated by an appropriate magnetic field source. A variety of animal studies have demonstrated the efficacy of the technique; however, only a handful of Phase I/II clinical trials have taken place.[36-37] In 1983, Widder et al demonstrated the targeting of doxorubicin to tumors implanted in rat tails.[38] Total remission was achieved in the magnetically targeted group compared with controls, in which 10 times the dose of untargeted doxorubicin was administrated. Since then, other groups demonstrated the efficacy of magnetic targeting in a variety of animal models.[39] Clinical trials were performed for determining the potential toxicity of the particles or for cancer treatment, such as hepatocellular carcinomas.[36,39] They showed that the particles were well tolerated and targeted to the tumors with between 64% and 91% of the tumor volume affected.

Gene delivery by magnetofection has been developed throughout the past several years, and recent studies using plasmids or virus have shown that magnetofection offers numerous advantages.[4] In addition to high cellular uptake being reached within a few minutes, targeted and confined gene expression was also demonstrated. The work done by Jahnke et al aimed to determine possible toxicity and explore the feasibility of gene therapy with plasmid coding for feline GM-CSF in cats with fibrosarcomas (Figure 1).[40] In this Phase I study, 20 cats were treated with variable doses of DNA associated with magnetic nanoparticles. Following intratumoral injection of the DNA/nanoparticle complexes, a magnetic field was applied directly onto the tumour for magnetic guidance, essentially for retaining the injected dose in the tumor. The treatment did not show any toxicity and 10 out of 20 cats were recurrence-free after 360 days without any side effects, rendering this approach feasible for a Phase II study.[41] This Phase I clinical trial revealed feGM-CSF gene delivery by magnetofection to be a well tolerated, feasible, and a promising neoadjuvant treatment in cats with fibrosarcomas. These findings are only a step toward a more complete monitoring of the transfected therapeutic gene expression and its consequences. Magnetofection was used to control the localization of gene transfer, thus preventing a more systemic transfection. The principal distinct benefit compared to viral vectors is the lack of specific immune response and oncogenic effects.[42] This allows for gene therapy with low plasmid doses while maintaining efficient gene expression.

A recent article reports the guidance of aerosols to specific regions of the lung using an external magnetic field. In one experiment, this aerosol approach comprised magnetically responsive nanoparticles and DNA.[41] "Nanomagnetosols" were generated with nebulizers and used magnetism to direct magnetizable aerosol droplets specifically to desired regions of the lung.[43] This is the first study to demonstrate its feasibility in an intact animal model. This approach overcomes the natural deposition mechanism of inhaled aerosol droplets in the lungs that only allows targeting on the central airways or lung periphery but not local regions in the lung. A two-fold higher dose of plasmid DNA was found in the magnetized right lung than in the unmagnetized left lung, thus opening a way to gene therapy by magnetofection.

Delivery of genes to the brain and spinal cord across the blood-brain barrier (BBB) has not yet been achieved. One report showed that the AAV-9 virus injected intravenously could bypass the BBB and target cells of the central nervous system.[44] More commonly, in utero electroporation is applied on embryonic rats for transfection after DNA injection in the lateral ventricle of embryos. Using this method, a DNA construct coding for an shRNA targeting the 3'-UTR region of the DCX gene led to DCX-/- mice and resulted in a morphologically relevant cortical band heterotopia.[45] Magnetic nanoparticles associated with lentivirus have been used to concentrate and target viral transduction in the brain. Preliminary results showed a significant enhancement of gene expression compared with standard infection and most importantly a magnetic targeting (Figure 2). A

GFP-lentivirus injected in the facial vein of rat embryos can be targeted in some of the cortex zone, depending on the magnet location on the skull surface. This approach combines the efficiency of a virus with fine magnetic targeting and represents a promising gene therapy approach.

ACKNOWLEDGEMENT

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REFERENCES

1. Cavazzana-Calvo M et al. Gene therapy of human severe combined immunodeficiency (SCID)-X1 disease. Science. 2000;288:669-672.
2. Website: http://www.wiley.co.uk/genetherapy/clinical/. John Wiley & Sons;2007.
3. Mehier-Humbert S, Guy RH. Physical methods for gene transfer: improving the kinetics of gene delivery into cells. Adv Drug Deliv Rev. 2005;57:733-753.
4. Plank C et al. Enhancing and targeting nucleic acid delivery by magnetic force. Expert Opin Biol Ther. 2003;3:745-758.
5. Schillinger U et al. Advances in magnetofection - magnetically guided nucleic acid delivery. J Magn Mag Mater. 2005;293:501-508.
6. Mykhaylyk O, Sanchez Antequera Y, Vlasko Vlaskou D, Plank C. Generation of magnetic nonviral gene transfer agents and magnetofection in vitro. Nature Protocols. 2007;2:2391-2411.
7. Scherer F et al. Magnetofection: enhancing and targeting gene delivery by magnetic force in vitro and in vivo. Gene Ther. 2002;9:102-109.
8. Plank C et al. The magnetofection method: using magnetic force to enhance gene delivery. Biol Chem. 2003;384:737-747.
9. Sauer AM et al. Dynamics of magnetic lipoplexes studied by single particle tracking in living cells. J Control Release. 2009;137:136-145.
10. Satoh K et al. Virus concentration using polyethyleneimine-conjugated magnetic beads for improving the sensitivity of nucleic acid amplification tests. J Virol Methods. 2003;114:11-19.
11. Sacha JB et al. Differential antigen presentation kinetics of CD8+ T-cell epitopes derived from the same viral protein. J Virol. 2008;82:9293-9298.
12. Sacha JB et al. Gag-specific CD8+ T lymphocytes recognize infected cells before AIDS-virus integration and viral protein expression. J Immunol 2007;178:2746-2754.
13. Morishita N et al. Magnetic nanoparticles with surface modification enhanced gene delivery of HVJ-E vector. Biochem Biophys Res Commun. 2005;334:1121-1126.
14. Orlando C et al. Facilitation of lentiviral-mediated transduction of airway epithelial cells by magnetofection. J Cystic Fibrosis 2008;7:S22.
15. Kadota S et al. Enhancing of measles virus infection by magnetofection. J Virol Methods. 2005;128:61-66.
16. Steele IA et al. Helicobacter and gastrin stimulate Reg1 expression in gastric epithelial cells through distinct promoter elements. Am J Physiol Gastrointest Liver Physiol. 2007;293:G347-G354.
17. Nagata D et al. Molecular mechanism of the inhibitory effect of aldosterone on endothelial NO synthase activity. Hypertension. 2006;48:165-171.
18. Sbai O et al. Vesicular trafficking and secretion of matrix metalloproteinases-2, -9, and tissue inhibitor of metalloproteinases-1 in neuronal cells. Mol Cell Neurosci. 2008;39:549-568.
19. Couchoux H et al. Loss of caveolin-3 induced by the dystrophy-associated P104L mutation impairs L-type calcium channel function in mouse skeletal muscle cells. J Physiol. 2007;580:745-754.
20. Megias J et al. Heme oxygenase-1 induction modulates microsomal prostaglandin E synthase-1 expression and prostaglandin E(2) production in osteoarthritic chondrocytes. Biochem Pharmacol. 2009;77:1806-1813.
21. Lee CH et al. Simple, efficient, and reproducible gene transfection of mouse embryonic stem cells by magnetofection. Stem Cells Dev. 2008;17:133-141.
22. Ivanov A et al. Drebrin A regulates dendritic spine plasticity and synaptic function in mature cultured hippocampal neurons. J Cell Sci. 2009;122:524-534.
23. Buerli T et al. Efficient transfection of DNA or shRNA vectors into neurons using magnetofection. Nat Protoc. 2007;2:3090-3101.
24. Guzman-Beltran S et al. Nordihydroguaiaretic acid activates the antioxidant pathway Nrf2/HO-1 and protects cerebellar granule neurons against oxidative stress. Neurosci Lett 2008;447:167-171.
25. Uchida Y et al. Semaphorin3A signalling is mediated via sequential Cdk5 and GSK3beta phosphorylation of CRMP2: implication of common phosphorylating mechanism underlying axon guidance and Alzheimer's disease. Genes Cells 2005;10:165-179.
26. de Lartigue G, Dimaline R, Varro A, Dockray GJ. Cocaine- and amphetamine-regulated transcript: stimulation of expression in rat vagal afferent neurons by cholecystokinin and suppression by ghrelin. J Neurosci. 2007;27:2876-2882.
27. Burdyga G et al. Cholecystokinin regulates expression of Y2 receptors in vagal afferent neurons serving the stomach. J Neurosci. 2008;28:11583-11592.
28. McCaig C et al. The role of matrix metalloproteinase-7 in redefining the gastric microenvironment in response to Helicobacter pylori. Gastroenterol. 2006;130:1754-1763.
29. Deleuze V et al. TAL-1/SCL and its partners E47 and LMO2 up-regulate VE-cadherin expression in endothelial cells. Mol Cell Biol. 2007;27:2687-2697.
30. Sapet C et al. Thrombin-induced endothelial microparticle generation: identification of a novel pathway involving ROCK-II activation by caspase-2. Blood. 2006;108:1868-1876.
31. Mykhaylyk O, Zelphati O, Rosenecker J, Plank C. siRNA delivery by magnetofection. Curr Opin Mol Ther. 2008;10:493-505.
32. Mykhaylyk O et al. Recent advances in magnetofection and its potential to deliver siRNAs in vitro. Methods Mol Biol. 2009;487:111-146.
33. Krotz F et al. Magnetofection - a highly efficient tool for antisense oligonucleotide delivery in vitro and in vivo. Mol Ther. 2003;7:700-710.
34. Mannell H et al. Inhibition of the tyrosine phosphatase SHP-2 suppresses angiogenesis in vitro and in vivo. J Vasc Res. 2008;45:153-163.
35. Gilchrist RK et al. Selective inductive heating of lymph nodes. Ann Surg. 1957;146: 596-606.
36. Lubbe AS et al. Preclinical experiences with magnetic drug targeting: tolerance and efficacy. Cancer Res. 1996;56:4694-4701.
37. Koda J, Venook A, Walser E. Phase I/II trial of hepatic intra-arterial delivery of doxorubicin hydrochloride adsorbed to magnetic targeted carriers in patients with hepatocarcinoma. Eur J Cancer. 2002;38:S18.
38. Widder KJ et al. Selective targeting of magnetic albumin microspheres to the Yoshida sarcoma: ultrastructural evaluation of microsphere disposition. Eur J Cancer Clin Oncol. 1983;19:141-147.
39. Wilson MW et al. Hepatocellular carcinoma: regional therapy with a magnetic targeted carrier bound to doxorubicin in a dual MR imaging/conventional angiography suite - initial experience with four patients. Radiol. 2004;230:287-293.
40. Jahnke A et al. Intra-tumoral gene delivery of feIL-2, feIFN-gamma, and feGM-CSF using magnetofection as a neoadjuvant treatment option for feline fibrosarcomas: a Phase-I study. J Vet Med A Physiol Pathol Clin Med. 2007;54:599-606.
41. Huttinger C et al. Neoadjuvant gene delivery of feline granulocyte-macrophage colony-stimulating factor using magnetofection for the treatment of feline fibrosarcomas: a Phase I trial. J Gene Med. 2008;10:655-667.
42. Niidome T, Huang L. Gene therapy progress and prospects: nonviral vectors. Gene Ther. 2002;9:1647-1652.
43. Dames P et al. Targeted delivery of magnetic aerosol droplets to the lung. Nat Nanotechnol. 2007;2:495-499.
44. Foust KD et al. Intravascular AAV9 preferentially targets neonatal neurons and adult astrocytes. Nat Biotechnol. 2009;27:59-65.
45. Ackman JB et al. Abnormal network activity in a targeted genetic model of human double cortex. J Neurosci. 2009;29:313-327.

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MODIFIED RELEASE

Modified-Release Hydrogel Matrix Tablets & Encapsulated Multi-Particulate Beads: A Formulator's Perspective

By: Jaidev S. Tantry, PhD, Gloria A. Rood, PhD, and Sarah M. Betterman

ABSTRACT

Today's pharmaceutical development scientist can select from several technology platforms when developing a formulation to meet an oral modified-release target product profile. Two technologies that may be utilized are hydrogel matrix tablets and encapsulated multi-particulate beads, which have their advantages and challenges. The formulator may select one technology over the other depending on several factors, including simplicity of design, ease of manufacture, stability of the drug, and type of drug release desired. The following provides an overview of these technologies and discusses the options available to the formulator to develop an effective oral modified-release drug product.

INTRODUCTION

The most common drug delivery technologies are modified-release oral dosage forms. A review of IMS sales from 2006 shows that marketed drug delivery products generated US revenues of $63.1 billion. Oral modified-release products contributed $33 billion of that total. The value proposition of a modified-release product is strong. Because these products are typically designed to sustain (extend) the release of the API, usually only a single dose is required to be administered per day, as compared to the several doses needed with a conventional, immediate-release product. This has shown to improve patient compliance.[1,2] The pharmacokinetic profile of the API is optimized by maintaining the drug plasma concentration within the therapeutic window for a longer duration. This often improves safety and minimizes side effects of the drug product.

Of the technologies available to modify the release of the API from solid oral dosage forms, hydrogel matrix tablets and encapsulated multi-particulate beads have been viable options that Upsher-Smith Laboratories, Inc. has utilized in development programs. The intent of this article is to provide a formulator's perspective on these technologies. This discussion highlights the proposed mechanisms of release, development criteria, manufacturing processes, and other considerations to be made when selecting the appropriate technology.

HYDROGEL MATRIX TABLETS

An oral tablet, formulated with water-soluble, swellable polymers, is a valuable technique for providing the modified release of APIs. The hydrophilic matrix tablet requires water to activate the drug-release mechanism.[3] Upon immersion in water, the hydrophilic matrix quickly forms a gel layer around the tablet, which impedes further liquid penetration into the tablet core. Drug release is governed by the permeation of water through this gel layer; the diffusion of drug through the swollen, hydrated matrix; and erosion of the gelled layer.[1] The aqueous solubility of the API determines whether the diffusion or the erosion mechanism dominates.[4] When the API is moderately to highly soluble, diffusion is the principle mechanism of drug release; whereas, when solubility of the API is very low, drug release is mainly by surface erosion of the gel layers. Increasing the polymer concentration generally results in a decrease in the API release rate. Also, high molecular weight polymers typically form highly viscous gel layers when hydrated, which is likely to result in a slower release of the API from the matrix. The higher viscosity of the hydrated matrix also renders the tablet relatively less susceptible to erosion, with diffusion being the primary release mechanism. The incorporation of lower viscosity polymers into this system would result in a hybrid of diffusion and erosion release mechanisms.

Examples of polymers that hydrate in the aqueous environment of the gastrointestinal tract to yield a hydrogel matrix include hypromellose (hydroxypropylmethylcellulose, HPMC), hydroxypropyl cellulose (HPC), naturally derived gums (eg, xanthan gum and guar gum), alginate, carrageenan, and non-ionic

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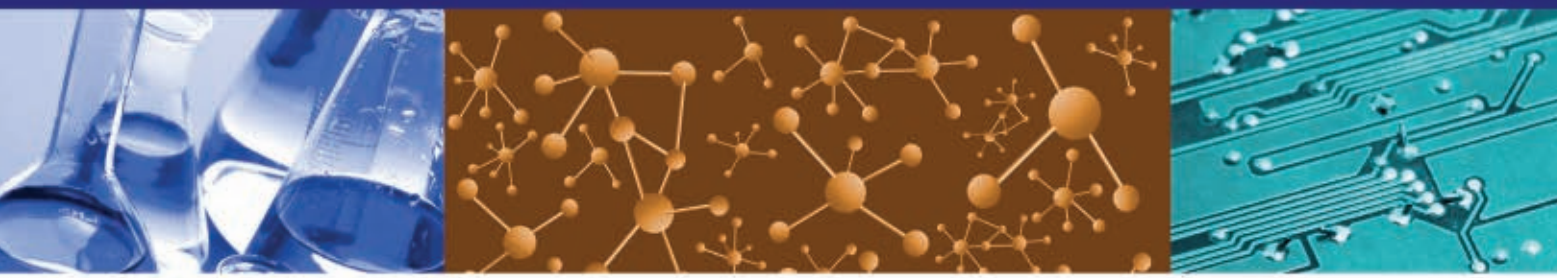

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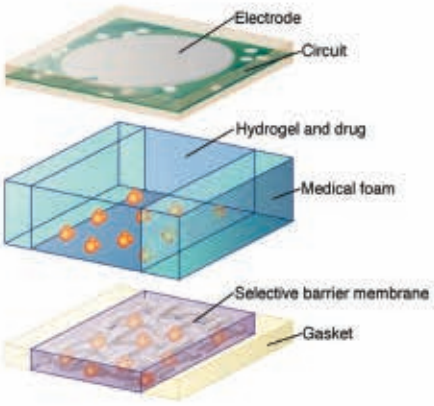

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poly (ethylene oxide) polymers.[4-11]

For any new drug product being developed, a range of dose strengths (eg, 5-, 10-, 20-, and 40-mg tablets of a given formulation) is often desired. A dose-weight proportional series of tablets compressed from a common blend will result in different sized tablets having different surface area-to-volume ratios. This difference can contribute to dissimilar drug-release profiles across the strengths. One way to overcome this is to prepare dose-weight similar formulations for the range of tablet strengths. In this case, the tablet size of all the strengths is designed to be the same, though the drug load varies, thus maintaining the same surface area-to-volume ratio.

Hydrogel matrix tablets can be manufactured by direct compression, dry granulation, or wet granulation. The direct compression process, which is usually the first choice, is summarized in the flow down map in Figure 1. The dosage form has a simplistic design wherein the API is mixed with (a) the release-retarding polymer; (b) a diluent/filler, such as microcrystalline cellulose (MCC) or lactose; and (c) a lubricant, such as magnesium stearate, to obtain a uniform blend, which is then compressed into tablets. A taste-masking film coat or a non-functional, aesthetic film coat may optionally be applied to these tablets. Critical product attributes include the tablet weight, the tablet hardness, and the dissolution profile. The typical equipment used in the direct compression process is shown in Figure 2.

Two of the critical process parameters that must be considered when manufacturing a hydrogel tablet by direct compression are:

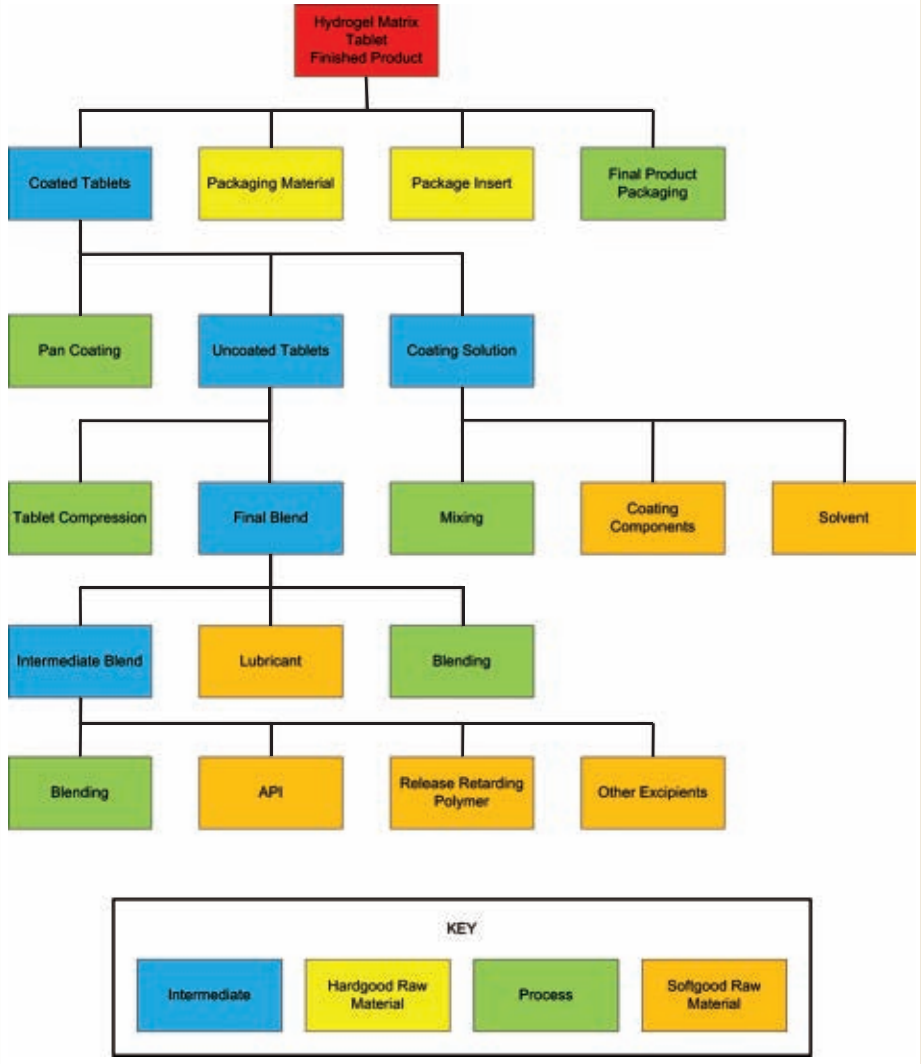
BLEND UNIFORMITY OF THE API & POLYMER(S): Both API and release-retarding polymer(s) must be homogeneously distributed in the blend to ensure that all tablets conform to the drug product release criteria.

POWDER FLOW PROPERTIES: The dry powder blend must flow predictably into the compression die cavities. Some polymers (eg, HPMC), at higher levels (> 30% w/w), may cause inconsistent flow, resulting in variable tablet weights.

Numerous pharmaceutical hydrogel tablets are commercially available, probably owing to the straight-forward direct compression process involved in their manufacture as compared to available multi-particulate manufacturing processes. Key processing advantages for direct compression include a manufacturing process that utilizes standard tableting equipment, a minimal number of unit operations, and a non-aqueous process, which may help to mitigate the instability of moisture-sensitive APIs.

One of the main challenges of the hydrogel matrix system is obtaining multiple release profiles, eg, a fast/immediate-release and a slow-release profile from a single tablet. Although such specialized release profiles can be obtained by having bilayered/multi-layered tablets or by incorporating the API in an immediate-release tablet coating, the resulting tablet design would be more complex.

FIGURE 1



Flow down map of the hydrogel matrix tablet manufacturing process.

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ENCAPSULATED MULTI-PARTICULATE BEADS

Multi-particulate systems can be a very attractive technology platform for modified-release dosage forms because of the following advantages:

- The mutual contact of incompatible APIs can be minimized by formulating them independently, as separate coated bead formulations, and then encapsulating them together.
- Different coated bead compositions within a capsule can yield a product having multiple release profiles. This provides flexibility and versatility to this dosage form, thus offering considerable clinical advantages in delivering specialized release profiles.
- As compared to extended-release tablets, encapsulated extended-release beads have a reduced impact of dose dumping. This is because the dose of the drug is divided among several discrete delivery entities, and thus rapid release of the API by a few beads would not be catastrophic.
- These systems are less affected by gastric emptying rates.
- There is a lower tendency for local irritation as the drug is more widely distributed in the gastrointestinal tract.

Typically, multi-particulate products are manufactured by extrusion-spheronization, drug layering, or rotary granulation. Extrusion-spheronization is the preferred manufacturing approach when working with drug loads above 50% w/w. The product manufactured by this process generally consists of an immediate-release core that is then coated with a release-controlling polymer, followed by encapsulation. The mechanism of drug release from these beads is primarily diffusion through the polymer layer, but can also be driven by osmotic pressure.[12]

In contrast to the minimal steps involved in the direct compression method used in hydrogel matrix tablet manufacturing, the extrusion-spheronization process usually consists of eight unit operations. A flow down map of the extrusion-spheronization manufacturing process is shown in Figure 3.

