

ORAL DRUG DELIVERY

WHEN YOU FIND THE HOLY GRAIL



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“Oral drug delivery: when you find the Holy Grail”

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Oral drug delivery: when you find the Holy Grail.

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INTRODUCTION



Despite phenomenal advances in the inhalable, injectable, transdermal, nasal and other routes of administration, the unavoidable truth is that oral drug delivery remains well ahead of the pack as the preferred delivery route. There are of course many applications and large markets for non-oral products and the technologies that deliver them. However, if it is a viable option, oral drug delivery will be chosen in all but the most exceptional circumstances. Moreover, if the