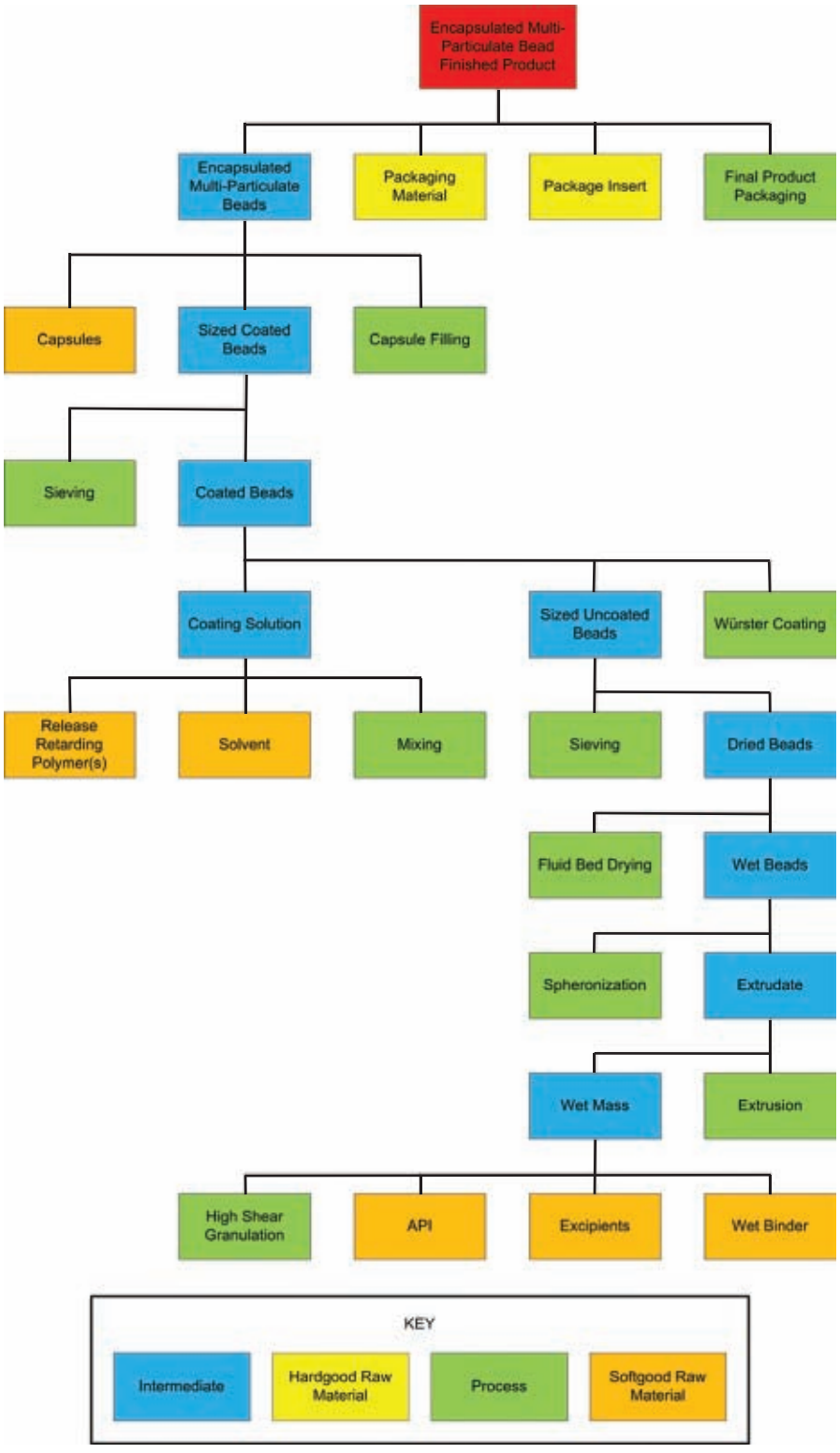
The first step in the manufacturing process is high-shear granulation in which the API and excipients are combined with a wet binder (commonly water) to produce a wet mass. Typical excipients for an extrusion-spheronization process cover the categories of filler and dry binder. MCC is most commonly used as the bulk excipient (filler) due to its amorphous character. Two models exist that attempt to describe the role of MCC in this wet granulation process: (1) the crystallite-gel-model and (2) the sponge model.[13-14] Commonly used dry binders are water-soluble polymers, such as HPMC, povidone (polyvinylpyrrolidone), polyethylene oxide, and starch.[15] The wet mass generated by the high shear granulation process is then fed through an extruder, equipped with a die having a selected pore diameter, to produce the extrudate. Next, the extrudate is charged into a spheronizer in which the spaghetti-shaped material is formed into beads. Lastly, the beads are dried in a fluid bed processor and subsequently screened to obtain the desired size fraction. The typical equipment used in the extrusion-spheronization process is shown in Figure 4.

Drug release from the core beads is controlled by a polymeric film coating applied to the beads using a Würster coating process. Many polymer options exist, allowing customization of the drug release. Water-insoluble polymers, including ethylcellulose and methyl acrylates, serve as the main retardant to drug release. Plasticizers, such as triethyl citrate, diethyl phthalate, and dibutyl sebacate, are commonly added to the coating system to provide flexibility to the coating film by lowering the glass transition temperature of the polymer. In addition, pore formers can be incorporated into the insoluble film to help modify drug release. Pore formers, eg, HPMC, povidone, and polyethylene glycol, are typically water-soluble polymers. Release rates, including first-order and zero-order profiles, are shown in Figure 5. These profiles can be obtained by varying the types and relative

FIGURE 2

Typical equipment used in the direct compression process to manufacture hydrophilic matrix tablets.

FIGURE 3



Flow down map of the encapsulated multi-particulate bead manufacturing process.

proportions of the polymers, along with the amount of coating material deposited on the core beads. Enteric polymers, which provide a delay in drug release due to their pH-dependent solubility, can be included to further modify the overall drug release. Most of the polymers described are applied via a solution in an organic solvent or in a mixture of an organic solvent and water. Many marketed aqueous dispersions, such as Surelease®, Aquacoat®, and various types of Eudragit®, are also available, which eliminate the concerns related to volatile organic compound emissions. Once the coated beads have been manufactured, they are typically filled into capsules to complete the dosage unit.

Unlike the hydrogel matrix tablet, dose-weight proportional formulations are easily achieved with a multi-particulate technology. A single, coated, bead formulation can be filled to different weights into capsules of different sizes, providing a range of dose strengths, all having the same drug release. This becomes difficult only when the range of dose strengths required is very large. In this case, more than one formulation, having differing drug loads, would need to be manufactured.

One of the most critical attributes of the product made by the extrusion-spheronization process is the particle size distribution of the beads. This can be controlled by many factors, including water content of the wet mass, pore diameter of the extruder die, and the spheronizer plate speed. It is very important to develop a manufacturing process to achieve consistent particle size distribution from batch to batch as this directly affects the available surface area for coating.

Another critical product attribute of this type of technology is the thickness of the coating deposited on the beads. Drug release from a multi-particulate system is primarily governed by Fick's first law of diffusion (see Equation 1).

Equation 1.

$$J = -D\frac{dC}{dx}$$

Here, J is the flux of the drug in amount/area-time, D is the diffusion coefficient in area/time, C is the concentration, and x is the distance (coating thickness).[2] Because the film coating thickness directly affects the drug release from the bead, it is important to have a consistent coating process that gives a smooth, uniform film coating across batches. This can be achieved by choosing the right solids content of the coating system as well as appropriate processing parameters, such as atomization air pressure, fluidization air volume, spray rate, and product temperature.

A drawback with the multi-particulate technology is that the first unit process, high shear granulation, typically involves the use of water, which could affect the stability of moisture-sensitive APIs. One way to mitigate this problem would be to replace water with a hydro-alcoholic solvent. Another significant challenge is the number of steps in the manufacturing process. Each unit operation involves many processing parameters, all of which are interrelated. In comparison to the direct compression process, longer development timelines may be necessary for the identification and definition of the many critical process parameters to ensure the quality of the finished product.

CONCLUSION

Hydrogel matrix tablet and encapsulated multi-particulate bead technologies have both been used to successfully develop modified-release oral solid dosage forms. As a general guide, Table 1 summarizes the comparison between the two technologies, aiding the formulator in selecting the right technology platform to meet the established formulation objectives.

FIGURE 4

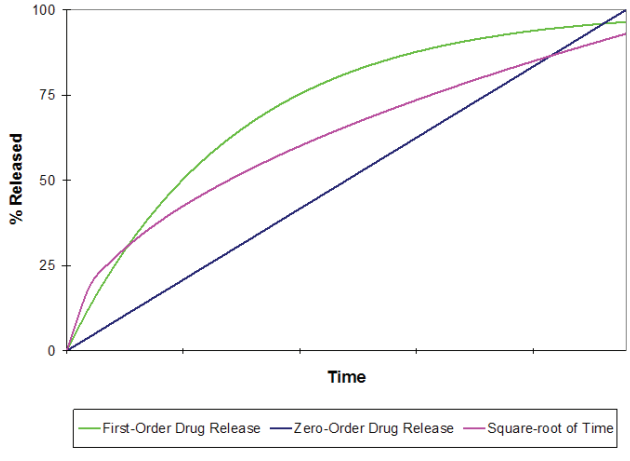
Typical equipment used in the extrusion-spheronization process to manufacture encapsulated multi-particulate beads.

TABLE 1

Attribute	Hydrogel Matrix Tablet	Encapsulated Multi-particulate Beads
Number of Unit Operations	Few	Several
Manufacturing Equipment	Standard equipment (blender, tablet press)	Some specialized equipment (extruder, spheronizer, encapsulator)
Drug Loading	Preferably less than 45% w/w	Easily up to 65% w/w
Use of a Common Blend (Dose-Weight Proportionality)	Challenging if (1) the surface area-to-volume ratios of the various tablet strengths are different because this usually leads to differences in their release profiles, and (2) if the dose range is big (eg, smallest dose is 5 mg and largest dose is 640 mg)	Challenging only if the dose range is large
Ease of Achieving Target Drug-Release Profiles	Large number of experiments needed; many blends, with different types and concentrations of release- retarding polymers, have to be prepared	Few experiments needed; a common core formulation can be prepared and then coated with different amounts of a single coating formulation
Suitability of Technology for Moisture-Sensitive API	Preferred method of manufacturing (direct compression) because it is a non-aqueous process	Less desirable; routinely involves an aqueous wet granulation process
Ease of Scale-Up	Reasonably predictable and straight-forward	May not be directly scalable; scale-up may require a longer time

A formulator's guide for comparing modified-release hydrophilic matrix tablets & encapsulated multi-particulate beads.

FIGURE 5



Examples of drug release profiles.

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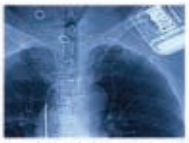
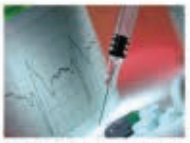

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REFERENCES

1. Lordi NG. Sustained release dosage forms. In: Lachman L, Lieberman HA, Kanig JL, eds. The Theory and Practice of Industrial Pharmacy. 3rd ed. Philadelphia, PA: Lea & Febiger;1986:430-456.
2. Longer MA, Robinson JR. Sustained-release drug delivery systems. In: Gennaro AR, Chase GD, Marderosian AD, Harvey SC, Hussar DA, Medwick T, Rippie EG, Schwartz JB, Swinyard EA, Zink GL, eds. Remington's Pharmaceutical Sciences. 18th ed. Easton, PA: Mack Publishing Company;1990:1676-1693.
3. Chang R, Robinson JR. Sustained drug release from tablets and particles through coating. In: Lieberman HA, Lachman L, Schwartz JB, eds. Pharmaceutical Dosage Forms: Tablets, Vol 3. 2nd ed. Revised and Expanded. New York, NY: Marcel Dekker, Inc.;1990:199-302.
4. Reynolds TD, Mitchell SA, Balwinski KM. Investigation of the effect of tablet surface area/volume on drug release from hydroxypropylmethylcellulose controlled-release matrix tablets. Drug Dev Indust Pharmacy. 2002;28(4):457-466.
5. Alderman DA. Sustained release compositions comprising hydroxypropyl cellulose ethers. US Patent No. 4,704,285. November 3, 1985.
6. Tantry JS. Design and evaluation of modified release solid dosage forms. PhD (Tech.) Thesis, University of Mumbai, India, June 1998.
7. Talukdar MM, Michoel A, Rombaut P, Kinget R. Comparative study on xanthan gum and hydroxypropylmethyl cellulose as matrices for controlled-release drug delivery I. Compaction and in vitro drug release behaviour. Int J Pharmaceut. 1996;129(1-2):233-241.
8. Kullar P, Khar RK, Agarwal SP. Evaluation of guar gum in the preparation of sustained-release matrix tablets. Drug Dev Indust Pharmacy. 1998;24(11):1095-1099.
9. Sriamornsak P, Thirawong N, Korkerd K. Swelling, erosion and release behavior of alginate-based matrix tablets. Eur J Pharmaceut Biopharmaceut. 2007;66(3):435-450.
10. Campo VL, Kawano DF, da Silva DB Jr, Carvalho I. Carrageenans: Biological properties, chemical modifications and structural analysis – A review. Carbohydrate Polymers. 2009;77(2):167-180.
11. The Dow Chemical Company, POLYOX™ Water Soluble Resins NF in Pharmaceutical Applications, 2004.
12. Ozturk AG, Ozturk SS, Palsson BO, Wheatley TA, Dressman JB. Mechanism of release from pellets coated with an ethylcellulose-based film. J Controlled Rel. 1990;14:203-213.
13. Kleinebudde P. The crystallite-gel-model for microcrystalline cellulose in wet-granulation, extrusion, and spheronization. Pharmaceut Res. 1997;14(6):804-809.
14. Ek R, Newton JM. Microcrystalline cellulose as a sponge as an alternative concept to the crystallite-gel model for extrusion and spheronization. Pharmaceut Res. 1998;15(4):509-512.
15. Trivedi NR, Rajan MG, Johnson JR, Shukla AJ. Pharmaceutical approaches to preparing pelletized dosage forms using the extrusion-spheronization process. Critical Rev Therapeut Drug Carrier Syst. 2007;24(1):1-40.

BIOGRAPHIES

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Intranasal Delivery of Stem Cells & Genetically Engineered Cells to the Brain

By: William H. Frey II, PhD, and Lusine Danielyan, MD

ABSTRACT

Non-invasive intranasal delivery, previously used to bypass the blood-brain barrier (BBB) and target therapeutic proteins, polynucleotides, and small molecules to the central nervous system (CNS), has now been shown to deliver stem cells and genetically engineered cells to the brain in rodents. This new method of delivery could revolutionize the way cell-based therapy is conducted for CNS disorders.

INTRANASAL DRUG DELIVERY & REGENERATIVE MEDICINE

Neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, and ALS, along with stroke and traumatic brain injury, are responsible for a great deal of morbidity and mortality, not to mention loss of quality of life. In addition, a number of individuals are born without certain key enzymes or are missing certain brain cell functions, resulting in premature death, disability, or both. The discovery that the human brain is capable of repair under certain circumstances and that even the adult brain contains stem cells capable of neurogenesis has encouraged the growth of the field of regenerative medicine for the treatment of brain disorders.

One approach has been to utilize the non-invasive intranasal delivery method for bypassing the BBB, originally discovered by William H. Frey II to target neurotrophins, such as IGF-I, NGF, and FGF-2 to the brain to stimulate repair and regeneration.[1-7] Researchers have reported that intranasal neurotrophins are therapeutic in animal models of stroke, Alzheimer's disease, and other CNS disorders, and recently intranasal insulin has been shown to improve memory in both patients with Alzheimer's disease and normal adults.[8-17]

Most relevant, however, is the demonstration by Jin and Greenberg that intranasal FGF-2 stimulates neurogenesis in endogenous stem cells found in the subventricular zone of the adult mouse brain.[18] The ability to non-invasively stimulate neurogenesis in the adult brain is a major step forward.

INTRANASAL DELIVERY OF THERAPEUTIC CELLS

While delivery of neurotrophic proteins as previously described for neurodegenerative disorders and other drugs, including polynucleotides to treat brain tumors, has been reported; intranasal delivery of entire cells, including stem cells and genetically engineered cells, into the adult brain represents an unanticipated and surprising discovery.[19-20] Certainly, the sheer size of cells alone makes this a surprising finding. While a molecule may have an effective diameter from perhaps 1 to 4 nm and can only be seen with electron microscopy, animal cells are generally 10,000 times larger, about 10 to 30 micrometers in diameter, big enough to be seen with light microscopy.

Danielyan et al have recently reported that within 1 hour of intranasal administration of fluorescently labeled rat mesenchymal stem cells to the upper third of the nasal cavity of naïve rats and mice, the stem cells were observed to cross the cribriform plate along the olfactory neural pathway and migrate into not only the subarachnoid space and olfactory bulb but also into other brain regions, including the thalamus, hippocampus, cerebellum, and cerebral cortex.[20]

Intranasal delivery of stem cells to the brain was increased two-fold by pretreatment of the nasal mucosa with hyaluronidase 30 minutes prior to intranasal application of the stem cells.[20] Hyaluronidase acts on the extracellular matrix to catalyze the hydrolysis of hyaluronic acid, a major constituent of the interstitial barrier. By doing so, hyaluronidase increases tissue permeability. These initial studies demonstrated that at least 2,000 stem cells reached the mouse brain within 1 hour after a single intranasal application of 3 x 10^5 cells, and substantial numbers of cells remained in the olfactory epithelium at that time, suggesting that additional migration of cells was still possible over time and may continue for hours or even days.[20]

The two primary routes of cell migration were: (1) migration along the olfactory pathway through the cribriform plate into the olfactory bulb and to other parts of the brain parenchyma, which likely involves perivascular transport, which has been proposed by others to allow for rapid distribution of molecules within the brain and for delivery of molecules from the nose to the brain, and (2) migration along the olfactory route into the CSF with subsequent movement along the surfaces of the brain and into the brain parenchyma.[5,20-25]

ADVANTAGES & UNANSWERED QUESTIONS

The safety and efficacy of cell-based therapies for CNS diseases depends very significantly on the method of cell administration. Intranasal delivery and targeting of stem cells and genetically engineered cells to the brain is non-invasive, avoiding the use of expensive neurosurgical implantation of cells with its safety issues. It also avoids the neuroinflammation caused by neurosurgical implantation that has been shown to kill a high percent of stem cells implanted with this invasive method.[26-29] Further, intranasal administration allows for repeat dosing and multiple treatments, including gradually increasing the dose over time. Intranasal delivery of therapeutic cells not only rapidly delivers cells to the CNS, but also reduces unwanted systemic exposure, which occurs with intravenous administration. Finally, intranasal stem cell delivery is user friendly and can be administered by any healthcare professional without the use of anesthesia.[20]

While intranasal delivery of stem cells targets the cells to the CNS, there is still the question of the degree of targeting to the degenerated or damaged area of the brain that will occur when a patient is treated for a neurodegenerative condition or brain injury. It has been shown that neural stem cells actively migrate to sites of CNS injury and that this migration may be directed by products of the inflammation that occur at those sites. Imitola et al have reported that human neural stem cells migrate toward an infarcted area where astrocytes and endothelium up-regulate the inflammatory chemoattractant stromal cell-derived factor 1alpha (SDF-1alpha).[30] They demonstrated that neural stem cells express CXC chemokine receptor 4 (CXCR4), the cognate receptor for SDF-1alpha, and that exposure of SDF-1alpha to quiescent neural stem cells enhances proliferation, promotes chain migration and transmigration, and activates intracellular molecular pathways mediating engagement. Therefore, they suggest that inflammation may be viewed not only simply as playing an adverse role but also as providing stimuli that recruit cells with a regenerative homeostasis-promoting capacity.[30] This homing behavior of therapeutic stem cells may help direct intranasally delivered stem cells to their therapeutic target(s) in the diseased or damaged CNS.

SUMMARY & FUTURE PERSPECTIVES

It is important to recognize that the recent work published by Danielyan et al represents only the first step in developing intranasal therapeutic cell delivery to the CNS.[20] Further developments are likely to include additional delivery-enhancing agents aside from hyaluronidase. Such agents may include neuregulin, migration-inducing activity, and leukemia inhibitory factor.[31] For example, neuregulin-1 has been shown to influence the migration of a variety of cell types in the developing brain, and migration-inducing activity has been reported to induce the migration of olfactory bulb interneuron precursors, increasing the number of migrating cells and the distance they move.[32,33] Leukemia inhibitory factor not only promotes migration of certain cell types but also appears to promote neural stem cell self-renewal, preventing the emergence of more differentiated cell types, resulting in an expansion of the stem cell pool, which may be useful, in combination with other factors, in promoting regeneration in the adult brain.[34-35]

Future developments of this delivery technology are also likely to include the use of regulatory agents that can promote the survival and differentiation of the intranasally delivered therapeutic cells, such as growth factors like IGF-I and NGF.[31] Additional formulation components may include immunosuppressive agents to enhance the viability of the therapeutic cells through protection from inflammatory response and/or activation of host immunocompetent cells, which may occur as part of the neurodegenerative disorder itself or in response to the delivered therapeutic cell in some situations.[31] Antibiotics may also be developed as part of the formulation to further protect the patient undergoing therapeutic cell therapy from bacteria that may occur in the nasal cavity.[31]

Clearly, a great deal of additional work is needed to determine the safety and effectiveness of intranasal therapeutic stem cell delivery in animals and to translate this new delivery technology to humans with CNS disorders. Success will depend not only on this new method of delivering and targeting therapeutic cells to the CNS but also on the safety and efficacy of the therapeutic stem cells and genetically engineered cells it is used to deliver.

REFERENCES

1. Frey WH II. US Patent No. 5,624,898: Method of Administering Neurologic Agents to the Brain. 1997 (priority date 5.12.89) [http://patft.uspto.gov/]. US Patent and Trademark Office.
2. Frey WH II. Bypassing the blood-brain barrier to delivery therapeutic agents to the brain and spinal cord. Drug Delivery Technol. 2002;5:46-49.
3. Dhanda DS, Frey WH II, Leopold D, Kompella UB. Approaches for drug deposition in the human olfactory epithelium. Drug Delivery Technol. 2005;5:64-72.
4. Hanson LR, Frey WH II. Intranasal delivery bypasses the blood-brain barrier to target therapeutic agents to the central nervous system and treat neurodegenerative disease. BMC Neuroscience. 2008;9(Suppl 3):S5.
5. Thorne RG, Pronk GJ, Padmanabhan V, Frey WH II. Delivery of insulin-like growth factor-I to the rat brain and spinal cord along olfactory and trigeminal pathways following intranasal administration. Neuroscience. 2004;127:481-496.
6. Chen X-Q, Fawcett JR, Rahman Y-E, Ala TA, Frey WH II. Delivery of nerve growth factor to the brain via the olfactory pathway. J Alz Dis. 1998;1:35-44.
7. Frey WH II, Liu J, Chen X, Thorne RG, Fawcett JR, Ala TA, Rahman Y-E. Delivery of 125I-NGF to the brain via the olfactory route. Drug Deliv. 1997;4:87-92.
8. Liu XF, Fawcett JR, Hanson LR, Frey WH II. The window of opportunity for treatment of focal cerebral ischemic damage with noninvasive intranasal insulin-like growth factor-I in rats. J Stroke Cerebrovasc Dis. 2004;13:16-23.
9. Yu YP, Xu QQ, Zhang Q, Zhang WP, Zhang LH, Wei EQ. Intranasal recombinant human erythropoietin protects rats against focal cerebral ischemia. Neurosci Lett. 2005;387:5-10.
10. Capsoni S, Giannotta S, Cattaneo A. Nerve growth factor and galantamine ameliorate early signs of neurodegeneration in anti-nerve growth factor mice. Proc Natl Acad Sci USA. 2002;99:12432-12437.

11. de Rosa R, Garcia AA, Braschi C, Capsoni S, Maffei L, Berardi N, Cattaneo A. Intranasal administration of nerve growth factor (NGF) rescues recognition memory deficits in AD11 anti-NGF transgenic mice. Proc Natl Acad Sci USA. 2005;102:3811-3816.
12. Frey WH II. US Patent No. 6313093: Method for Administering Insulin to the Brain. 2001 [http://patft.uspto.gov/]. US Patent and Trademark Office.
13. Reger MA, Watson GS, Frey WH II, Baker LD, Cholerton B, Keeling ML, Belongia DA, Fishel MA, Plymate SR, Schellenberg GD, Cherrier MM, Craft S. Effects of intranasal insulin on cognition in memory-impaired older adults: modulation by APOE genotype. Neurobiol Aging. 2006;27:451-458.
14. Reger MA, Watson GS, Green PS, Baker LD, Cholerton B, Fishel MA, Plymate SR, Cherrier MM, Schellenberg GD, Frey WH II, Craft S. Intranasal insulin administration dose-dependently modulates verbal memory and plasma amyloid-beta in memory impaired older adults. J Alz Dis. 2008;13:323-331.
15. Reger MA, Watson GS, Green PS, Wilkinson CW, Baker LD, Cholerton Fishel MA, Plymate SR, Breitner JC, DeGroodt W, Mehta P, Craft S. Intranasal insulin improves cognition and modulates beta-amyloid in early AD. Neurol. 2008;70:440-448.
16. Benedict C, Hallschmid M, Hatke A, Schultes B, Fehm HL, Born J, Kern W. Intranasal insulin improves memory in humans. Psychoneuroendocrinol. 2004;29:1326-1334.
17. Benedict C, Hallschmid M, Schmitz K, Schultes B, Ratter F, Fehm HL, Born J, Kern W: Intranasal insulin improves memory in humans: superiority of insulin aspart. Neuropsychopharmacol. 2007;32:239-243.
18. Jin K, Xie L, Childs J, Sun Y, Mao XO, Logvinova A, Greenberg DA. Cerebral neurogenesis is induced by intranasal administration of growth factors. Ann Neurol. 2003;53:405-409.
19. Hashizume R, Ozawa T, Gryaznov SM, Bollen AW, Lamborn KR, Frey WH II, Deen DF. New therapeutic approach for brain tumors: intranasal delivery of telomerase inhibitor GRN163. Neuro Oncol. 2008;10:112-120.
20. Danielyan L, Schäfer R, von Ameln-Mayerhofer A, Buadze M, Geisler J, Klopfer T, Burkhardt U, Proksch B, Verleysdonk S, Ayturan M, Buniatian GH, Gleiter CH, Frey WH II. Intranasal delivery of cells to the brain. Eur J Cell Biol. 2009;88, 315-324.
21. Gregory TF, Rennels ML, Blaumanis OR, Fujimoto KA. Method for microscopic studies of cerebral angioarchitecture and vascular-parenchymal relationships, based on the demonstration of 'paravascular' fluid pathways in the mammalian central nervous system. J Neurosci Methods. 1985;14,5-14.
22. Rennels ML, Gregory TF, Blaumanis OR, Fujimoto K, Grady PA. Evidence for a 'paravascular' fluid circulation in the mammalian central nervous system, provided by the rapid distribution of tracer protein throughout the brain from the subarachnoid space. Brain Res. 1985;326,47-63.
23. Rennels ML, Blaumanis OR, Grady PA. Rapid solute transport throughout the brain via paravascular fluid pathways. Adv Neurol. 1990;52,431-439.
24. Cserr HF, Ostrach LH. Bulk flow of interstitial fluid after intracranial injection of blue dextran 2000. Exp Neurol. 1974;45,50-60.
25. Hadaczek P, Yamashita Y, Mirek H, Tamas L, Bohn MC, Noble C, Park JW, Bankiewicz K. The 'perivascular pump' driven by arterial pulsation is a powerful mechanism for the distribution of therapeutic molecules within the brain. Mol Ther. 2006;14,69-78.
26. Björklund A. Cell therapy for Parkinson's disease: problems and prospects. Novartis Found Symp. 2005;265:204-211.
27. Helt CE, Hoernig GR, Albeck DS, Gerhardt GA, Ickes B, Reyland ME, Quissell DO, StrÖmberg I, Granholm AC. Neuroprotection of grafted neurons with a GDNF/caspase inhibitor cocktail. Exp Neurol. 2001;170:258-269.
28. Coyne TM, Marcus AJ, Reynolds K, Black IB, Woodbury D. Disparate host response and donor survival after the transplantation of mesenchymal or neuroectodermal cells to the intact rodent brain. Transplantation. 2007;84:1507-1516.
29. Coyne TM, Marcus AJ, Woodbury D, Black IB. Marrow stromal cells transplanted to the adult brain are rejected by an inflammatory response and transfer donor labels to host neurons and glia. Stem Cells. 2006;24:2483-2492.
30. Imitola J, Raddassi K, Park KI, Mueller F-J, Nieto M, Teng YD, Frenkel D, Li J, Sidman RL, Walsh CA, et al. Directed migration of neural stem cells to sites of CNS injury by the stromal cell-derived factor 1{alpha}/CXC chemokine receptor 4 pathway. PNAS. 2004;101(52):18117-18122.
31. Frey WH II, Danielyan L, Gleiter CH. US Patent Application No. 2009/0068155 A1: Methods, Pharmaceutical Compositions and Articles of Manufacture for Administering Therapeutic Cells to the Animal Central Nervous System 2009 [http://patft.uspto.gov/]. US Patent and Trademark Office.
32. Ritch PA, Carroll SL, Sontheimer H. Neuregulin-1 enhances motility and migration of human astrocytic glioma cells. J Biol Chem. 2003;278(23):20971-20978.
33. Mason HA, Ito S, Corfas G. Extracellular signals that regulate the tangential migration of olfactory bulb neuronal precursors: inducers, inhibitors, and repellents. J Neurosci. 2001;21:7654-7663.
34. Horita H, Kuroda E, Hachisuga T, Kashimura M, Yamashita U. Induction of prostaglandin E2 production by leukemia inhibitory factor promotes migration of first trimester extravillous trophoblast cell line, HTR-8/SVneo. Hum Reprod. 2007;22:1801-1809.
35. Bauer S, Patterson PH. Leukemia inhibitory factor promotes neural stem cell self-renewal in the adult brain. J Neurosci. 2006;26:12089-12099.

BIOGRAPHIES

Dr. William H. Frey II is Director of the Alzheimer's Research Center at Regions Hospital in St. Paul, MN, a faculty member in Pharmaceutics, Oral Biology, Neurology and Neuroscience at the University of Minnesota and consultant to the pharmaceutical and biotechnology industry. His patents, owned by Novartis, Stanford University, the HealthPartners Research Foundation, and others target non-invasive delivery of therapeutic agents, including stem cells, to the brain and spinal cord for treating neurological disorders, psychiatric disorders, and obesity. Dr. Frey's non-invasive intranasal method for bypassing the blood-brain barrier to target CNS therapeutic agents to the brain while reducing systemic exposure and unwanted side effects has captured the interest of both pharmaceutical companies and neuroscientists. With over 100 publications in scientific and medical journals, such as Journal of Biological Chemistry, Proceedings of the National Academy of Sciences, JPET, Brain Research, EJCB, etc, Dr. Frey has been interviewed on Good Morning America, The Today Show, 20/20, All Things Considered, and numerous other television and radio shows in the US, Europe, and Asia. Articles about Dr. Frey's research have appeared in Neurology Today, Nature Methods, the Wall Street Journal, The New York Times, US News and World Report, and other magazines and newspapers around the world. Dr. Frey earned his BA in Chemistry at Washington University in 1969 and his PhD in Biochemistry at Case Western Reserve University in 1975. He can be contacted at (651) 261-1998 or at alzheimr@umn.edu.

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Controlled Release of Highly Water-Soluble Drugs From the SQZgel™ Oral Drug Delivery System

By: Kirk P. Andriano, PhD

INTRODUCTION

The concept of controlled drug release has emerged from the need for effective management of diseases. Site-specific controlled-release systems offer many distinctive advantages over classical methods of drug delivery. These include delivery of the drug to a particular part of the body, ensurance of treatment continuity in the nocturnal phase, drug stability, reduced need for follow-up care, and optimized drug absorption.[1] A variety of drug delivery systems developed so far exhibit pH-dependent drug release.[2] Controlled-release systems have been developed over a range of pH-domains in the body, eg, for periodontal, oral, gastric, and intestinal applications.[3-5] There have been several reports describing the use of hydrogels as controlled-release systems.[6,7] Hydrogels are polymeric materials that do not dissolve in water at physiological temperature and pH but swell considerably in aqueous media.[8] They are of special interest in controlled-release applications because of their soft tissue biocompatibility, the ease of drugs able to be dispersed in the matrix, and the high degree of controlled release achieved by selecting the physical and chemical properties of the polymer network.

pH-dependent hydrogels can be made by polymerizing monomeric unsaturated acids. In such hydrogels, crosslinking agents are used for the creation of covalent bonds that are required for gel formation. The resulting hydrogels formed from monomeric acids swell at higher (basic) pH values and collapse at lower (acidic) pH values. However, hydrogels formed from monomeric bases show the opposite behavior.

Cationic hydrogels with pH-dependent swelling properties have been proposed as candidates for drug delivery systems.[9] Such matrices could provide adequate drug release in gastric (low pH) environments. Chitosan, a cationic-polysaccharide, is obtained by alkaline deacetylation of chitin, the principle exoskeletal component in crustaceans.[10] Chitosan is reported to be non-toxic and bioabsorbable; toxicity depends on the dose and the route of administration, while absorbability depends on the degree of deacetylation.[11] Chitosan has been explored for the release of many drugs, eg, buoyant release tablets of nifedipine.[12-14] However, all the pH-dependent, semi-synthetic chitosan hydrogels presently known are covalently crosslinked.[15] Although the use of covalently crosslinked pH-dependent hydrogels that collapse at physiological pH and swell at stomach pH is well known, no specific polymer blend is known in the open literature that exhibits these properties, ie, rapidly swells in acidic conditions, slowly and extensively collapses in more basic conditions, contains no covalent crosslinking, is substantially insoluble in acid, and is safe for oral drug delivery. The lack of covalent crosslinking in a polymer hydrogel is extremely attractive from a regulatory point of view.

SQZgel™ ORAL DRUG DELIVERY SYSTEM

The SQZgel tablet is an oral drug delivery platform composed of a pH-dependent, water-swellable polymer blend of chitosan and polyethylene glycol (PEG) and a highly water-soluble drug, enclosed in a microporous coated tablet. The microporous coating is a mixture of cellulose acetate and sorbitol.

The novel polymer blend of chitosan and PEG, when exposed to aqueous conditions, forms a hydrogel that swells when exposed to an acidic environment (such as that found in the stomach) and collapses when exposed to a more neutral to alkaline environment (such as that found in the small and large intestines).

The pH-dependency of the hydrogel was used to develop the SQZgel oral drug delivery system. This configuration provides for controlled release of highly water-soluble drugs in an easy-to-swallow oral dosage formulation, which provides dose delivery in less-frequent administrations than a traditional tablet formulation and thus enhances patient compliance (Figure 1).

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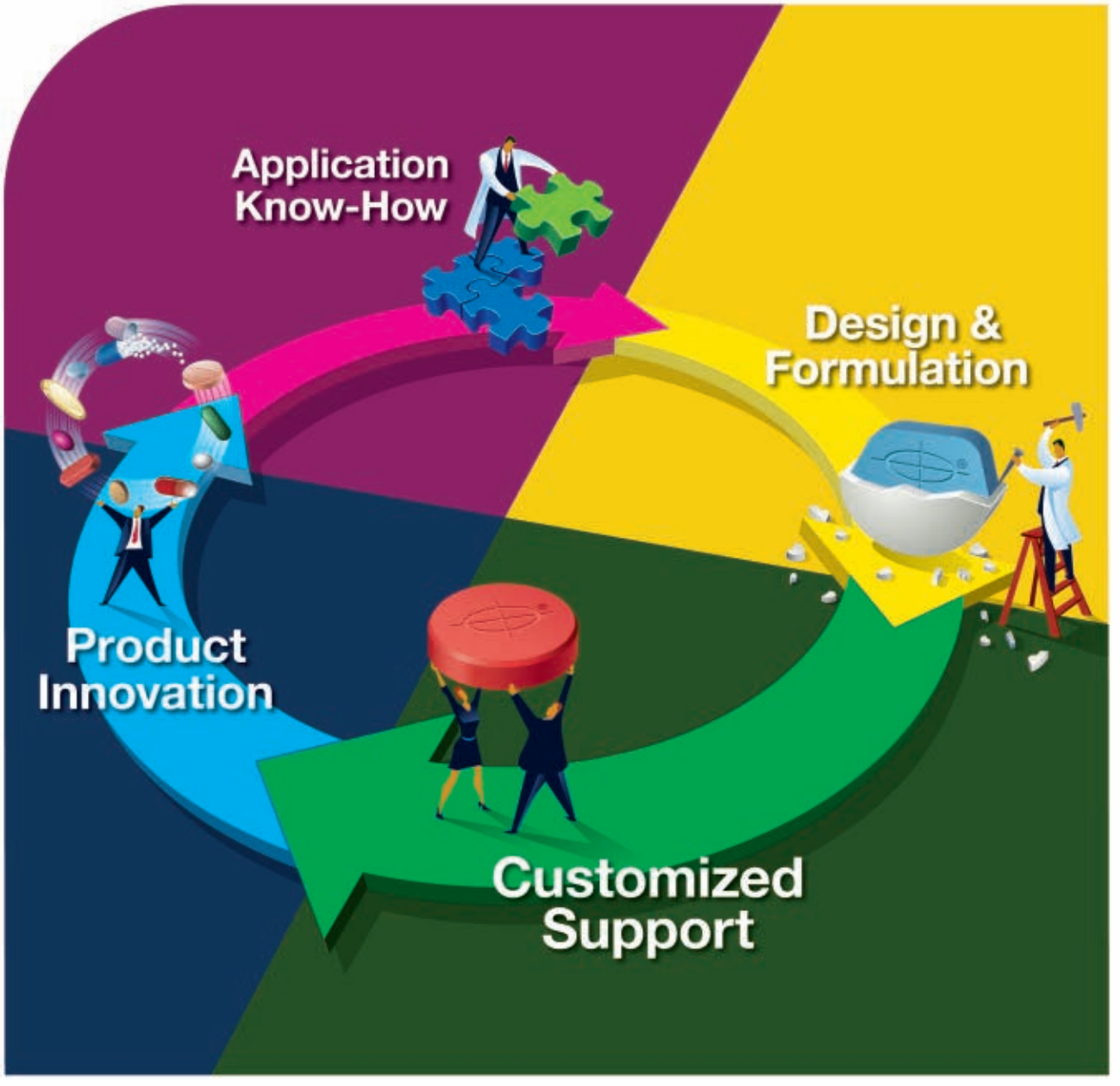

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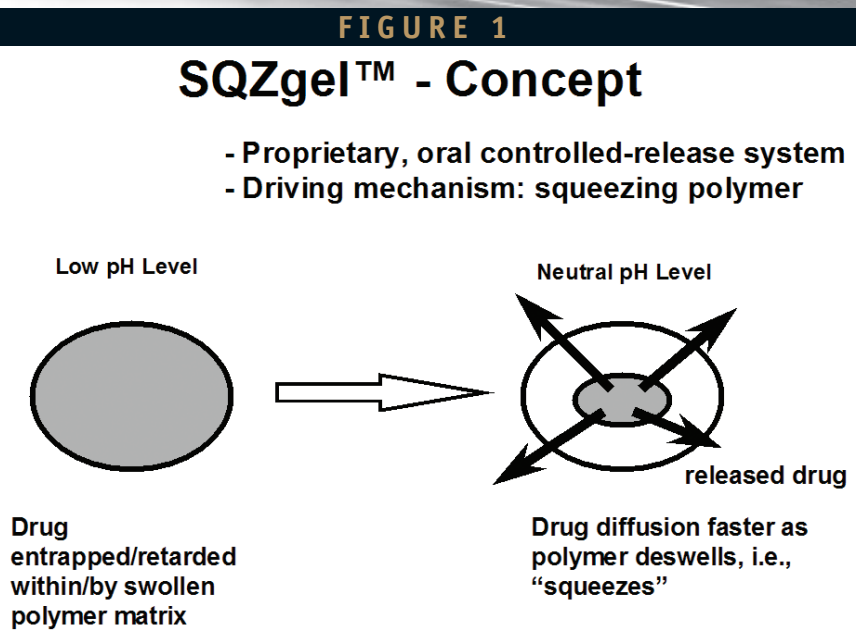
SWELLING-COLLAPSING KINETICS

Figure 2 shows results of swelling-collapsing kinetics for solution-blended chitosan-PEG polymer hydrogel films. Regardless of the environmental conditions, none of the exposed hydrogel films showed any signs of dissolving. In acidic media (pH 2.0), film specimens swelled to more than 60x their dry weight in 2 hours and did not collapse when they were kept in the acidic media for an additional 8 hours. When swollen hydrogel films were removed from the acidic environment after 2 hours and placed in a basic media (pH 7.4), they collapsed slowly in a linear fashion over 8 hours exposure to about 15x their original dry weight. Finally, when dry film specimens were placed in basic media, they swelled to about 10x their original dry weight in approximately 1 hour, and there was no change in the swelling ratio for the remainder of the experiment.

pH-dependency in swelling of solution-blended chitosan-PEG hydrogels was confirmed because the hydrogel swelling ratio was greater in SGF (acidic pH) than SIF (basic pH), 60x versus 15x, respectively. Dry film specimens, when placed in 1.0 N acetic acid, completely dissolved in several hours, indicating the chitosan-PEG polymer blend is not chemically crosslinked.

In general, acetic acid is considered a "good" solvent for chitosan with a degree of deacetylation greater than 70%, while dilute HCl, 0.1 N, (eg, SGF) in comparison is considered a "poor" solvent for such materials.

FIGURE 1



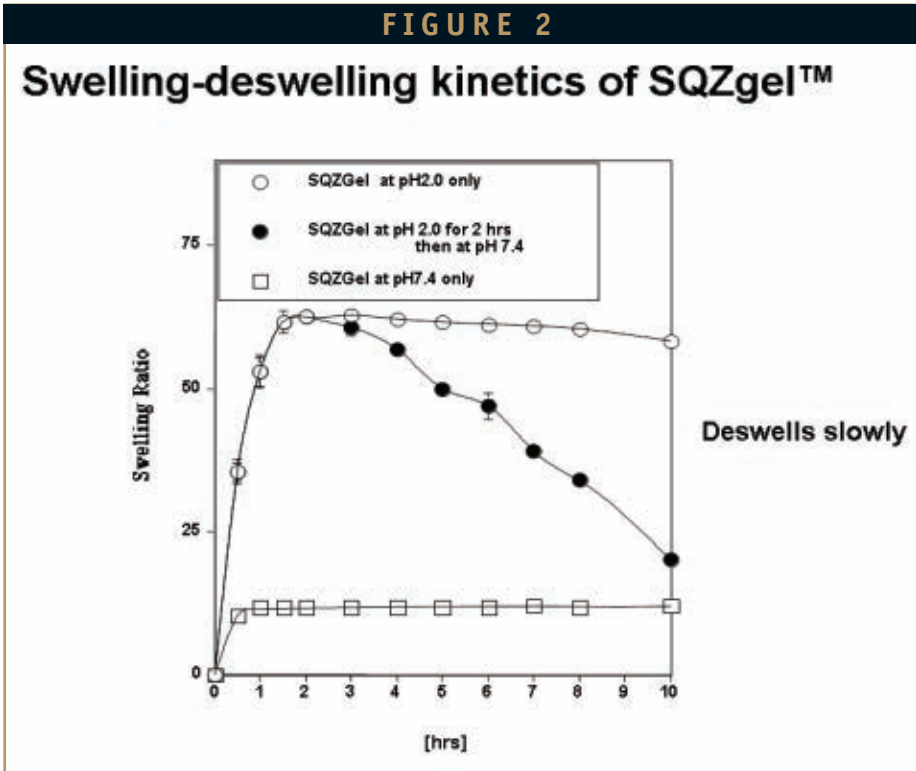
Schematic drawing showing the concept of the SQZgel™ controlled release oral drug delivery system.

TABLE 1

	SQZgel™ - Fasted (n=6)	Dilacor XR - Fasted (n=6)
AUC (ng h/mL)	6296	5840
Cmax (ng/mL)	348	370

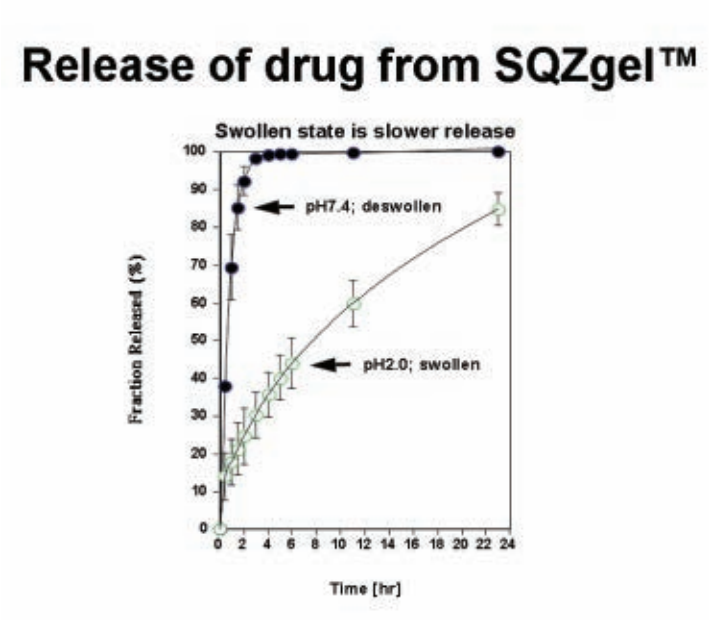
Geometric Mean Pharmacokinetic Parameters of Diltiazem HCl (240 mg) Test & References Formulations

FIGURE 2



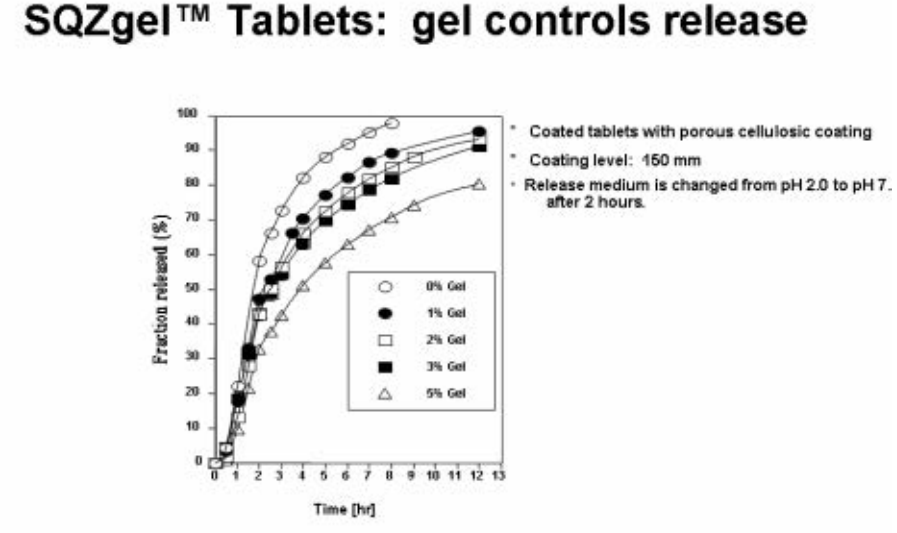
Swelling-collapsing kinetics of chitosan-PEG solution blended polymer films in acidic media (pH 2.0), basic media (pH 7.4), and acidic media for 2 hours followed by exposure to basic media (pH 2.0 then pH 7.4).

FIGURE 3



In vitro release of buspirone HCl from swollen drug-loaded chitosan-PEG solution blended polymer films (pH 2.0) and deswollen drug-loaded chitosan-PEG solution blended films (pH 7.4) showing drug release is slower from drug-loaded films in the swollen state.

FIGURE 4



In vitro release of buspirone HCl from SQZgel™ tablets with 0%, 1%, 2%, 3%, 4%, and 5% solution-blended chitosan-PEG hydrogel showing that increasing the polymer blend content slows drug release. The release medium was changed from pH 2.0 to pH 7.4 after 2 hours.

Other investigators have reported swelling-collapsing behavior for air-dried and freeze-dried, crosslinked chitosan-PEG hydrogel films.[15] Their results showed freeze-dried, crosslinked chitosan-PEG films swelled to about 22x their original dry weight after 2 hours exposure to SGF.

The greater swelling seen in solution-blended chitosan-PEG films is most likely due to the lack of crosslinking and also to the difference in the ratio of chitosan to PEG used to prepare the polymer blends; 2:1 in the solution-blended films versus 4:1 in the freeze-dried, crosslinked chitosan-PEG film specimens. Crosslinking could possibly limit the elastic ability of the hydrogel to swell, while a greater amount of PEG could increase the hydrophilicity of the bulk material.

EFFECT OF DIFFERENT PH VALUES ON DRUG RELEASE

Figure 3 shows results for in vitro release profiles of buspirone HCl from drug-loaded chitosan-PEG hydrogel films under differing pH conditions, ranging from near pH neutral to acidic. When the hydrogel blend was in a collapsed state, approximately 85% of the drug was released in about 2 hours. But when the hydrogel film was fully swollen, it took 24 hours for 85% of the drug to be released. This strongly suggests that when the hydrogel film is in the swollen state, diffusion is retarded, but while in the collapsed state, diffusion of a water-soluble drug from the hydrogel film out of the containment capsule is significantly increased.

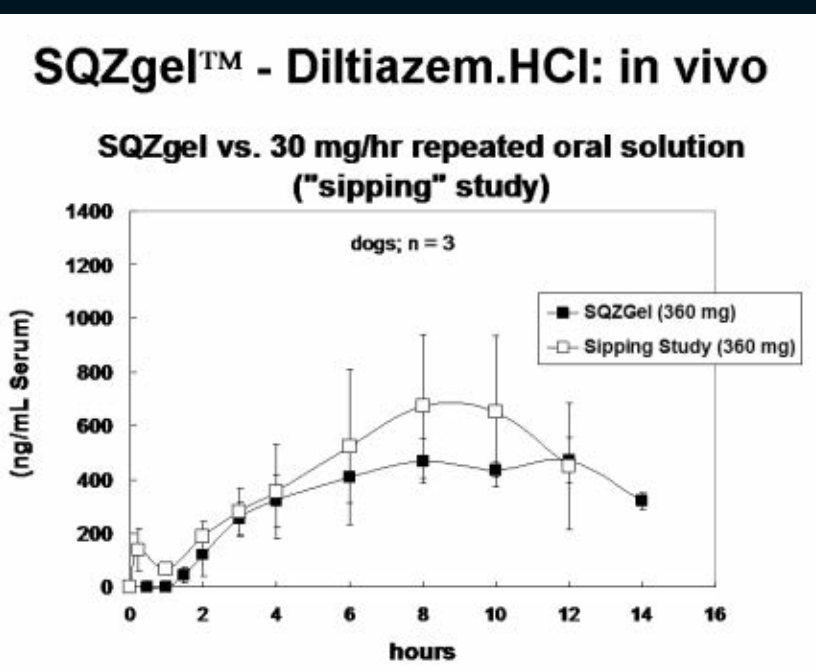
EFFECT OF DIFFERENT CONCENTRATIONS OF THE POLYMER BLEND ON DURG RELEASE

Figure 4 shows results for in vitro release of buspirone HCl from SQZgel tablets with differing amounts of the dry chitosan-PEG polymer blend. It is important to point out in this experiment the polymer blend starts out in the dry state in the tablet before it is exposed to an aqueous environment. The in vitro release of the drug from tablets with 0% of the polymer blend was 100% after 8 hours exposure. For tablets containing 5% by weight of the polymer blend, approximately 70% of the drug was released after 8 hours. Results for the buspirone HCl formulation, when the coating thickness and porosity are held constant, show that varying the amount of the polymer blend can control release of the drug from a microporous coated tablet.

PROOF-OF-CONCEPT STUDY: TABLE VERSUS SIPPING

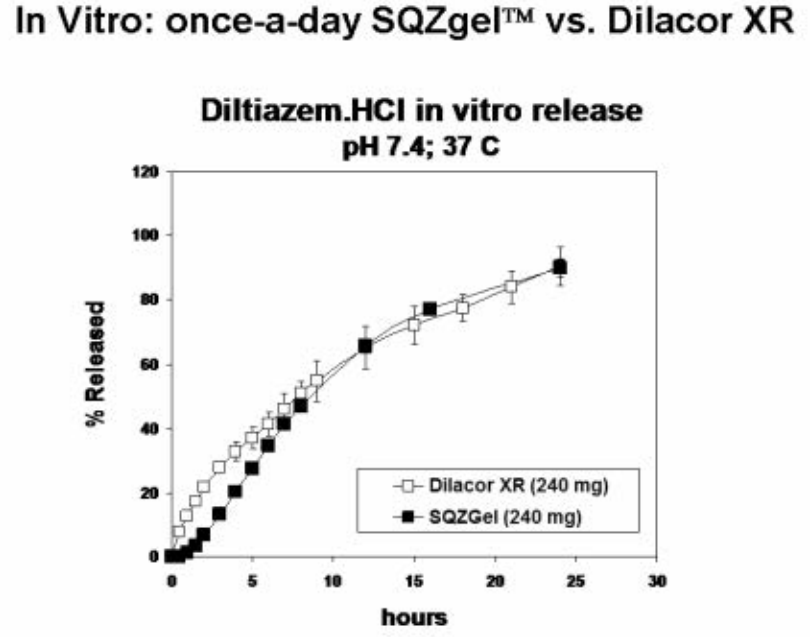
The purpose of this study was to compare the controlled-release kinetics of diltiazem HCl from SQZgel tablets against a standard test for controlled release: repeated oral dosing of a drug solution. Figure 5 shows canine serum concentrations of diltiazem HCl released from SQZgel tablets (360 mg) versus repeated oral sipping of a solution of diltiazem HCl dosed 30 mg/hr for 12 hours. The results show serum concentrations of diltiazem HCl from SQZgel tablets are similar to those of the repeated oral dosing of a diltiazem HCl solution, suggesting 12 hours of controlled release was achieved with the SQZgel/diltiazem HCl tablets.

FIGURE 5



In vivo release of diltiazem HCl from SQZgelTM tablets (360 mg) versus repeated oral sipping solution of diltiazem HCl (30 mg/hr for 12 hrs) in dogs (n=3).

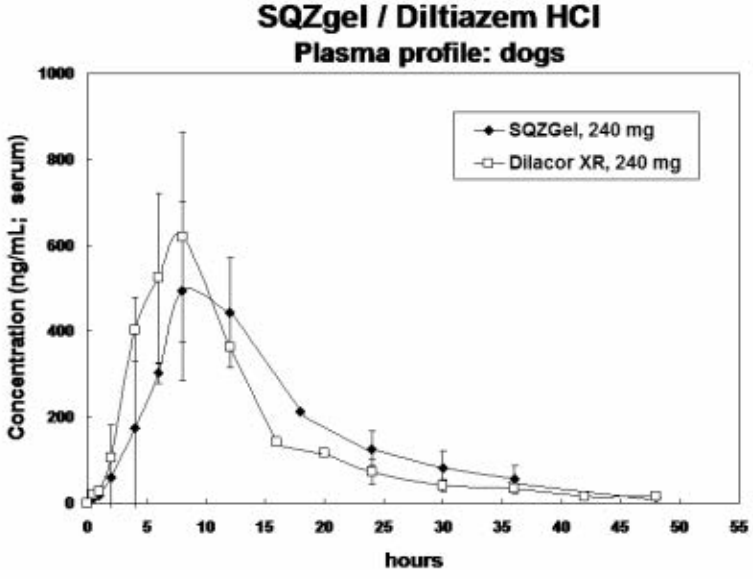
FIGURE 6



In vitro/in vivo release of diltiazem HCl from SQZgelTM tablets (240 mg). The release rate is near zero-order for both in vitro and in vivo.

FIGURE 7

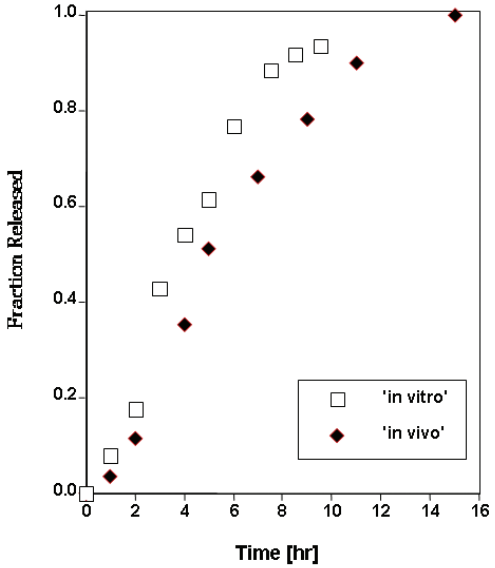
In Vivo: once-a-day SQZgel™ vs. Dilacor XR



In vitro release of diltiazem HCl from SQZgelTM tablets (240 mg) versus Dilacor XRTM tablets (240 mg).

FIGURE 8

SQZgel™ Tablets: in vitro / in vivo (dog) release
(240 mg Diltiazem)



SQZgel tablets release same in vivo / in vitro

Release is complete and near zero-order

In vivo release of diltiazem HCl from SQZgelTM tablets (240 mg) versus Dilacor XRTM tablets (240 mg) in dogs (n=3).

IN VITRO/IN VIVO COMPARISON: SQZgel™/DILTIAZEM HCL VERSUS DILACOR™

Figures 6 and 7 show in vitro and in vivo release kinetics of diltiazem HCl, respectively, from SQZgel tablets (240 mg of diltiazem HCl) versus Dilacor XR tablets (240 mg of diltiazem HCl). For the in vitro release study, release of diltiazem HCl was practically identical, with both formulations showing approximately 100% release of the drug after 24 hours. The in vivo study exhibited excellent correlation between pharmacokinetic parameters (Cmax and AUC) for both dosage forms (Table 1).

Figure 8 shows in vitro/in vivo correlation for diltiazem HCl release from SQZgel tablets. The tablets released diltiazem HCl the same in vivo as in vitro. Release was complete and near zero-order.

CONCLUSION

SQZgel is an oral drug delivery platform composed of a pH-dependent, swellable-collapsible solution blend of chitosan and PEG, enclosed in a microporous coated tablet. The in vitro and in vivo release of diltiazem HCl from SQZgel tablets is the same. The release kinetics were near zero-order. SQZgel/diltiazem HCl tablets showed bioequivalence to a commercially available controlled-release formulation of diltiazem HCl, Dilacor XR. SQZgel is a promising oral delivery system for once-a-day or twice-a-day dosing regimens of water-soluble drugs.

REFERENCES

1. Dumitriu S, Dumitriu M. Polymeric drug carriers. In: S Dumitriu, ed. Polymeric Biomaterials. New York, NY: Marcel Dekker;1994:447-448.
2. Jarvinen K, Akerman S, Svarfvar B, Tarvainen T, Viinikka P, Paronen P. Drug release from pH and ionic strength responsive polyacrylic acid grafted poly(vinylideneflouride) membrane bags in vitro. Pharam Res. 1998;15:802-805.
3. Needleman IG, Smales FC, Martin GP. An investigation of bioadhesion of periodontal and oral mucosal drug delivery. J Clin Periodontol. 1997;24:394-400.
4. Desphande AA, Shah NH, Rhodes CT, Malick W. Development of a novel controlled release system for gastric retention. Pharma Res. 1997;14:815-819.
5. Hari RP, Chany T, Sharma CP. Chitosan/calcium alginate microcapsules for intestinal delivery of nitrofurantoin. J Microencap. 1996;13:319-329.
6. Cascone MG, Sim B, Downes S. Blends of synthetic and natural polymers as drug delivery systems for growth hormone. Biomaterials. 1995;16:569-574.
7. Bronsted H. Kopecek J. Hydrogels for site specific drug delivery to the colon: in vitro and in vivo degradation. Pharma Res. 1992;9:1540-1545.
8. Ratner BD. Biomedical applications of hydrogels: review and critical appraisal. In: DF Williams, ed. Biocompatibility of Clinical Implant Materials II. Boca Raton, FL: CRC Press;1981:146.
9. Siegle RA, Falamarzian M, Firestone BA, Moxley BC. pH controlled release from hydrophobic/polyelectrolyte copolymer hydrogel. J Cont Rel. 1988;8:179-182.
10. Muzzarelli M, Jeuniaux C, Gooday G. Chitin in Nature and Technology. New York, NY: Plenum Press;1986.
11. Muzzarelli M, Baldassarre V, Conti F, Ferrara P, Biagini G, Gazzanelli G, Vasi V. Biological activity of chtiosan: ultra structural study. Biomaterials 1988;9:247-252.
12. Inouye K, Machida Y, Sanna T, Nagi T. Bouyant sustained release tablets based on chitosan. Drug Design Del. 1988;2:165-175.
13. Chandy T, Sharma CP. Chitosan matrix for oral sustained delivery of ampicillin. Biomaterials. 1993;14:939-944.
14. Chandy T, Sharma CP. Chitosan beads and granules for oral sustained delivery of nifedipine. Biomaterials. 1992;13:949-952.
15. Patel VP, Amiji MM. Preparation and characterization of freezed-dried chitosan/poly(ethylene oxide) hydrogels for site specific antibiotic delivery in the stomach. Pharma Res. 1996;13:588-593.

BIOGRAPHY

Dr. Kirk Andriano currently serves as the Chief Technical Officer of ProChon Biotech, Ltd. He has more than 20 years of experience in research, development, and commercialization of orthopaedic biomaterials and drug delivery. Prior to joining ProChon, Dr. Andriano was Chief Science Office of Curative Bioscience, Inc., and was responsible for the executive management of Research & Development. While at Inion, he was Vice President of Research & Development, where he played a participatory role in leading the company's $75M IPO as the first Finnish company on the London Stock Exchange. He was responsible for overall research, development, intellectual property, product development, preclinical, clinical, and regulatory approval of biodegradable polymer and bioceramic implants in five therapeutic areas. Prior to Inion, he held various senior level management positions at MacroMed, Inc., and Atrix Laboratories, Inc., both drug delivery companies. Dr. Andriano earned his BS in Chemistry and Biology from Utah State University and his MS and PhD in Bioengineering from the University of Utah. He has held post-doctoral research positions at the University of Utah and the Advanced Polymer Systems Research Institute. He was a National Institutes of Health research fellow and a visiting professor and research scholar at Kyoto University in Kyoto, Japan

On The Rise

Drug Delivery Companies You Should Know About

By: Cindy H. Dubin, Contributor

Figure 3. Q Chip's MicroPlant™ technology is a bioencapsulation production system that enables the packaging and stabilization of biological materials in micron-scale polymer beads without the use of solvents or harsh temperatures.

The drug delivery market is changing significantly due to the introduction of new techniques and routes of delivery. R&D spending, along with increasing competition, patent expiries, new technologies, an international marketplace, and a changing customer base, is creating a new kind of market for drug delivery systems.

The global market for advanced drug delivery systems amounted to almost $139 billion in 2009 and is projected to increase to $196.4 billion by 2014, according to an August 2009 report from BCC Research. The largest segment of the market is targeted drug delivery, which reached $50.9 billion in 2009, and is expected to increase to $80.2 billion in 2014.

Despite considerable advances in drug delivery technologies, there continues to be a high unmet clinical need for safer and better-tolerated drugs, sites June 2009 research from Espicom Business Intelligence. Suboptimal compliance and failure to persist with drug treatments are important determinants of therapeutic non-response and are of significant cost to healthcare providers. Advanced targeted drug delivery technologies will help overcome some of these issues by improving pharmacokinetics, increasing tolerability, and reducing dose-limiting off-target effects. By 2018, more than 30 new products will be launched, resulting in a global market for advanced targeted delivery products worth more than $8.5 billion. While the majority of targeted delivery systems under evaluation incorporate passive carrier systems, there will be a shift toward the use of actively targeted carriers to increase the therapeutic index of existing and new products.

A new generation of targeted delivery systems is under development that should provide greater control over the selective targeting of tissue, either with active moieties or inactive moieties that may be activated within the tissue by biological (enzymes), chemical (pH), or physical means (light, ultrasound) in order to release the active agent. The multitude of delivery platforms will lend themselves to the delivery of both small molecules and macromolecules, and to a variety of target sites and delivery routes.

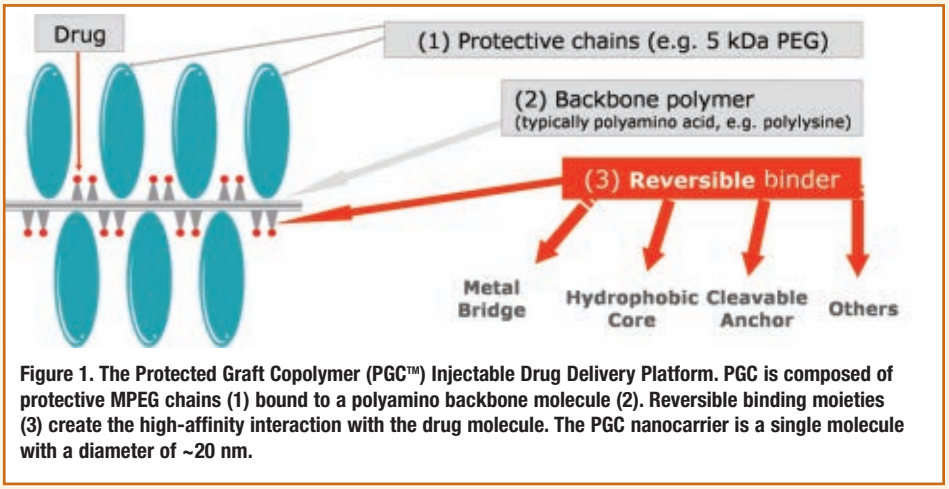


Figure 1. The Protected Graft Copolymer (PGC™) Injectable Drug Delivery Platform. PGC is composed of protective MPEG chains (1) bound to a polyamino backbone molecule (2). Reversible binding moieties (3) create the high-affinity interaction with the drug molecule. The PGC nanocarrier is a single molecule with a diameter of ~20 nm.

OTHER DELIVERIES TO WATCH

While much interest is aimed at targeted delivery, other methods of administration are making drug delivery inroads. Sustained-release products have the second largest market share in the drug delivery space, with estimated sales of $36.1 billion in 2009 and $45.8 billion in 2014, according to BCC Research. This boost is from formulators combining technologies to produce specialized applications, such as using liposomes and polymers in sustained-release oral drug delivery.

The controlled-release market was worth nearly $21 billion globally in 2008, dominated by oral controlled-release formulations in key therapeutic areas, such as the central nervous system, cardiovascular, metabolic, and respiratory diseases. Epsicom estimates there are about 60 approved controlled-release products, which will generate global sales of $29.5 billion in 2017.

As the field of nanotechnology gains momentum and nano-enabled platforms address the need for improved bioavailability and less toxicity, this market is expected to grow significantly throughout the next decade. By 2018, the established nanotechnology product market will be $10.2 billion. Finally, the nucleic acid delivery market is maturing with more than 1,450 clinical trials underway worldwide. The majority of these are in early clinical development (approximately 60%) with just over 3% in Phase III trials. Analysts indicate that up to 35 novel nucleic acid products could reach the market between 2008 and 2018. Worth just over $80 million globally in 2008, Epsicom anticipates the nucleic acid technology market will mature by 2018 as late-stage clinical programs come to fruition and drug delivery companies overcome issues surrounding safety and efficiency.

With all of these maturing methods, experts say drug delivery is now a major component of the pharmaceutical industry's future and critical to bringing novel therapies to market. In this third annual exclusive to *Drug Delivery Technology* magazine, we introduce you to some of the up-and-coming companies to watch for in the drug delivery space: PharmaIN Corp., PharmaNova, Q-Chip Ltd., RXi Pharmaceuticals, SoluBest Ltd., and to-BBB.

PHARMAIN CORP.–AFFINITY-BASED DELIVERY OF PROTEINS & PEPTIDES

PharmaIN of Seattle, WA, develops affinity-based delivery solutions for biotech and pharmaceutical applications. The company's Protected Graft Co-

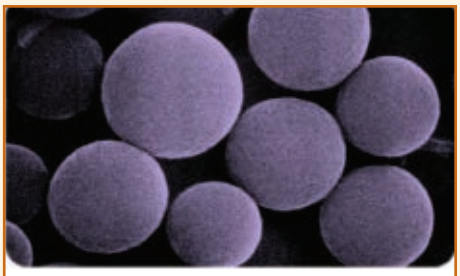


Figure 2. This scanning electron microscope image (magnification X 30,000) illustrates the regular sphericity of NovaSperse-generated amorphous nanoparticles.

polymer (PGC) drug delivery system uses proprietary carrier molecules and reversible payload binding chemistries to create new drug therapies or make existing drugs more effective, less toxic, and easier to use (Figure 1). The current focus is on injected drugs. PGC is a co-polymer composed of a poly-amino backbone derivatized with short polyethylene glycol (PEG) chains. On the balance of the backbone amino groups, a reversible binding moiety is attached, tailored to the drug being delivered. Due to its size (~20 nm), the resulting copolymer can passively accumulate in areas of abnormal vasculature.

"The core concept of the technology is that the drug is bound to the carrier by a high-affinity, but non-covalent, interaction with the reversible binding moiety," explains Elijah Bolotin, PhD, founder and President of PharmaIN. "As a result, the drug will have high affinity for the carrier to protect it from non-specific interactions *in vivo*, but not as high as the drug affinity for its biological target."

The composition of the copolymer is perceived as an excipient by the FDA. The resulting formulation forms a stable, aqueous solution, injectable with small-gauge needles. Proteins and peptides have been formulated with PGC, and several products are in development. The most advanced is PGC GLP-1, a peptide hormone involved in insulin secretion and gastric emptying. It is being developed to treat types 1 and 2 diabetes and may have the potential to prevent and even reverse type 1 diabetes through increased islet cell proliferation, says Dr. Bolotin.

Second is PGC Anti-MRSA, a formulation of a protein with known activity toward MRSA infection. To date, PharmaIN has shown improved half-life and anti-bacterial activity *in vivo* relative to the unformulated drug. According to Dr. Bolotin, the MSRA formulation has been shown to improve pharmacokinetics and significantly enhance the anti-infective power relative to the unformulated protein without modifying the active drug.

Third is PGC Insulin, a basal once-a-day formulation of native, unmodified human insulin. And finally, PGC Vasoactive Intestinal Peptide (VIP) has been formulated as a therapeutic for rheumatoid arthritis and inflammation. Dr. Bolotin says that VIP, which is being developed through funding by the National Institutes of Health, takes advantage of PGC's ability to extend circulation time and enable selective accumulation of the drug to inflamed tissue.

According to Dr. Bolotin, PharmaIN is attractive to large pharmaceutical companies that have many injectable proteins and peptides in their pipeline, as well as high-revenue biologics nearing the end of their patents. Small companies also have shown interest in co-developing proteins and peptides that require targeted delivery.

"Our PGC technology has the potential to be a widely used injectable delivery platform, to improve multiple blockbuster drugs, and to enable novel drugs in the very large markets, such as anti-infectives, inflammation, diabetes, and oncology, where individual drug sales are substantial," he says.

PHARMANOVA, INC.– STABILIZED NANOPARTICLES FOR VARIOUS DELIVERIES

PharmaNova, Inc. of Rochester, NY, provides clinically important, commercially valuable medicines based on its NovaSperse[SM] nanoparticle technology (Figure 2), providing pharmaceutical companies with the ability to enhance the properties of existing medicines and/or to repurpose them for additional clinical use, thereby extending the life cycle of already approved products, particularly those that may be approaching patent expiry.

The NovaSperse process employs precisely controlled solvent displacement principles that facilitate the customized preparation of nanoparticles to as small as ~50 nm in diameter with a narrow size distribution around the mean, describes Rodney A. Brown, President of PharmaNova. NovaSperse particles are amorphous, spherical, and stable. The company has a library of nanoparticulate APIs from 200 to 1,200 molecular weight and of wide-ranging complexity and physico-chemical properties.

"NovaSperse nanoparticles, stabilized as suspensions or lyophilized powders for reconstitution, have advantages as proprietary formulations suitable for many routes of administration," says Mr. Brown. While NovaSperse is appropriate for multiple routes of administration and therapeutic areas, PharmaNova is currently focused on topical ophthalmic, anti-infective medications, and injectable oncolytic projects.

Based on these therapeutic focuses, the company seeks and collaborates with large or niche pharma companies operating in these fields. PharmaNova also conducts client-sponsored projects in which clients have a need to address development issues, such as with new chemical entities.

"We are also particularly excited about the emerging potential that NovaSperse offers for intranasal and respiratory products," says Mr. Brown. "Our library of nanoparticulate formulations contains anti-viral, anti-fungal, anti-inflammatory, anti-convulsant, and oncolytic compounds."

He adds that PharmaNova has a treatment for glaucoma in co-

development with partner Altacor Pharma Ltd., a Cambridge, UK-based ophthalmology company, and has its own new product in development for dry eye. Advantages for the eye include the opportunity for increased drug loading and lower instillation volume, a reduced need for solubilizers and irritating excipients, potential for improved corneal permeation, and multiple formulation options for controlled release and absorption, explains Mr. Brown.

"Importantly, for ocular use, particles ≤ 200 nm are optically invisible, improving patient compliance, and permit sterilization by filtration and the avoidance of preservatives. There are many degrees of difficulty encountered when developing even 200-nm particles of API with reasonably good reproducibility and stability. But PharmaNova has been successful in reproducibly developing stable batches with average particle size well below 100 nm."

Continued efforts have resulted in the development of nanoparticle formulations that can be lyophilized for enhanced stability, and subsequently reconstituted. The latter is of added importance to the value and significance NovaSperse has in both enhancing and facilitating new parenteral formulations of poorly soluble APIs, avoiding the use of potentially irritating and unsafe excipients, such as Cremophor®, explains Mr. Brown. NovaSperse also accommodates particle surface modification for tissue and organ targeting, and extended circulation time. Many of these same features offer related advantages for other routes of administration, such as dermal or intranasal for local topical use or for systemic delivery, and for improved, controlled bioavailability by the oral route, says Mr. Brown.

"Nanoparticle technology is revolutionizing pharmaceutical formulation science and, in that respect, the market is boundless and relatively untapped," says Mr. Brown. "Within the field of nanoparticle technology, however, there are numerous variants addressing different needs and niche requirements. NovaSperse will satisfy many of these, and the market value will be driven by the combined potential of the products to which it is applied and the exclusivity that any prospective user/licensee might seek."

Q CHIP LIFE SCIENCES–SUSTAINED-RELEASE THERAPEUTICS

This past year was one of transformation for the Wales, UK-based Q Chip Life Sciences, changing from a bioencapsulation company to a pure biopharmaceutical firm. Along with the redefinition came an increased focus on sustained drug delivery. Q Chip's MicroPlant™ technology (Figure 3, see first page) is a bioencapsulation production system that enables the packaging and stabilization of biological materials in micron-scale polymer beads without the use of solvents or harsh temperatures, says Jo Daniels, PhD, Chief Scientific Officer of Q Chip.

The MicroPlant technology has enabled the development of Q-Sphera™ for sustained-release peptide/protein therapeutics, which is being used to develop a range of sustained-release biosimilars. Q-Sphera, formerly Biologix, is an enabling technology for peptide and protein delivery and a lower-cost formulation and production platform for biosimilars, explains Dr. Daniels. Q-Sphera microparticles are monodispersed with a CV (coefficient of variance) of less than 2%.

"Particle size significantly influences drug-release characteristics, and there is a direct correlation between consistent particle size and consistent drug release and therapeutic performance," says Dr. Daniels. "Q-Sphera microspheres have a high drug load with a correspondingly high activity."

The first two peptide drugs under development using Q-Sphera are Q-Leuprolide (primary indications in prostate cancer and endometriosis) and Q-Octreotide (primary indications in acromegaly and palliative care). Q-Leuprolide and Q-Octreotide are 3- and 1-month sustained-release microsphere formulations, respectively. Both Q-Leuprolide and Q-Octreotide are in preclinical phase with bioequivalence studies planned for completion in 2011.

"Typically, proteins and peptides have a short life when injected, but by formulating them with our platform to create a sustained release, patients can avoid daily injections," explains Dr. Daniels.

Q-Sphera aims to overcome issues associated with biotherapy delivery, most notably by minimizing protein and peptide degradation. The Q-Sphera drug-loaded microspheres are produced using bioresorbable polymers, and at 80 microns in diameter, are injectable using 27 to 29 needle gauge devices.

In addition to developing its own pipeline of products, Dr. Daniels says Q Chip is looking for partners that are interested in sustained release of their own drugs. In keeping step with its new biopharmaceutical focus, Q Chip is in the process of divesting its ReaX™ and ReaX+™ bead formats, also developed

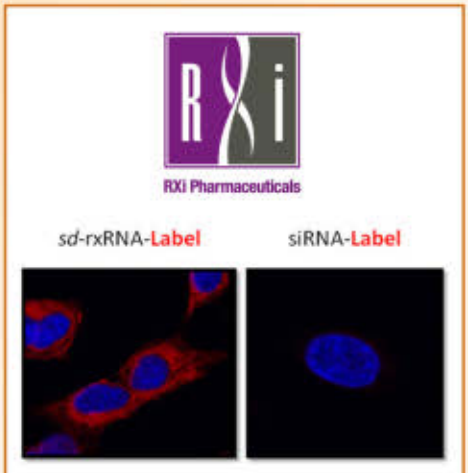


Figure 4. Cells with blue nuclei (Hoechst staining) after brief exposure to red fluorescent-labeled RNAs. sd-rxRNA versions (left) are in the cytoplasm (right), siRNA cannot be seen in the cell at all.

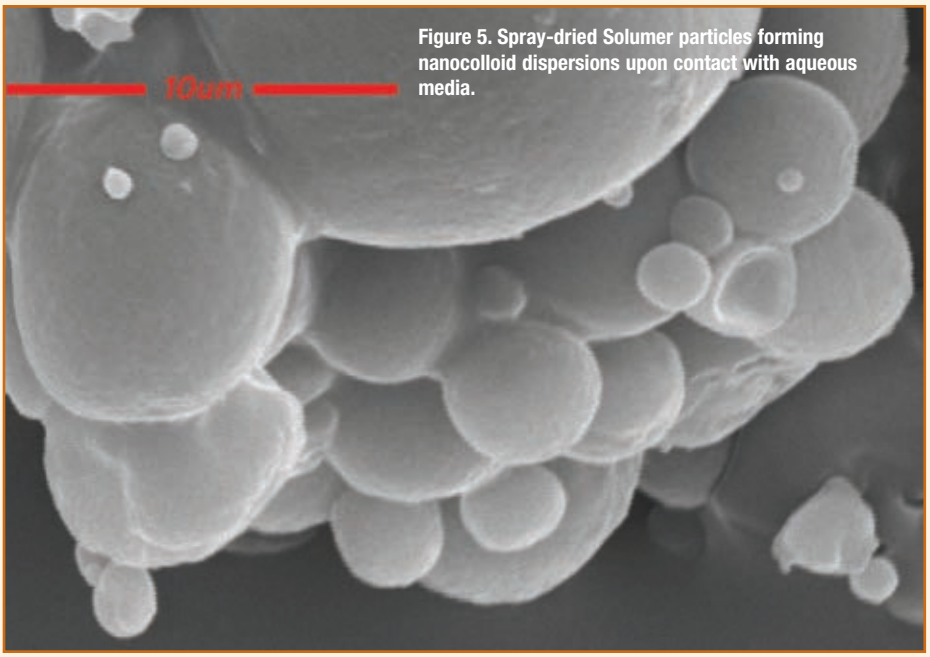


Figure 5. Spray-dried Solumer particles forming nanocolloid dispersions upon contact with aqueous media.

with the MicroPlant platform. ReaX beads are designed for immunodiagnostics assays encapsulation, and they are formulated from polysaccharides and/or polyethers to produce dry, solid bioencapsulated assays.

RXI PHARMA–SELF-DELIVERING RNA

This biopharmaceutical company is developing treatments for human diseases using a technology called RNA interference (RNAi), discovered by co-founder Dr. Craig Mello, who was awarded the 2006 Nobel Prize for his work in this area.

"By harnessing the power of RNAi, we believe RXi Pharmaceuticals can develop a new class of therapeutic products that could have a number of distinct advantages over today's drugs," says Dr. Tod Woolf, scientific advisory board member and former President and CEO.

RNAi is a naturally occurring mechanism for the regulation of gene expression that has the potential to selectively inhibit the activity of any human gene. As a result, RNAi may potentially treat human diseases by "turning-off" genes and blocking the production of disease-causing proteins before they are made. RXi is building a portfolio of potential therapeutic product candidates using its RNAi platform, which includes both RNAi compounds and delivery methods.

Delivery is a key factor in RNAi drug development and Worcester, MA-based RXi is pursuing a delivery program that takes advantage of both self-delivering RNAi compounds and administration of RNAi compounds using a delivery vehicle.

The self-delivering rxRNA (sd-rxRNA™) technology (Figure 4) may provide advantages in efficacy, toxicity, ease of administration, and manufacturing cost because the compounds do not require an additional delivery vehicle to reach the desired tissues and cells in the body, explains Dr. Woolf.

"First-generation RNAi compounds had significant delivery issues as it gets removed by the kidney in the first pass," he says. "The challenge is to keep it in the bloodline long enough to reach the tissue. Self-delivery via local injection or inhalation can do that."

RXi has chemically modified the RNA to allow it to bind to serum proteins and prevent kidney clearance. Other delivery approaches include using delivery vehicles, such as nanotransporters and Glucan Encapsulated RNAi Particles (GeRP) to deliver rxRNA compounds to various tissues, including the liver and macrophages. The GeRP delivery system could potentially be used to treat inflammatory diseases, such as rheumatoid arthritis, psoriasis, Chron's disease, and ulcerative colitis. The GeRP delivery system uses hollow, porous, micron-sized shells that can be filled with one or more types of RNAi compounds. Once in the macrophage, the RNAi compounds are presumed to be released from the GeRP shell into the cytoplasm, where they would silence the specific target gene. As the macrophage migrates from the intestine/GALT to the other tissues in the body, the RNAi compound continues to silence the gene(s)-causing disease. Therapeutic areas for RNAi include obesity, ocular diseases, ALS, oncology, and inflammatory diseases.

"The variety of therapeutics are enormous and the market is big," says Dr. Woolf.

SOLUBEST–BRINGING SOLUBILITY TO MARKET

This Israeli-based start-up has spent the past 8 years evolving its technology to improve drug solubility using off-the-shelf polymers in a rapid, friendly, and cost-effective industrially scale process. Now, the firm is looking to offer that intellectual property to the pharmaceutical space.

Employing proprietary "smart" polymer self-assembly concepts, SoluBest's scientists have developed a platform for improving the bioperformance of poorly soluble drugs. This technological platform, Solumer™ (Figure 5), can be applied to a range of pharmaceuticals and requires a relatively short time for screening potentially feasible candidates (a few weeks per project) and to prepare formulated API for clinical trial (up to ~6 months).

Solumerization enables the design and production of new self-assembled drug-polymer complexes with unique physico-chemical properties. Once in the body, these formulations disintegrate into nanocolloid dispersions, significantly increasing drug solubility and oral absorption, thus improving the performance of poorly soluble active substances.

Solubility, or the lack thereof, is the single most significant issue in the formulation of drugs: more than 40% of the drugs on the market and up to 60% of drugs currently in development are poorly soluble, presenting drug developers with severe problems in effectively delivering these drugs to patients, says Dr. Irene Jaffe, VP Corporate Strategy for SoluBest.

"Solubility transcends all therapeutic fields," says Dr. Jaffe. "But small molecules present a great solubility challenge. We take polymers known and approved by the FDA for oral delivery and assemble them in a novel way with poorly soluble APIs to produce formulations having specific identifiable properties and features."

These collective "fingerprint" features, including the reduced lattice energy of APIs and their ability to produce nanocolloid dispersions upon contact with aqueous solutions, ensure significant solubility improvement and hence increased bioavailability. Solumerized drugs demonstrate uncompromised stability of the drug-polymer constructs having at least a 2-year shelf stability of the formulations, as well as excellent batch-to-batch reproducibility.

SoluBest has conducted extensive testing of its platform through its proof-of-concept compounds:

SoluFeno: A reformulation of Fenofibrate, which has been shown to be bioequivalent to the leading marketed nanoparticle product Tricor 145 - currently more than a $1 billion dollar drug in the US market alone;

SoluRes: The insoluble anti-oxidant Resveratrol in its solumerized form has been clinically proven to have at least three times better bioavailability versus the unformulated form;

SoluAlbendazole: Albendazole is an anti-parasitic agent shown to have significantly better bioavailability when solumerized, leading to increased efficacy, the latter very important, as multiple treatments are currently needed to successfully eliminate the parasite and its eggs.

SoluBest is seeking to divest Solumer to companies for them to commercialize their own drugs or, if a contract manufacturer, other companies' drugs. SoluBest has received increasing interest from companies in the US and Europe.

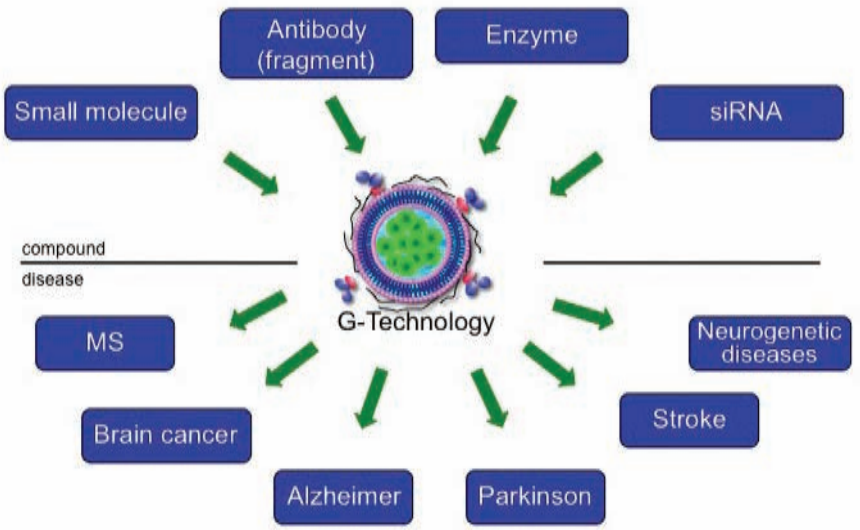
"We are not a manufacturer, we develop enabling technology," says Dr. Jaffe. "The recession gave us the time to reassess who we are and where we want to go, and we are now taking our concepts to oral formulation of biomolecules. We are too small and young to dabble in manufacturing and commercialization. We need to interest companies in the small molecule space that want to bring in a proprietary delivery technology that can improve the performance of both marketed and new discovery drugs."

to-BBB–BREAKING DOWN BRAIN BARRIERS

to-BBB is a Dutch biotechnology company focused on enhanced drug delivery across the blood-brain barrier (BBB). The company is developing treatments for brain disorders for which there is currently no effective treatment by combining existing drugs with its proprietary G-Technology™ brain delivery platform (Figure 6).

G-Technology, which to-BBB in-licensed from the Industrial Technology Research Institute in Taiwan, consists of liposomes coated with glutathione-conjugated PEG to mediate safe targeting and enhance the delivery of drugs to the brain. Intravenous injections of PEGylated liposomes are already on the market (Doxil/Caelyx), as are high dosages of glutathione in supportive

Figure 6. to-BBB's proprietary G-Technology can potentially be used to deliver a wide range of compounds to the brain to treat a variety of diseases.



therapy in cancer.

"Glutathione, a natural anti-oxidant, is found at high levels in the brain, and its receptor is abundantly expressed at the BBB," says Willem van Weperen, CEO of to-BBB. "Therefore, glutathione uniquely minimizes common risks like adverse immunological reactions or interference with life-essential physiologic pathways."

Proof-of-concept studies with peptides and small molecules in pain, brain tumors, and viral encephalitis demonstrated that the G-Technology is effectively and safely enhancing the delivery of drugs to the brain, adds Mr. van Weperen.

Next to safety and efficacy, an advantage of G-Technology is the ability to include a range of molecules into the liposomes, which provides clear platform capabilities for brain delivery, continues Mr. van Weperen.

"The biggest advantage is that these molecules do not need to be chemically modified to be incorporated into the liposomes. This will ensure that the efficacy and safety profile is not changed. The liposomes have a long half-life in plasma (in the range of several hours or even several days in humans), and thus a large and long availability of the molecule to be delivered to the brain. Glutathione as a targeting ligand can be used from mouse to men, enabling us to readily move forward from preclinical to clinical research."

Furthermore, a technological and mechanistic validation has shown that the higher the amount of glutathione coating of the brain-targeted liposomes, the more free drug was actually delivered to the brain, says Mr. van Weperen.

Typically, the neuroprotective BBB prevents most disease-modifying biologics and small-molecule drugs from reaching the brain in sufficient amounts to exert an effect.

"Pharma companies have identified this as an urgent need and are actively looking for solutions," says Mr. van Weperen. In the past decades, academia and small biotech have made progress in this area, but safety has been a major obstacle. A specific opening of the barrier turned out to be toxic and many potential transporters are failing due to immunogenicity or interference with essential physiologic pathways."

to-BBB has a two-legged strategy of developing products. First, internal development formulates off-patent medication with G-Technology. Second, to-BBB has partnered with pharma companies, such as Shire, MedImmune, and Genzyme, to deliver their patented compounds to the brain.

"These research collaborations will provide proof-of-concept and, if successful, will be followed by license deals," says Mr. van Weperen.

Primary interest for G-Technology is from pharma and biotech companies that have a CNS focus. to-BBB's potential therapies for brain cancer, Alzheimer's, ALS, MS, and Parkinsons are all in early preclinical stage and could be interesting for out-licensing later during their development.

to-BBB's lead product (2B3-101, dubbed Brain-Doxil) involves doxorubicin glutathione-PEG liposomes. Doxorubicin is a conventional anthracycline that, either as free drug or encapsulated in (PEGylated) liposomes, is used as an anticancer treatment. However, these doxorubicin formulations do not effectively cross the BBB to exert an effect in the brain. The use of Glutathione-PEG (G-Technology) enhances brain uptake and shows clear efficacy in brain tumor models, explains Mr. van Weperen. 2B3-101 is currently being manufactured in large preclinical batches by to-BBB's manufacturing partner TTY in Taiwan and is moving through preclinical development.

In 2007, the CNS drug market was $109 billion, with a large potential of diseases currently being untreated or undertreated, according to the 2008 NeuroInsights' Neurotechnology Report. Currently, CNS disorders represent 11% of global disease; in 2010 this is expected to rise to 14%, predominantly driven by increasing life expectancy. Traditional small molecules will not be able to address these diseases adequately, and more complex small molecules and biologics are needed to achieve disease modification.

"to-BBB's proprietary brain delivery platform can hopefully play a key role in the coming decade to get these disease modifying compounds better into the brain," says Mr. van Weperen. ◆

BIOGRAPHY

Ms. Cindy H. Dubin has been a professional journalist since 1988. She is currently a Contributing Editor to Drug Delivery Technology as well as Editor of its Specialty Pharma section. Prior to these positions, she spent several years focusing her writing on pharmaceutical formulation and development. She has been recognized by the American Society of Business Press Editors for an article she wrote on nanotechnology, and her writing has been awarded by the prestigious Neal Award Committee for Journalistic Excellence. Ms. Dubin earned her BA in Journalism from Temple University in Philadelphia and her certificate in Business Logistics from Pennsylvania State University.

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Highly Bioavailable Nasal Calcitonin - Potential for Expanded Use in Analgesia

By: Edward T. Maggio, PhD; Elias Meezan, PhD; DKS Ghambeer, MD; and Dennis J. Pillion, PhD

INTRODUCTION

Nasal calcitonin is currently indicated for the treatment of postmenopausal osteoporosis in females greater than 5 years post menopause with low bone mass relative to healthy premenopausal females. Injectable calcitonin is indicated for the treatment of Paget's disease and for hypercalcemia, as well as for postmenopausal osteoporosis. Throughout the past 2 decades, numerous reports of the highly effective analgesic properties of calcitonin have appeared.[1-20] Because calcitonin increases plasma beta-endorphin levels, acting at the hypothalamic and/or at the pituitary level, it is able to relieve pain independently of its peripheral effects on bone.[1]

Calcitonin is regarded as a highly safe drug because single doses of salmon calcitonin nasal spray up to 1600 IU, doses up to 800 IU per day for 3 days, and chronic administration of doses up to 600 IU per day have been studied without serious adverse effects.[21] However, the bioavailability of current FDA-approved nasal salmon calcitonin products is poor, averaging only 3% compared to the bioavailability achieved via the alternate subcutaneous injection route, with a two-order-of-magnitude variable range of 0.3% to 30.3%.[21] As a result of the low bioavailability and high variability, most studies related to the use of calcitonin in ameliorating pain have been conducted using injected calcitonin rather than the nasally administered calcitonin, presumably to move up the dose-response curve in anticipation that higher systemic blood levels are more efficacious, and to avoid unacceptable variability in systemic blood levels.

The advent of highly effective and non-irritating alkylsaccharide absorption-enhancement agents, designated Intravail® excipients, affords a practical opportunity to reconsider the broader use of calcitonin as a highly effective non-invasive analgesic for a variety of bone pain indications.[22-28]

HIGHLY BIOAVAILABLE NASAL CALCITONIN

Salmon calcitonin has been shown to be highly effective for reducing osteoporotic and vertebral bone fracture pain, opioid resistant metastatic bone cancer pain, post-operative phantom limb pain (acute), sickle-cell bone crisis, post herpetic (shingles) pain, and neuropathic pain.[2-20] While injected calcitonin achieves substantially higher circulating blood levels, a non-invasive format is preferred in terms of patient compliance, convenience, ease of self-administration, and avoidance of needlestick injuries for patients or caregivers.

An open label, balanced, randomized, three-treatment, three-period, three-sequence, single-dose, cross-over bioavailability study to compare the bioavailability of calcitonin from three different formulations (two nasal sprays and a subcutaneous formulation) in 10 healthy adult human subjects under fed conditions was conducted to determine the enhancement in bioavailability resulting from inclusion of Intravail A3 (n-dodecyl-β-D-maltoside) in a standard salmon calcitonin formulation. The addition of Intravail A3 to a standard metered nasal spray calcitonin formulation resulted in a five-fold increase in average bioavailability from 6.6% for the control without Intravail A3 to 35.9%. Increased systemic bioavailability is expected to increase the clinical usefulness of calcitonin as a safe, non-invasive, non-opioid, analgesic in a number of important underserved clinical indications.

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absorption enhancers that allow intranasal delivery, or more broadly, transmucosal delivery, of peptide, protein, and non-protein macromolecular therapeutics having molecular weights up to and in excess of 20 KDa, with bioavailabilities up to and in excess of 50% compared to injection.[26,29]

The particular alkylsaccharides shown to be effective absorption enhancers are non-toxic, non-irritating, chemically synthesized molecules composed of a sugar, typically a disaccharide, and an alkyl chain, typically 10 to 16 carbon atoms in length, linked by an ester or glycosidic bond metabolized to CO_2 and H_2O through the corresponding sugar and fatty acid.[30] They provide controlled transient permeation of the nasal mucosal barrier with no irritation.

Preclinical studies in animal models have shown that selected alkylglycosides increase intranasal absorption of salmon calcitonin in a dose-dependent manner. For example, at a tetradecylmaltoside (TDM) concentration of 0.125%, intranasal absorption of salmon calcitonin in the rat is approximately 52% compared to intravenous administration.[25] Similar results for increased bioavailability of nasally administered peptides are observed for Intravail A3 at the same concentration.[27] Rapid onset of action in 7.5 to 10 minutes was observed, which is important for pain applications. While studies of transmucosal absorption in the rat or rabbit are useful indicators of comparative bioavailability trends, direct extrapolation from animal model bioavailability to bioavailability in humans is not possible.

The purpose of the present study was to determine the effectiveness of Intravail A3 alkylsaccharide in increasing absorption of calcitonin in humans in anticipation of its possible use in non-invasive treatment of a number of underserved or orphan indications. The addition of Intravail A3 excipient to a standard metered nasal spray calcitonin formulation resulted in an average bioavailability of 35.9% compared to 6.6% for the control, a five-fold increase in bioavailability. These results are highly encouraging and suggest the clinical use of nasally administered calcitonin may be extended to include a number of important indications in the pain management area.

TABLE 1

Test Article	Cmax	AUC (0-4 hrs)	Tmax	Relative Bioavailability
	pg/mL	pg.hr/mL	hrs	
sCalcitonin Injection (Formulation A)	52.62	78.92	0.75	100%
sCalcitonin Nasal Spray Without Dodecylmaltoside (Formulation B)	12.89	5.22	0.5	6.6%
sCalcitonin Nasal Spray With 0.18% Dodecylmaltoside (Formulation C)	26.18	28.35	0.25	35.9%

Effect of A3 Upon Pharmacokinetic Parameters for Intranasal Salmon Calcitonin Administration in 10 Normal Female Subjects

MATERIALS

Salmon calcitonin is commercially available as nasal spray and injectable formulations sold under the brand names Calcimar and Miacalcin. The concentration of salmon calcitonin in the intranasal formulation is 2200 IU/mL, providing 200 IU of synthetic salmon calcitonin per 91 microliter spray dose. The concentration of salmon calcitonin in the injectable dosage form is 200 IU/mL.

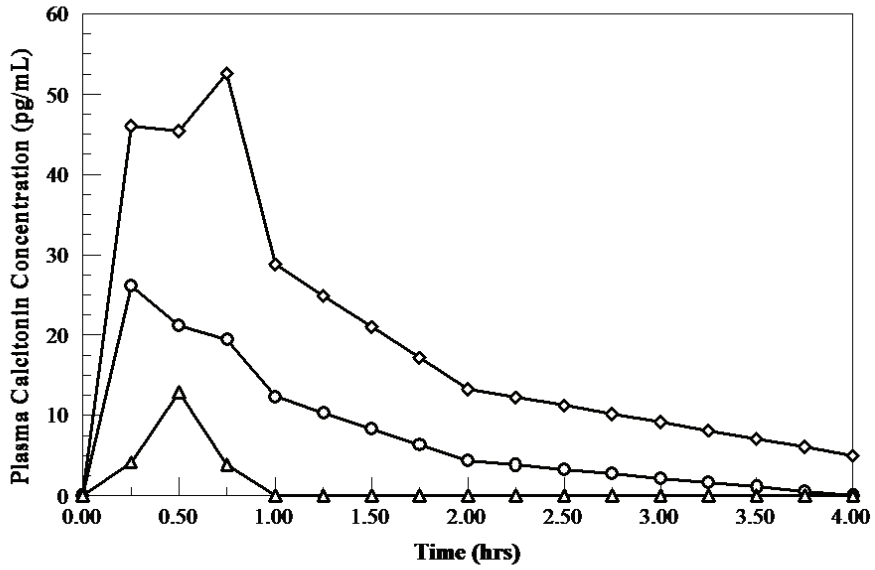
METHODOLOGY

Formulation Preparation

The injectable salmon calcitonin control used in this study (Formulation A) consisted of a 0.33-mL subcutaneous injection of unaltered commercially available injectable salmon calcitonin administered according to the manufacturer's directions, providing a total dose of salmon calcitonin of 66.6 IU, corresponding to 11.1 micrograms based on the international standard value of 6,000 IU/mg.[31]

The nasal salmon calcitonin test articles for this study were obtained by diluting the commercial nasal formulation 1:3 with 30 mM pH 4.5 sodium acetate buffer containing either a) no Intravail, or b) 0.27% (2.7 mg/mL) Intravail A3 excipient in sterile distilled water to yield a first test article containing a final concentration of 733.3 IU/mL salmon calcitonin and no Intravail

FIGURE 1



Pharmacokinetic profile for nasally administered salmon calcitonin with and without A3 compared to the injected control at equal dose levels. Legend: (◊) Formulation A; (Δ) Formulation B; (o) Formulation C.

(Formulation B), and a second test article containing 733.3 IU/mL salmon calcitonin and 0.18% Intravail A3 (Formulation C). Each of these two test articles provides 66.6 IU of salmon calcitonin per each 91 microliter spray dose. 1-mL aliquots of each of the two test articles were placed into amber screw-top vials and closed by attaching a 91-microliter metered spray pump manufactured by Pfeiffer GmbH (Radolfzell, Germany) for each subject. Vials were stored and used in an upright position, and the spray pump was primed to displace air bubbles in the pump chamber by depressing the pump two or three times until a uniform fine spray was observed, immediately or shortly prior to administration to the subjects.

Subjects/Study Center

The study was conducted at Apothecaries Limited, 579, Devli, East Sainik Farms, New Delhi 110 018, India. All participating subjects gave their informed consent. This research was carried out according to the Good Clinical Practice Guidelines as enunciated by the Indian Council of Medical Research (ICMR) and the principles as enunciated in the Declaration of Helsinki, 2000. Informed consent documents, Protocols, and Investigator's Brochures were reviewed and approved by the Institutional Ethics Committee.

A total of 10 adult healthy postmenopausal female subjects between the ages of 40 to 55 years were selected for participation in this study. Subjects were randomized into two sequence groups. The randomization was performed in such a way that each subject received either of the nasal test articles during the first period and the other during the second period. All subjects received the injectable test article in the third period. All test articles were administered in the study center by the study personnel to ensure compliance with the study protocol. Blood samples were drawn at appropriate intervals to allow determination of plasma salmon calcitonin concentrations.

Analytical Methods

Salmon calcitonin levels in plasma were measured using a commercial Ultrasensitive ELISA salmon calcitonin enzyme immunoassay kit (No. DSL-10-3600) manufactured by Diagnostic Systems Laboratories, Inc., a Division of Beckman Coulter, from DSL India. The theoretical sensitivity, or minimum detection limit, as calculated by interpolation of the mean minus two standard deviations of 13 replicates of the 0 pg/mL salmon calcitonin standard, is 4.2 pg/mL. The standards supplied with the kit for estimation of salmon calcitonin were subjected to a linearity test using the standards provided with the kit, and found to be linear in the range of 7.0 pg/ml to 330 pg/ml of salmon calcitonin. The intra assay precision was ≤ 5%, and the inter assay precision was ≤ 9.1%. The AUC, Tmax, Cmax, and bioavailability was calculated from the plasma level data.

RESULTS & DISCUSSION

The pharmacokinetics profile for the three formulations of calcitonin tested are shown in Figure 1. Six out of 10 subjects showed complete calcitonin clearance at the 4-hour data point, and two subjects showed complete clearance at 2 hours. Therefore, AUC (0 to 4 hrs) was calculated for all 10 subjects. The average values are shown in Table 1.

The AUC (0 to 4) was found to be 5.22 pg.hr/ml for Formulation B and 28.35 pg.hr/ml for Formulation C. The relative bioavailability of Formulation B was 6.6%, and Formulation C was 35.9%

with respect to Formulation A after 4 hours of drug administration. The presence of Intravail in Formulation C increases the overall relative bioavailability of calcitonin in plasma. The Cmax for the injection was approximately 2 to 4 times the values obtained for the nasal spray formulations. The Tmax ranged from 0.25 to 0.75 hours for the three formulations. The addition of A3 to the salmon calcitonin formulation resulted in a five-fold increase in bioavailability compared to the commercial injectable formulation without A3. The precision observed for the formulation containing Intravail was ± 17%.

In contrast, for the current commercial product, which provides 3% average bioavailability, the precision spans two-orders of magnitude, from 0.3% to 30.6% (Novartis Package Insert). Hence, it can be concluded that Formulation C (calcitonin with A3) showed comparatively better bioavailability compared to Formulation B (calcitonin without Intravail). The presence of Intravail excipient in Formulation C increases the overall relative bioavailability of calcitonin in plasma.

More than two dozen scientific publications throughout the past 2 decades have indicated that salmon calcitonin has significant potential in the treatment of a variety of underserved pain treatment applications, such as opioid-resistant metastatic bone cancer pain, acute phantom limb pain following amputation, vertebral fractures, and Sickle Cell disease-related bone pain. Most of the reported studies utilized injectable calcitonin, presumably because of the very low bioavailability and high variability observed with the current commercially available metered nasal spray products.

TABLE 2

Test Article	Excipient	Absolute Bioavailability	Total Dose Administered	Reference
Intravenous Calcitonin Control	None	100%	10 IU/kg	32
Nasal Calcitonin, in pH 4 Isotonic Phosphate Buffer	1% Chitosan Free Amine	2.45%	10 IU/kg	
Nasal Calcitonin in pH 4 Isotonic Phosphate Buffer	5% Dimethyl-beta-cyclodextrin	1.91%	10 IU/kg	
Nasal Calcitonin in pH 4 Isotonic Phosphate Buffer Control	None	1.22%	10 IU/kg	
Nasal Calcitonin in pH 3.75 6 mM Sodium Acetate, 0.9% Sodium Chloride	0.125% Tetradecyl Maltoside	52%	8 IU/kg	25

Comparison of Observed Bioavailabilities for Calcitonin in the Rat

Calcitonin has been shown to be a safe and effective drug for current applications, even at concentrations considerably higher than those used to induce analgesia. Because of its peptidic nature, calcitonin is essentially free of any chemical toxicity issues. Calcitonin is also non-addictive and therefore not subject to abuse or diversion to non-clinical applications. In addition, it is free of many undesirable side effects associated with opioid administration, such as respiratory and circulatory depression, apnea, respiratory arrest, constipation, light-headedness, dizziness, and sedation.

Previously, a number of attempts have been made to overcome these limitations, in particular using two classes of extensively studied absorption-enhancement excipients, namely the chitosans and the cyclodextrins. In a side-by-side comparison, the absorption-enhancement properties of representative members of each of these families for calcitonin compared to intravenous administration were studied, allowing an absolute intranasal bioavailability in the rat to be determined.[32] The results for chitosan, dimethyl beta cyclodextrin, and tetradecyl maltoside, a representative alkylsaccharide excipient, are summarized and compared in Table 2. The formulation containing alkylsaccharide excipient is significantly more effective than either of the formulations containing chitosan or dimethyl beta cyclodextrin.

CONCLUSION

Salmon calcitonin formulations containing Intravail provide greatly increased systemic bioavailability. The increased bioavailability and decreased

variability may provide opportunities for increased non-invasive applications of salmon calcitonin in the treatment of pain for a number of underserved clinical indications, such as opioid-resistant metastatic bone cancer pain, acute phantom limb pain following amputation, vertebral fractures, and Sickle Cell disease-related bone pain.

REFERENCES

1. Franceschini R, Cataldi A, Cianciosi P, Garibaldi A, Corsini G, Barreca T, Rolandi E. Calcitonin and beta-endorphin secretion. Biomed Pharmacother. 1993;7:305-309.
2. Blau LA, Hoehns JD. Analgesic efficacy of calcitonin for vertebral fracture pain. Ann Pharmacother. 2003;37:564-570.
3. Knopp JA, Diner BM, Blitz M, Lyritis GP, Rowe BH. Calcitonin for treating acute pain of osteoporotic vertebral compression fractures: a systematic review of randomized, controlled trials. Osteoporos Int. 2005;16:1281-1290.
4. Konno S, Kikuchi S. Therapeutic effects of calcitonin on back pain in the patients with osteoporosis. Clin Calcium. 2005;15:168-173.
5. Tanaka K, Yoshizawa M, Yoh K. Improvement of QOL in osteoporotic patients by calcitonin treatment. Clin Calcium. 2005;15:174-178.
6. Laroche M, Cantogrel S, Jamard B, et al. Comparison of the analgesic efficacy of pamidronate and synthetic human calcitonin in osteoporotic vertebral fractures: a double-blind controlled study. Clin Rheumatol. 2006;25:683-686.
7. Ofluoglu D, Akyuz G, Unay O, Kayhan O. The effect of calcitonin on beta-endorphin levels in postmenopausal osteoporotic patients with back pain. Clin Rheumatol. 2007;26:44-49.
8. Hindley AC, Hill EB, Leyland MJ, Wiles AE. A double-blind controlled trial of salmon calcitonin in pain due to malignancy. Cancer Chemother Pharmacol. 1982;9:71-74.
9. Allan E. Calcitonin in the treatment of intractable pain from advanced malignancy. Pharmatherapeutica. 1983;3:482-486.
10. Egawa J, Kawada Y, Abe M, et al. Effect of porcine calcitonin on pain caused by cancer-induced bone destruction. Gan No Rinsho. 1984;30:251-258.
11. Hirota Y, Kondou S, Okamura H, et al. Effectiveness of synthetic calcitonin derivative (elcatonin) on the bone pain and serum calcium concentration in multiple myeloma. Gan To Kagaku Ryoho. 1990;17:1059-1063.
12. Szanto J, Ady N, Jozsef S. Pain killing with calcitonin nasal spray in patients with malignant tumors. Oncol. 1992;49:180-182.
13. Jelic S, Borkovacki R, Babovic N, Kovcin V, Milanovic N. Anti-pain effect of salmon calcitonin in bone metastases of malignant tumors with the exception of breast and prostatic carcinoma. Vojnosanit Pregl. 1995;52:151-154.
14. Mystakidou K, Befon S, Hondros K, Kouskouni E, Vlahos L. Continuous subcutaneous administration of high-dose salmon calcitonin in bone metastasis: pain control and beta-endorphin plasma levels. J Pain Symptom Manage. 1999;18:323-330.
15. Simanski C, Lempa M, Koch G, Tiling T, Neugebauer E. Therapy of phantom pain with salmon calcitonin and effect on postoperative patient satisfaction Chirurg. 1999;70:674-681.
16. Wall GC, Heyneman CA. Calcitonin in phantom limb pain. Ann Pharmacother. 1999;33:499-501.
17. Jaeger H, Maier C, Wawersik J. Postoperative treatment of phantom pain and causalgias with calcitonin. Anaesthesist. 1988; 37:71-76.
18. Jaeger H, Maier C. Calcitonin in phantom limb pain: a double-blind study. Pain. 1992;48:21-27.
19. Quevedo SF. Use of calcitonin in sickle cell bone crisis. Blood. 1996;88:1520.
20. Qin H, Cai J, Yang FS. Could calcitonin be a useful therapeutic agent for trigeminal neuralgia? Med Hypotheses. 2008;71:114-116.
21. Novartis. Miacalcin Nasal Spray Package Insert. Available from http://www.fda.gov/medwAtch/SAFETY/2006/Jan_PI/Miacalcin_PI.pdf . Accessed April 15, 2009.
22. Pillion DJ, Atchison JA, Gargiulo C, Wang RX, Wang P, Meezan E. Insulin delivery in nosedrops: new formulations containing alkylglycosides. Endocrinol. 1994;135:2386-2391.
23.m Pillion DJ, Atchison JA, Stott J, McCracken D, Gargiulo C, Meezan E. Efficacy of insulin eyedrops. J Ocul Pharmacol. 1994;10:461-470.
24. Pillion DJ, Hosmer S, Meezan E. Dodecylmaltoside-mediated nasal and ocular absorption of lyspro-insulin: independence of surfactant action from multimer dissociation. Pharm Res. 1998;15:1637-1639.
25. Ahsan F, Arnold J, Meezan E, Pillion DJ. Enhanced bioavailability of calcitonin formulated with alkylglycosides following nasal and ocular administration in rats. Pharm Res. 2001;18:1742-1746.
26. Arnold J, Ahsan F, Meezan E, Pillion DJ. Nasal administration of low molecular weight heparin. J Pharm Sci. 2002;91:1707-1714.
27. Pillion DJ, Ahsan F, Arnold JJ, Balusubramanian BM, Piraner O, Meezan E. Synthetic long-chain alkyl maltosides and alkyl sucrose esters as enhancers of nasal insulin absorption. J Pharm Sci. 2002;91:1456-1462.
28. Arnold JJ, Ahsan F, Meezan E, Pillion DJ. Correlation of tetradecylmaltoside induced increases in nasal peptide drug delivery with morphological changes in nasal epithelial cells. J Pharm Sci. 2004;93:2205-2213.
29. Hussain A, Yang T, Zaghloul AA, Ahsan F. Pulmonary absorption of insulin mediated by tetradecyl-beta-maltoside and dimethyl-beta-cyclodextrin. Pharm Res. 2003;20:1551-1557.
30. Weber N, Benning H. Metabolism of orally administered alkyl beta-glycosides in the mouse. J Nutr. 1984;114:247-254.
31. Rafferty B, Corran P, Bristow A. Multicenter collaborative study to calibrate salmon calcitonin by bioassay and high-performance liquid chromatography: establishment of the third international standard. Bone. 2001;29(1):84-89.
32. Sinswat P, Tengamnuay P. Enhancing effect of chitosan on nasal absorption of salmon calcitonin in rats: comparison with hydroxypropyl- and dimethyl-beta-cyclodextrins. Int J Pharm. 2003;257:15-22.

BIOGRAPHIES

Dr. Edward T. Maggio currently serves as the CEO of Aegis Therapeutics. He has been a founder and board member of 7 public and private life science companies in San Diego and one in Copenhagen. He serves on various departmental advisory boards for NYU's Polytechnic Institute, the University of California, Cal State University. Dr. Maggio has co-authored more than 30 book chapters and scientific articles and is an inventor on more than three dozen issued and pending US and foreign patents in the biotechnology area.

Dr. Elias Meezan is Professor Emeritus and former Chairman of Pharmacology and Toxicology at the University of Alabama at Birmingham and is a co-inventor of the patented Intravail® drug delivery technology. He has authored or co-authored more than 100 scientific publications in areas including the development of widely used methods for the isolation of brain and retinal microvessels and the biochemical pharmacology of alkylmaltosides and their applications in treating diabetes and cystic fibrosis.

Dr. DKS Ghambeer is a Clinical Trials Investigator at Apothecaries Limited in New Delhi, India, and has conducted sponsored clinical research studies on a range of medical devices and drugs for Apothecaries' multinational client base.

Dr. Dennis Pillion is Professor of Pharmacology & Toxicology at the UAB School of Medicine and is co-inventor of the patented Intravail® drug delivery technology. He has been a diabetes researcher and educator for the past 30 years and is studying non-invasive delivery of long-acting and short-acting insulins and other peptide therapeutics using ocular, nasal, or oral formulations containing novel absorption-enhancing agents.

PARTICLE SIZE ANALYSIS

Laser Diffraction Particle Size Analysis: A Powerful Tool for Rapidly Screening Nebulizer Formulations

By: Lei Mao, PhD; David Wilcox, and Paul Kippax, PhD

INTRODUCTION

Nebulizers are widely used to deliver inhaled drugs for both local and systemic action. Of great importance in this type of system is the particle size distribution (PSD) of the delivered aerosol droplets, which directly influences deposition behavior in the lungs and subsequently clinical efficacy. PSD therefore becomes a critical parameter when characterizing nebulizer performance. PSD of the inhalation aerosols can be measured aerodynamically by cascade impaction (CI) or geometrically by a laser diffraction technique. Traditionally, routine measurements of aerodynamic PSD in inhaled formulations are made using the CI technique, but this can be a labor-intensive and time-consuming process. The advent of Quality by Design (QbD) potentially heralds greater regulatory flexibility but intensifies the need for new tools and techniques capable of delivering increased amounts of data more rapidly. This following discusses the use of laser diffraction particle size analysis, a technique complementary to CI, to rapidly screen nebulizer formulations with directly comparable results.

UNDERSTANDING NEBULIZERS

Nebulizers are used increasingly for pulmonary drug delivery and offer some particular advantages. For example, they inflict little mechanical damage hence are suitable for delivering fragile molecules such as proteins and peptides. They also provide a continuous delivery profile that is especially beneficial for geriatric and pediatric patients, and they allow the easy delivery of high doses of drugs under tidal breathing conditions.

Delivering medication directly to the lungs results in rapid onset of the therapeutic effect, but effective delivery depends on droplet size and distribution of the aerosols generated by nebulizers or inhalers. Therapeutic operation of an inhalation device is characterized by the proportion of active pharmaceutical ingredient (API) aerosolized in particles of a certain size or below, typically 5 microns. The fraction of a dose that deposits in the lungs is called the respirable fraction or the fine particle fraction (FPF). The upper size limit for central airway deposition lies between 4 and 6 microns, with optimum particle deposition at around 2 to 4 microns.[1] In general, oversized particles will deposit in the proximal airways outside the chest cavity, while those too small will be exhaled. The other parameters representing PSD are the mass median aerodynamic diameter (MMAD) and geometry standard deviation (GSD).

Analysis of a nebulizer's rate of drug delivery and droplet size involves a combination of dose collection and cascade impactor analysis. These are lengthy techniques and provide less information about variations in nebulizer output influenced by a patient's inhalation patterns due to limited number of tests. Laser diffraction analysis is much more rapid, giving complementary data that support accelerated formulation and device development times.

AEROSOL CHARACTERIZATION

Measuring aerodynamic PSD is critical during product development and for quality control of all inhaled products. Cascade

TABLE 1

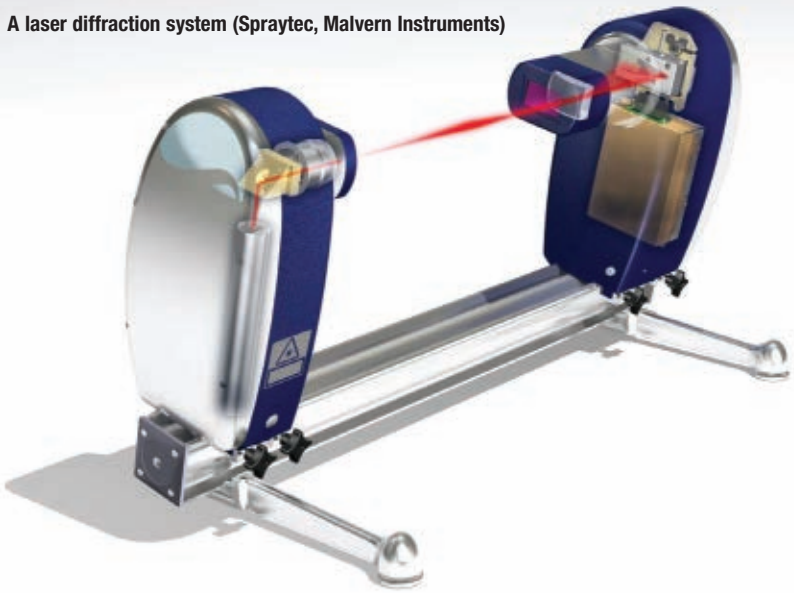
	Technoneb Model 3		Pari	
	Formulation A	Formulation B	Formulation A	Formulation B
Spraytec (% < 5 microns)	68.52 (1.2)	68.78 (2.2)	48 (0.3)	44.42 (1.16)
NGI (% < 5 microns)	72.11 (2.01)	70.06 (0.79)	48.94 (1.95)	45.52 (1.42)

Results from a study comparing particle size analysis of nebulizer aerosols using a Spraytec RTSizer laser diffraction analyzer and a Next Generation Pharmaceutical Impactor (NGI). Numbers in parentheses represent relative standard deviation (RSD).

impaction remains the gold standard, uniquely providing particle size measurement of the API rather than the complete formulation. Impaction is specified by the regulators and the international pharmacopoeias for all inhalation products testing, but manual testing limits productivity to a typical five to eight tests per day. The adoption of a QbD, knowledge-based approach in inhalation product design now demands greater understanding of Critical Quality Attributes (CQAs), factors such as FPF that directly influence clinical performance. It therefore increases the requirement for detailed particle size information and more rapid screening capabilities, as well as the ability to study the dynamics of spray behavior and formation in real time. Developers need incisive data early to help streamline formulation and device development protocols and define the design space.

FIGURE 1

A laser diffraction system (Spraytec, Malvern Instruments)

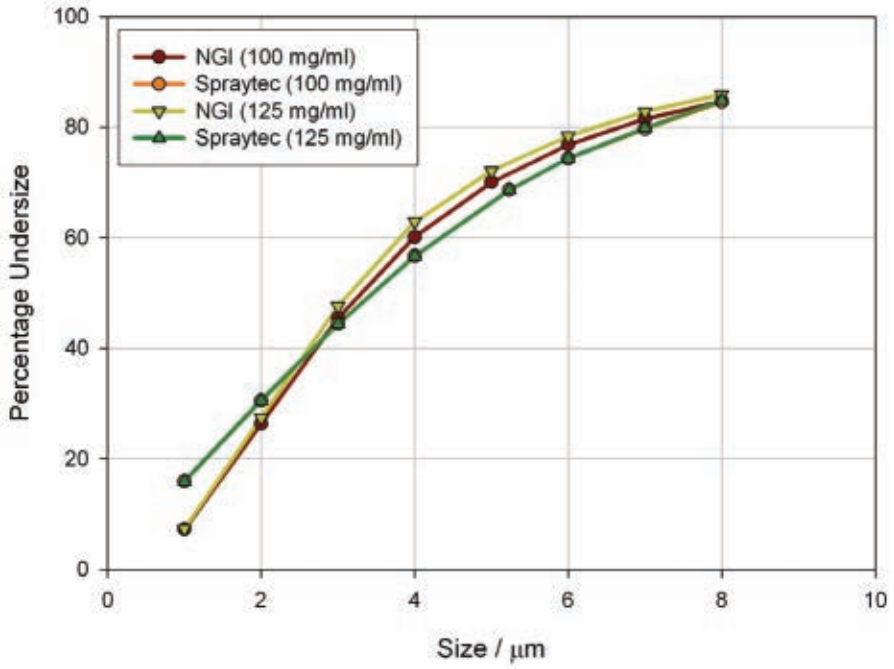


LASER DIFFRACTION

Rapid and non-destructive, laser diffraction particle sizing provides detailed dynamic information. Data acquisition rates of up to one measurement every 100 microseconds allow investigators to follow atomization dynamics in real time. In a typical set-up for laser diffraction aerosol measurements (Figure 1), a laser light source provides illumination sufficiently intense to enable measurements over a wide range of both concentration and particle size (0.1 to 2000 microns). Droplet size distributions are obtained by measuring the angular intensity of light scattered from a spray passing through a laser beam, and analyzing the scattering pattern using an appropriate optical model.

To a good approximation, laser diffraction is a volume-based technique in which the reported droplet size is defined as the diameter of the sphere that has an

FIGURE 2



Comparison of cumulative particle size distribution of Formulations A (125 mg/mL) and B (100 mg/mL) delivered from the Technoneb™ Model 3003 Nebulizer as measured by using the Spraytec and the NGI.

equivalent volume to the droplet passing though the measurement zone. This differs from aerodynamic measurement techniques, such as cascade impaction, where the reported droplet size relates to the diameter of the sphere of unit density that falls through air with the same terminal velocity as the droplet being measured. These differences in the definition of the droplet size must be considered when comparing the two techniques, especially when measuring non-spherical particles. Although cascade impaction and laser diffraction measure particle size in very different ways, the results can be comparable, as the following study shows.

TESTING THE THEORY

A comparative study of two commercially available nebulizers included particle size measurements made using both a Spraytec laser diffraction system (Malvern Instruments) and a Next Generation Pharmaceutical Impactor (NGI) (Copley Scientific, Nottingham, UK). Results were analyzed to assess comparability of the data generated by the two methods.

Nebulized solution formulations A (125 mg/mL) and B (100 mg/mL) were prepared with the same active ingredient and excipient. Nebulizers used were a Technoneb™ Model 3003 (Technology & Health LLC, USA) and a Pari Proneb® Ultra (Pari Innovative Manufacturers, Inc, USA).

As shown in Figures 2 and 3, this study yielded consistent results when particle size was measured using the Spraytec for both formulations (A and B) delivered from both nebulizers. Most importantly, comparison of results from the Spraytec with those measured by the NGI showed no evidence of significant difference in the fine particle fraction (FPF, < 5 microns).

Although the Spraytec reports a higher percentage below 2 microns in size than does the NGI, it is possible that this was caused by evaporation because the air streams were not humidified during measurement. It can be reasonably speculated that evaporation of the liquid in the small droplets in both Spraytec and NGI tests reduced the geometric PSD but impacted less on the aerodynamic PSD due to increased density of the resulting concentrated droplets. This might explain why a higher percentage below 2 microns was witnessed in the Spraytec results (measuring the geometric size) than the NGI results (measuring the aerodynamic size).

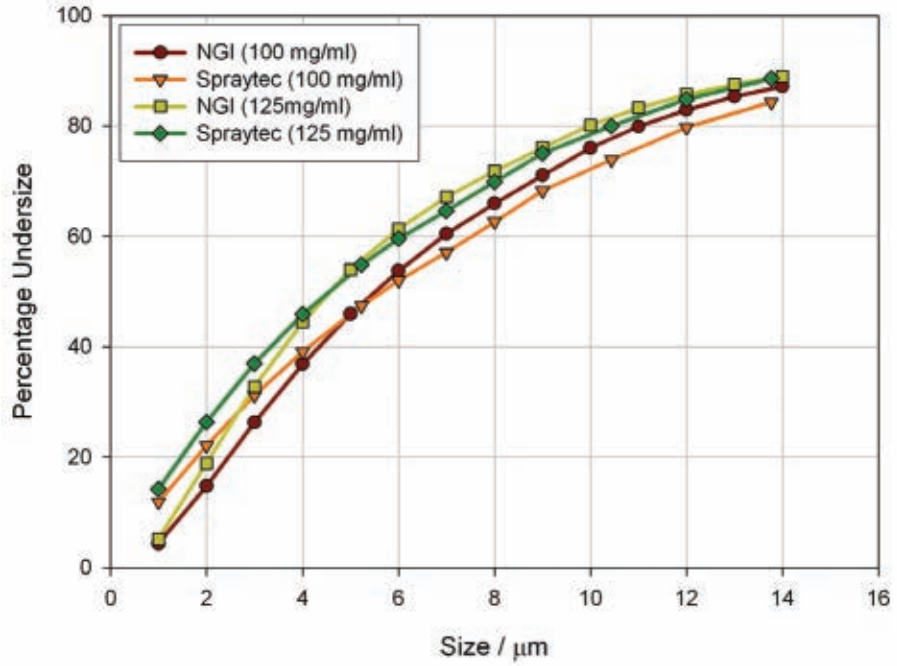
Table 1 shows a summary of the results, with relative standard deviations in parentheses. As evidenced, both techniques are in good agreement and show that the fine particle fraction (FPF) is similar for both formulations.

These results show the feasibility of using rapid laser diffraction measurements when screening the capabilities of different devices and formulations, before final performance validation using cascade impaction. One of the reasons the correlation achieved in this study is so good is because the measurements are of spherical droplets with density close to unity. This implies that equally precise correlations might be expected for similar studies involving other inhalation devices, such as nasal sprays and metered dose inhalers (MDIs).

CONCLUSION

Aerosolization efficiency is one of the key formulation performance measurements to be considered in developing nebulizer systems.

FIGURE 3



Comparison of cumulative particle size distribution of Formulations A (125 mg/mL) and B (100 mg/mL) delivered from the Pari Proneb® Ultra Nebulizer as measured by using the Spraytec and the NGI.

While it will remain essential to retain cascade impactor testing for validation and submission testing, laser diffraction particle size analysis offers fast, efficient access to the information developers need to screen device/formulation performance and to implement QbD. It offers the potential to cut both costs and timelines for inhalation product development.

A cross-validation study was carried out to assess the accuracy of laser diffraction relative to cascade impaction. Both the Spraytec and the NGI were used to determine the particle size distribution of aerosols of two nebulized formulations delivered from two different nebulizers. The FPF results from both measurement techniques were comparable, but there were differences in the cumulative percentage of the particles below 2 microns, a much less significant parameter. These differences may be attributable to evaporation of the liquid droplets during testing.

For the purpose of formulation screening to assess the aerosolization performance of nebulized formulations, dedicated laser diffraction systems may be considered to be a robust and efficient alternative to impaction techniques.

REFERENCE

1. Mitchell JP, Nagel MW. Particle size analysis of aerosols from medicinal inhalers. Powder and Particle No. 22. KONA. 2004:32-65

BIOGRAPHIES

Dr. Lei Mao is a Senior Scientist in the R&D group at Catalent Pharma Solutions based in Research Triangle Park, Morrisville, North Carolina. Prior to his current role, he was employed as a Section Leader at IVAX, UK, and subsequently, Senior Scientist, Principal Scientist, and Team Leader at Quadrant Healthcare plc, Elan Drug Delivery Ltd., Innovata plc, and Vectura plc, UK. Dr. Lei has over 15 years experience in inhalation drug delivery, predominantly in dry powder inhalation formulation and product development. He has over 20 publications in peer-reviewed journals/conference proceedings and 13 patent publications worldwide.

David Wilcox is a Senior Scientist in the R&D group at Catalent Pharma Solutions based in Research Triangle Park, Morrisville, North Carolina. Mr. Wilcox has over 10 years experience working with inhalation products, with most of his experience focused in metered dose inhaler formulation and product development.

Dr. Paul Kippax joined Malvern Instruments in 1997 as an Applications Scientist and in 2002, became Product Manager for the company's laser diffraction particle size analysis systems. He has worked closely with the pharmaceutical industry in understanding how laser diffraction techniques can be best applied to characterizing the performance of medical devices. This has included the publication of several joint research articles relating to the optimization of drug delivery from dry powder inhalers and nasal sprays. He has a degree in Chemistry and a PhD in Colloid and Interface Science, both obtained at the University of Nottingham in the UK.

DRUG DELIVERY Executive

UNILIFE MEDICAL SOLUTIONS: EMERGING STRONG IN THE PREFILLED SAFETY SYRINGES MARKET

Mr. Alan Shortall
CEO
Unilife Medical Solutions

"Unilife Medical Solutions is an emerging industry leader in the design, development, and supply of innovative safety medical devices. Since its public listing in 2002 (ASX: UNI), Unilife has built the foundation of a global business with the commercialization of its proprietary safety syringe technology, acquisition of FDA-registered US device manufacturing facilities, the signing of exclusive agreements with major pharmaceutical companies, and the development of a hand-picked world-class management team."

Unilife Medical Solutions Limited is an Australian publicly listed and US-headquartered designer, manufacturer, and supplier of innovative safety medical devices. Its core areas of business activity are the pharmaceutical market for prefilled syringes, the healthcare market for sharps safety devices, and medical device contract manufacturing. With a unique portfolio of prefilled and clinical safety syringes positioned to capitalize upon the global transition to safety syringes, a target NASDAQ listing, and partnerships with industry leaders, such as sanofi-aventis, Unilife is fast gaining a reputation as a company on the verge of global prominence. The ISO 13485-certified multinational business has its global headquarters in Pennsylvania and offices in Australia, France, and China. At the head of the fast-growing business is CEO Alan Shortall. Drug Delivery Technology recently interviewed Mr. Shortall to discuss Unilife's current business model, what makes them unique, and their approach to the future.

Q: Can you provide a brief overview of Unilife's product line?

A: Unilife has developed a full range of clinical (plastic) and prefilled (glass) syringes with fully automatic (passive) safety features that are integrated within the barrel. The key competitive differentiator of our proprietary technology is that operators can control the speed of passive needle retraction directly from the body into the barrel by relieving thumb or finger pressure on the plunger following full dose delivery. This unique technology reduces the risk of both needlestick injury and blood splatter. In addition, the syringes are virtually as compact in size and easy-to-handle as standard syringes to help improve operator functionality and minimize logistical costs and storage.

The Unitract 1-ml safety syringes are our first range of products to market. Designed for use within healthcare facilities and by patients who self-administer prescription medication such as insulin, they are approved for use in key markets, such as the US, Europe, Canada, and Australia. We commenced US production at our US facility in Pennsylvania this August with

commercial release expected to occur later this year.

I believe it's a credit to our operational capabilities that we fully designed, developed, built, and validated the automated assembly system for our Unitract 1-mL Syringes in-house. There are few companies in the world, particularly of our size, that can design, develop, and manufacture both the medical device and the assembly systems used to make them.

We are also in a 6-year collaboration with sanofi-aventis to develop the Unifill™ ready to fill syringe as the world's first known prefilled syringe equipped with passive and fully integrated safety features. The device offers pharmaceutical companies a way to comply with needlestick prevention legislation across North America and Europe and increase levels of drug differentiation without having to change dose filling and packaging processes used for standard prefilled syringes.

Q: Unilife is a globally represented company. How will the Unifill™ ready to fill syringe be distributed and used in the market place?

A: Our strategy is to design innovative products that address the specific safety and functionality requirements of all stakeholders within a target healthcare or pharmaceutical market. We are extremely excited about how we have designed the Unifill™ ready to fill syringe to become a product of choice within the pharmaceutical market for prefilled syringes.

We have established a strong relationship with sanofi-aventis, which is the world's largest purchaser of prefilled syringes. We were paid almost $15 million in July 2008 for the exclusive right to negotiate for the purchase of the product from us for 5 years. They are also funding our $25 million industrialization program, which also began in July 2008 and is targeted for completion in late 2010. That's 1 year ahead of the original schedule.

We have also retained the right to market the Unifill™ ready to fill syringe to other pharmaceutical companies for use within therapeutic drug classes outside of those desired by sanofi-aventis. Discussions with a number of other interested pharmaceutical companies have already commenced.

Q: How can Unilife products save and enhance lives?

A: This is the core mission of our company. More than 1.3 million people die from unsafe injection practices, such as needlestick injuries and syringe re-use every year. Industry sources indicate that more than 600,000 needlestick injuries are recorded in US healthcare facilities each year, with many more in Europe. To protect healthcare workers from the risk of infection with blood-borne diseases, such as HIV and hepatitis C, the US has introduced and is enforcing legislation requiring the mandatory use of safety syringes within healthcare facilities. Other healthcare markets, including Europe and Canada, are now following the US toward mandatory use of safety syringes.

Many of the safety syringe products currently on the market feature an active safety mechanism that requires manual activation by the operator. They are not failsafe, as the safety features of many devices are often activated incorrectly or not at all.

All Unilife safety syringe products, on the other hand, are fully passive to virtually eliminate the risk of needlestick injury. The retraction mechanism is activated automatically, while the needle is still inside the body. Following full dose delivery, the operator can control the rate of needle withdrawal directly from the body by relieving thumb or finger pressure on the plunger. This also minimizes any risk of infection associated with aerosol, commonly known as blood splatter.

Q: Your primary customer for the Unifill™ ready to fill syringe will be pharmaceutical companies. Why are they excited about the Unilife line?

A: More than 50 injectable drug products with total sales of more than $50 billion are currently available in a prefilled syringe format. Many pipeline drugs are also targeted for use in a prefilled syringe format. Pharmaceutical demand for prefilled syringes exceeds 2 billion units a year, with the market growing at more than 10% per year. A number of these drug products are now administered in prefilled syringes equipped with a needlestick-prevention device.

However, there is no prefilled syringe currently available with safety features that are fully integrated inside the glass barrel. To comply with legislation, many pharmaceutical companies purchase ancillary safety products that must be attached onto standard glass syringes. The bulky size of these ancillary safety devices can significantly increase the packaging and shipment costs of a pharmaceutical company. For patients who are needle-phobic, the relatively large size of these current safety products might also be intimidating.

We have designed the Unifill™ ready to fill syringe so that it is compatible with the drug filling and packaging systems currently used by pharmaceutical customers for standard prefilled syringes. The product is supplied in three sub-assembly pieces (a glass barrel, a seal, and a plunger) just like a standard prefilled syringe.
The passive safety features and relative ease-of-use of the Unifill™ ready to fill syringe can also allow pharmaceutical companies to increase levels of market differentiation for their injectable drug products, especially within therapeutic drug arenas that are highly competitive or threatened by generics. For drugs commonly used within healthcare facilities, pharmaceutical companies can use these needlestick prevention laws to their advantage as front-line healthcare workers now have a key vote in product selection based upon the performance of a safety-engineered device.

Furthermore, to contain healthcare costs, many pharmaceutical companies are strongly marketing injectable drug products that may be administered by patients at home. The passive integrated safety features and device functionality of the Unifill™ ready to fill syringe makes it ideal for convenient use and disposal by these patients.

Q: How do the materials used in production contribute to a superior product?

A: The Unifill™ ready to fill syringe is designed to serve as the primary drug container for injectable drugs and vaccines marketed across a range of therapeutic markets. From day one, we have made sure that all device materials within the fluid path are the same as those currently used with standard prefilled syringes or vials. As such, we believe we can significantly reduce potential concerns pharmaceutical companies may have otherwise had with regard to drug biocompatibility with our device.

As there are only about five key suppliers of glass barrels for prefilled syringes in the world, we have also sought to further de-risk our supply chain by designing the barrel of our product so that it only requires shaping at one end. This means that we can also utilize suppliers within the far more open market for glass cartridges. In general, our supply chain strategy is designed to help pharmaceutical companies facilitate the smooth transition or launch of drug products with our device. We are in discussions with a range of established material suppliers with strong pharmaceutical experience to

ensure our supply chain is as adaptable to customer requirements as possible.

Q: You were represented at the Parenteral Drug Association Conference in Venice, Italy this past year, what were your expectations at this event?

A: While developing our product portfolio, Unilife has been flying a bit under the radar. We are now positioned to announce our presence within the market as an emerging leader in the design, development, and supply of innovative safety medical devices. We sent a highly qualified team to Venice and were looking forward to speaking with interested pharmaceutical companies about how we can potentially assist them in their drug delivery device requirements.

Q: Unilife is planning a submission to the SEC to be listed on NASDAQ, how will that affect your business model?

A: We started as an Australian company listed on the Australian stock exchange. We have now begun to transition our business to the US. This process commenced last year when we relocated key corporate and operational functions to the FDA-registered facilities of our wholly owned medical device manufacturing subsidiary located in central Pennsylvania. Since then, we have employed more than 35 middle-to-upper management with a strong background in areas relating to the design, production, and supply of medical devices to pharmaceutical and healthcare customers. We currently employ more than 80 people, and expect to hire additional full-time staff by the end of the year.

We are now working toward completing this process with the full redomiciliation of our company to the US, and a proposed listing on NASDAQ. The US is the world's largest and most mature market for safety medical devices. The US capital market also has a clear understanding of how our products are in a competitive position to disrupt the current status quo. A listing on NASDAQ makes sense given our current position and future growth plans.

Q: Looking back, what key lessons have been learned along the way?

A: You can't afford to try and cut corners when it comes to manufacturing world-class medical devices. Never try to develop both the product and its production systems in parallel. Always make sure you design the device for high-volume engineering from day one. And focus on the development of products that fully address the needs of a target market, you can't try and force a square peg into a round hole.

It's also critical to make sure that you have the right operational expertise in-house to achieve your commercial goals, so surround yourself with the very best people who have a passion for excellence. And if you choose to outsource some sections of your manufacturing to others, you must have sufficient internal knowledge to ensure accountability and the delivery of project milestones.

Q: What are you able to tell us about Unilife's future plans for growth?

A: US production of our Unitract 1-ml Syringes has commenced, with key regulatory approvals already secured. As I mentioned earlier, we are also 1 year ahead of schedule in the industrialization program for the Unifill™ ready to fill syringe. We will continue to work with our pharmaceutical customers and appointed suppliers to build a strong position within the fast-growing pharmaceutical market for prefilled safety syringes. We also have several products in the pipeline that we intend to commercialize throughout the coming years. To achieve our business potential, we are also focused upon the full redomiciliation of our company in the US and its listing on NASDAQ. ◆

Technology Showcase

MDI Components

Enabling your success

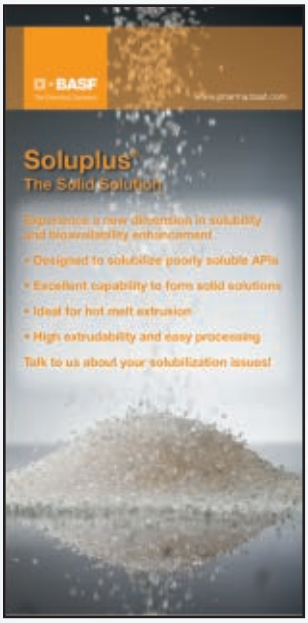
3M Drug Delivery Systems

3M Drug Delivery Systems has been a major supplier of metered-dose inhaler valves and canisters for more than 50 years. As the developers of the first CFC-free MDI, we are experienced at overcoming the challenges that designing components for use with CFC-free propellants presents. 3M is the only MDI component supplier that manufactures both valves and canisters, allowing optimization of these components simultaneously, ensuring compatibility, while delivering the convenience of a single source. For more information, contact 3M Drug Delivery Systems at (800) 643-8086 or visit **www.3M.com/dds.**

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.**

Solubility/Bioavailability Enhancement



Soluplus® is a graft copolymer composed of polyethylene glycol, polyvinylcaprolactam, and polyvinylacetate. It is designed to solubilize poorly soluble drugs and increase their bioavailability. It is ideally suited for preparation of solid solutions or solid dispersions by hot melt extrusion, spray drying, melt granulation, and co-precipitation processes. Soluplus is highly soluble in water at low and high pH and organic solvents. It is significantly less hygroscopic than many other polymers. Its low glass transition temperature (70°C) allows it to be extruded over a wide temperature range without the need for plasticizers. For more information, contact BASF at (800) 443-0627 or visit **www.soluplus.com.**

Prefillable Delivery Systems

BD Medical - Pharmaceutical Systems is dedicated to developing prefillable drug delivery systems designed to fit the needs of the pharmaceutical industry. BD offers a range of products, including glass and plastic prefillable syringes, a nasal spray system, and a variety of self-injection systems. We deliver cost-effective alternatives to conventional drug delivery methods, which differentiate pharmaceutical products and contribute to the optimization of drug therapy. With a broad range of innovative systems and services, BD provides pharmaceutical companies with support and resources to help them achieve their goals. Our worldwide presence, market awareness, and pharmaceutical packaging know-how allow us to propose suitable solutions for all regional markets and parenteral drug delivery needs. Only BD offers the range and depth of expertise and packaging solutions to guide your drug from early phase development through product launch and beyond. For more information, contact BD at (201) 847-4017 or visit **www.bd.com/pharmaceuticals.**

Technology Showcase

Orally Disintegrating Technologies

CIMA LABS INC. a world leader in the drug delivery partnering business, specializes in the formulation, taste-masking, and manufacturing of pharmaceuticals utilizing our orally disintegrating tablet (ODT), oral transmucosal (OTM), tamper deterrent, solubilization, and oral powder drug delivery technologies. OraSolv®, DuraSolv®, and Lyoc™ ODTs disperse quickly in the mouth without chewing or the need for water. OraVescent® is an oral transmucosal tablet that can be administered buccally or sublingually. OraGuard™ extended release/tamper deterrent technology provides a robust extended release PK profile, even during co-administration with alcohol, and is resistant against various tampering methods. CIMA has proven commercialization success with more than 20 products marketed in more than 70 countries around the world. For more information, contact CIMA at (763) 488-4843 or visit **www.cimalabs.com.**

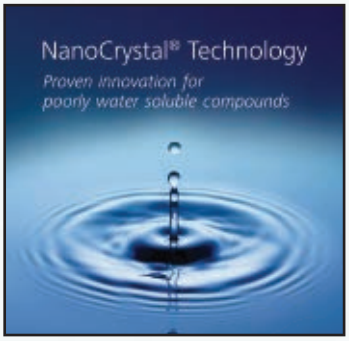
Formulation Service

HyperStart® is a service specially designed to provide a starting formulation for solid oral dosage (SOD) forms, which deliver immediate- and extended-release profiles. The HyperStart predictive formulation model is based on broad experience for design of immediate- and extended-release SOD forms, and is supported by mathematical relationships and extensive experimental data. The model generates an initial formula based on inputs, such as drug dose and solubility, dosage weight, and target-release profile. Formulations can be designed for various rates of release and have been validated for a variety of model actives. Access to this confidential service is available through Colorcon's specially designed questionnaire provided by our Technical Representatives or located on our website **(www.colorcon.com)** under Formulation Tools.

Development & Manufacturing

DPT is a contract development and manufacturing organization (CDMO) specializing in semi-solid and liquid dosage forms. DPT provides fully integrated development, manufacturing, and packaging solutions for biopharmaceutical and pharmaceutical products. DPT is the industry source for semi-solid and liquids — from concept to commercialization and beyond. Drug development services range from preformulation, formulation and biopharmaceutical development, analytical development, and validation through process development. Production capabilities include four cGMP facilities, clinical trial materials, full-scale commercial production, controlled substance registration Class II-V, and complete supply chain management. Packaging services encompass engineering and procurement resources necessary for conventional and specialized packaging. For more information, contact DPT at (866) CALL-DPT or visit **www.dptlabs.com.**

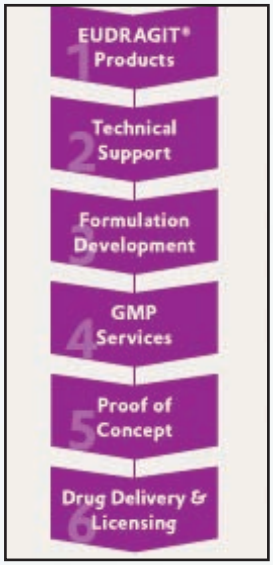
Bioavailability Enhancement



Elan Drug Technologies' NanoCrystal® technology is a drug enablement and optimization technology applicable to poorly water-soluble compounds. Improved bioavailability provided by the NanoCrystal technology can result in the following benefits: increased rate of absorption, reduction in fed/fasted variability, improved dose proportionality, rapid formulation development, and reduction in required dose with smaller and more convenient dosage forms. Five products incorporating the technology are now launched in over 100 markets worldwide with over $1.8 billion in market sales achieved in 2008. With over 1,300 patents/patent applications worldwide, it has been optimized and simplified from over 15 years in development. Applicable to all dosage forms, it has been manufactured at commercial scale since 2001. For more information on our range of technology solutions, contact Elan Drug Technologies at edtbusdev@elan.com or visit **www.elandrugtechnologies.com.**

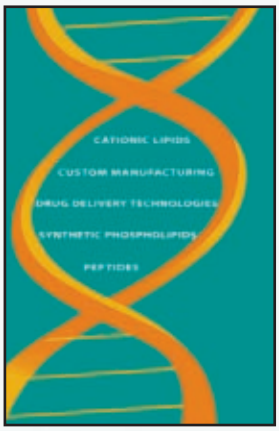
Technology Showcase

Pharma Polymers



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

Oligonucleotide-Based Delivery

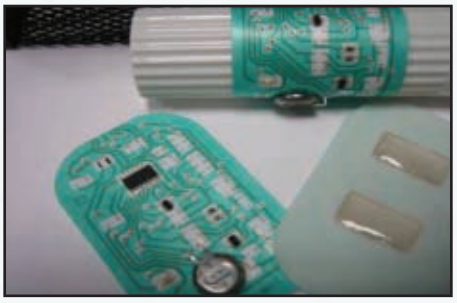


Due to the many challenges facing the delivery of RNA and DNA derivatives into cells, Genzyme Pharmaceuticals provides value-added solutions for delivering these oligonucleotide-based therapeutic actives using a unique combination of products, services, and technologies. Readily available products, such as synthetic phospholipids, cationic lipids, sphingolipids, and helper lipids can be used in liposomal and other lipid-based delivery systems. Through an integrated resource of custom manufacturing expertise with core competencies in lipids, peptides, polymers, carbohydrates, lipo-peptides, and other small molecules, we provide high-quality, GMP excipients needed for cutting-edge oligonucleotide-based delivery systems. LipoBridge® and LipoMask™ are two proprietary drug delivery technologies that may be considered for oligonucleotide delivery. For more information, contact Genzyme Pharmaceiuticals at (800) 868-8208 or pharmaceuticals@genzyme.com or visit **www.genzymepharmaceuticals.com.**

Combination Capsule Technology

InnerCap offers an advanced patent-pending multi-phased, multi-compartmentalized capsular-based delivery system. The system can be used to enhance the value and benefits of pharmaceutical and biopharmaceutical products. Utilizing two-piece hard shell capsules, the technology offers the industry solutions to problems affecting pharmaceutical companies, patients, and healthcare providers. The delivery system will be licensed to enhance pharmaceutical and biopharmaceutical products. It is a very effective way to deliver multiple active chemical compounds in different physical phases with controlled-release profiles. The delivery system provides the pharmaceutical and biopharmaceutical industries with beneficial solutions to the industry's highly publicized need to repackage and reformulate existing patented blockbuster drugs with expiring patents over the next 5 years. For more information, contact InnerCap Technologies, Inc., at (813) 837-0796 or visit **www.innercap.com.**

Iontophoretic Patch



Isis Biopolymer, Inc. is expanding the capabilities of active transdermal drug delivery with its breakthrough product, the Isis Patch. The first compact, wireless, active iontophoretic patch to be fully programmable by healthcare professionals, the Isis Patch enables physicians to control activation, monitor use, and adjust drug delivery to each patient. Proprietary hydrogels allow dosing of multiple drugs, as well as a wide variety of drugs. A smaller, softer, and more flexible design resembles a band-aid, while hypoallergenic, skin-friendly polymers eliminate irritation and enable the patch to be worn for up to 7 days with superior adherence to the skin. Isis Biopolymer's lower cost, environmentally friendly manufacturing process reduces the cost of conventional iontophoresis by much as 50%. For more information, contact Isis Biopolymer at (401) 921-6873 or visit **www.isisbiopolymer.com.**

Technology Showcase

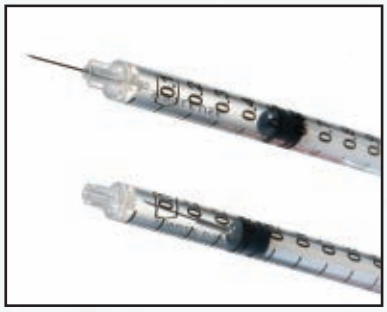
Knowledge Management

PharmaCircle is an innovative knowledge management company specializing in the drug delivery, pharmaceutical, and biotechnology fields, with a current client base ranging from start-up life science companies to world leaders in Big Pharma. Clients choose PharmaCircle's services and content for its comprehensive technical (pipeline, products, molecule, and technology) and business (deals, acquisitions, royalty, licensing, drug revenues, market information, etc) related information and analysis, which are ideal for all segments of small and large companies. PharmaCircle helps facilitate product life cycle management (LCM), partnering, licensing, and competitive intelligence efforts as well as supplements internal efforts and costs at a fraction of the cost if performed internally. For more information, contact PharmaCircle at (847) 729-2960 or visit **www.pharmacircle.com.**

Licensing Opportunities

Transdel Pharmaceuticals, Inc. is a specialty pharmaceutical company developing non-invasive, topically delivered products. The company's innovative-patented Transdel™ cream formulation technology is designed to facilitate the effective penetration of a variety of products. Products for license include Transdel's lead late-stage pain product, Ketotransdel® for the indication of acute pain, inflammation, and swelling associated with soft tissue injuries. Ketotransdel utilizes the Transdel technology to deliver the active drug, ketoprofen, an NSAID, through the skin directly into the underlying tissues where the drug exerts its well-known anti-inflammatory and analgesic effects as demonstrated in a completed Phase III clinical trial. Other partnership/licensing opportunities include cosmetic/cosmeceutical products and co-development opportunities for the transdermal delivery of new and existing drugs in any therapeutic area. For more information, contact Transdel Pharmaceuticals at (858) 457-5302 or visit **www.transdelpharma.com.**

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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The MEGGLE Group's Excipients & Technology Business Group supplies the pharmaceutical industry with carrier substances, such as pharmaceutical lactose. With outstanding product quality and intelligent innovations, we have gained a leading global position in the field of lactose and compounds. MEGGLE pharmaceutical lactose, for example, serves as a carrier substance in medicines. It behaves completely neutrally in the human organism and causes no undesired effects due to interaction with other components of the medicine. We also have developed a diversified product portfolio in the more than 50 years that we have been active in the market that contains excipients for granulation and capsule-filling as well as special modern products for direct compaction and dry-powder inhalers. Our customers are predominantly manufacturers of pharmaceutical products and dietary supplements. For more information contact the MEGGLE Group at (914) 682-6891 or visit **www.Meggle.com.**

DRUG DELIVERY Executive

Mr. Peter Thornton
Senior VP
Head of Product, Technology & Business Development

Elan Drug Technologies

"Elan Drug Technologies is in the position of being profitable, and we believe that our model as a true service provider, with unique technologies and experienced staff with established credentials in drug delivery, will allow us to not only survive but to prosper in these difficult economic times as we bring real benefits to our clients. It is also clear to us that the market for products incorporating drug delivery solutions is growing and will continue to grow at a faster pace than the overall pharmaceutical industry."

ELAN DRUG TECHNOLOGIES: STILL THE WORLD LEADER AFTER 40 YEARS!

Elan Drug Technologies, the world's leading drug delivery company, is currently celebrating its 40th year in business as a fully integrated drug delivery provider. Staying true to the original business model of developing clinically effective products for patients, through client-based alliances, they continue to grow the business through the expansion of their technology offerings. Drug Delivery Technology caught up with their Senior Vice President Head of Product, Technology, and Business Development, Peter Thornton to find out more about their 40 years of growth and future plans to continue leading the drug delivery market.

Q: Can you provide our readers with a little history of how Elan Drug Technologies began, and why this year is such an important one for your company?

A: In December 2009, Elan Drug Technologies (EDT) celebrated 40 years as a leading player in the drug delivery industry. Don Panoz, in 1969, founded EDT with a vision to develop and apply technologies and systems to drug formulation challenges that had remained unresolved. During the 70s and 80s, Elan and Alza, another industry pioneer, helped grow this industry by developing drug delivery technologies that addressed, in particular, patient compliance issues. While Alza was subsequently acquired in 2001, Elan Drug Technologies continued to develop new technologies and, as a result, better products that addressed unmet medical needs for patients. It is with great pride that we celebrate 40 years at the forefront of the drug delivery industry as the world's leading drug delivery company.

Q: Many companies say they are the leading drug delivery company worldwide. Why do you believe you merit that title?

A: EDT has been at the forefront of the drug delivery industry for 40 years, driving innovation and improved products for patients. Since 2001, 11 products have

been approved and launched in the US incorporating our technologies, making us, in terms of product launches, the most successful drug delivery company over the decade. We have built a reputation of delivering results for our clients. Throughout our history, our technologies have been used to develop 35 products that were launched in more than 100 countries worldwide, contributing to sales of more than $2.7 billion in 2008 for our clients.

We have leading capabilities and technologies underpinning our robust business. We have expanded our technology platforms to offer clients controlled-release, delayed-release, and pulsatile-release systems as well as technology solutions for poorly water-soluble compounds. Our NanoCrystal® technology, which is the leading technology to address compounds that are poorly water soluble, saw the market launch of its fifth licensed product in the third quarter of 2009. We have extensive product development, scale-up, and manufacturing capabilities in the US and EU with more than 500,000 sq ft of FDA/EMEA-licensed facilities under roof and the capacity to manufacture more than 3 billion solid oral dosages annually. This, together with our significant patent portfolio of more than 1,900 patents and patent applications, positions us as the leading drug delivery company in the business.

Q: So you do not, as many other drug delivery providers, consider yourself a specialty pharma company?

A: EDT is positioned as the provider of choice for drug delivery solutions to challenging formulation issues encountered by our clients. We are a client service focused business. We have stayed true to our original business model of developing clinically effective improved products for patients, through alliances with our clients. This business model has been successful for us, and so we continue to put all our energy into enhancing our technology offering and developing products exclusively for our clients.

Q: You say this model has been good to you. Do you believe other drug delivery companies are struggling in these stringent economic times?

A: Many drug delivery companies have struggled to achieve profitability, even in good times. Many have refocused their efforts, becoming specialty pharma companies, and some have had to downsize to survive. Elan Drug Technologies is in the position of being profitable, and we believe that our model as a true service provider, with unique technologies and experienced staff with established credentials in drug delivery, will allow us to not only survive but to prosper in these difficult economic times as we bring real benefits to our clients. It is also clear to us that the market for products incorporating drug delivery solutions is growing and will continue to grow at a faster pace than the overall pharmaceutical industry.

Q: Has the pharmaceutical industry changed over Elan's 40-year history?

A: In some ways, it has changed significantly, with declining R&D productivity, increasing development costs, and pending genericization of many pharmaceutical products. But in some ways, it has remained the same. The same needs ultimately drive the market - that is bringing drugs to market that address real patient needs. Most pharmaceutical companies understand and endorse that

extending the product life of a drug, if it offers true patient benefits, can result in significantly more revenue to a company. As drug delivery companies such as Elan Drug Technologies have evolved, they offer a whole range of sophisticated, robust technologies that can change the performance of drugs - reducing frequency of dosing, eliminating food effects, improving oral bioavailability, and in turn, improve the clinical outcomes of drugs.

Q: When you look back on the history of the company, what stands out as major achievements?

A: EDT has achieved many major milestones over its history. In the early years, we were the first Irish company listed on the New York Stock Exchange. Seeing our SODAS® technology applied to one of the first blockbusters - the Cardizem® franchise in the US was also a significant achievement for our then-small company. We have since witnessed the NanoCrystal® technology-based TriCor® 145 product achieve over $1 billion in annual sales in the US. We have also grown our manufacturing and scale-up facilities both in the US and Europe. With the launch of Invega® Sustenna™ last summer, our technology-associated product count in terms of commercialized products reached 35 products in 100+ international markets worldwide, over a 40-year period, which is a major achievement for a drug delivery company.

Q: Is the NanoCrystal® technology particularly an important technology for your business?

A: Our NanoCrystal® technology is one of our key technology platforms. 2009 marked the 10th anniversary of the filing with the US FDA of Elan Drug Technologies' first NanoCrystal® technology-based product. This technology, designed to overcome issues with poor water solubility, is particularly important for pharma portfolios. When one considers that there are fewer compounds making it through development, discarding the 40% or so of products that are believed to be poorly water soluble at the development stage is an extravagance few pharmaceutical companies can now afford. In late July 2009 the first approval of this technology for a long-acting injectable product was achieved, with Janssen's Invega® Sustenna™ for the treatment of schizophrenia. The product, which is administered as a once-monthly injection, was made possible through the application of our NanoCrystal® technology. By applying the NanoCrystal® technology, for the first time, healthcare professionals can provide patients with consistent medication coverage for 1 month, potentially helping them to improve compliance for schizophrenic patients. Four other products have also been developed and commercialized using this technology. Seeing this technology prove such a commercial success in the past 10 years is very gratifying.

Q: In addition to the NanoCrystal® technology, what other offerings do you provide your clients?

A: Of course we do have other technologies that are part of our platform of technology offerings. Our Oral Controlled Release (OCR) platform has been integral to the launch of dozens of products worldwide, as either tablet, capsule, or granulate dosage forms. Our OCR platform comprises a suite of technologies that enable tailored delivery profiles, which can,

among other things, reduce the frequency of dosing, optimize efficacy, and reduce side effects. Our model of offering formulation expertise, as well as strong intellectual property around our technology platforms, provides pharma companies with new and improved formulations of existing products. This helps them to maintain and enhance revenue streams, thereby improving their R&D productivity and cost effectiveness.

Q: What makes Elan's technology platforms unique? What advantages do they offer?

A: We have a unique platform of validated technologies - from OCR to nanoparticulate technologies - and a strong track record of developing commercially successful products for our clients. Throughout our history, our people have successfully met the challenges encountered in formulation development for all types of molecules. We have a complete range of capabilities from formulation development through to commercial-scale manufacture in modern facilities. Our technologies are supported by a robust patent estate and enable both the development of new products and the enhancement of existing ones.

Q: What would you put Elan Drug Technologies success down to?

A: Our success to date is ultimately due to the dedication, professionalism, quality, and innovation of our employees both current and past in all areas. Our reputation for being inventive, industrious, and goal-oriented has continued throughout our 40-year history. Elan Drug Technologies has talented professionals in Ireland and the US - characterized by a real determination and commitment to develop and manufacture products for our clients to meet their business needs. We are also keen to expand our technology offering, further leveraging and extending our past success. To maintain our position as the leading provider of drug delivery technologies, we continue to invest in the development and application of novel drug delivery technologies for the future.

Q: What does the future hold for Elan Drug Technologies?

A: We are focused on using our extensive experience, our drug delivery technologies, and our commercial capabilities to develop innovative products that deliver clinically meaningful benefits to patients and positive business results for our clients. We are always focused on innovation - whether in the products we are developing, advancing our existing technologies, or developing new technologies, driven by some of the best scientific talent in the area of drug delivery formulation. We continue to work diligently on strengthening our technology patent estate. We anticipate a number of product approvals for clients in the near to medium term. With more than a dozen pipeline products in the clinic, multiple preclinical programs also underway, and a strong client base, Elan Drug Technologies will remain a leader in the drug delivery sector. The drug delivery market is expected to be worth an estimated $131 billion in the US alone by 2012 and $292 billion worldwide. Elan Drug Technologies plans to maintain its position as the leading drug delivery company worldwide for at least the next 40 years. ◆

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What do you *really* know about end-users of drug delivery technologies?

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

FROST & SULLIVAN

Some Turnarounds Are Purely Academic

By: John A. Bermingham

I have the privilege of serving on the Board of Trustees at Saint Leo University, my alma mater. When I graduated from Saint Leo College, as it was known at that time, the school was a small 4-year Liberal Arts college with a diminutive student body. Today, Saint Leo University bears very little resemblance to its former self due principally to its President of the past 12 years, Dr. Arthur F. Kirk Jr.

From its beginnings back in the 1960s as a 4-year college to the end of 1996, the school struggled mightily to remain open. In that time, it had a series of Presidents who were not up to the task of growing the school, and so it entered a distressed state with mounting losses. I believe it is fair to say that St. Leo College was on the way out. Enter Dr. Kirk in January 1997 - the beginning of a classic turnaround.

Dr. Kirk quickly established his objectives for Saint Leo University and, like all great CEOs, quickly implemented his well-planned initiatives with one goal in mind - and that was to achieve his vision. Unlike most CEOs, he articulated this vision repeatedly to his staff, faculty, Board of Trustees, students, the press, anyone who would listen. He never wavered.

His vision was and still is, *To Become a Leading Catholic University of International Consequence for the 21st Century*. He supported his vision with six core values: Excellence, Community, Respect, Personal Development, Responsible Stewardship, and Integrity. Dr. Kirk executed all of the necessary steps a successful turnaround CEO should. He assessed the situation and immediately began to make changes and improvements in all areas, such as staff and faculty, his Board, systems, processes, discipline, accountability, sense of urgency, and culture change.

Dr. Kirk quickly developed a first-rate strategy and competitive advantage for profitable growth. He expanded his distribution channels, widened his product assortment, and focused heavily on his balance sheet, income statement, and cash flows. It looked to me as though he was turning around a business, not an institution for higher learning.

He also recognized that online education was becoming a major factor at the university level. So while he continued to increase on-campus enrollment at Saint Leo, he expanded his distribution into new channels, such as the military, stay-at-home parents, working single parents, and mature people to name a few, who wanted to or could only earn their undergraduate and graduate degrees online. The result: The University now has more than 1,000 students on the main campus plus 13,000 more at 17 education centers in seven states and online.

Dr. Kirk widened the University's product assortment by eventually offering more than 40 undergraduate majors as well as graduate degrees in business administration, education, teaching, criminal justice, instructional design, and theology. With this wider product assortment, he was able to reach out to a much larger customer base and successfully grew market share year over year. The result: Excellent financial strength. The income and cash flow statements are very strong, showing consistent growth in revenue, free cash flow, and EBITDA. In addition, the University's resident enrollment has tripled since 1997 and now has 10 applications for every available freshman seat.

Dr. Kirk's vision and strategy created a welcomed problem for the main campus. He had created a supply/demand ratio for the University such that many more students were applying for admittance than the campus could accommodate. In order to expand production capacity, Dr. Kirk built seven new buildings, purchased seven more off campus, and made extensive renovations to existing facilities. The result: The balance sheet is in excellent shape with a very strong current asset-to-current-liability ratio, resulting in liquidity that any business or academic institution would envy.

So my point is that great turnaround CEOs aren't just traditional business folks. They take many forms and work in many different industries to include academia. In Dr. Kirk's case, he did not just save a college. He provided the opportunity for thousands of people to earn their degrees, which might not have been possible without his turnaround ability.

I believe that my other alma mater, Harvard Business School, should develop a case study on Dr. Kirk and St. Leo University. Maybe I will give them a call. ◆

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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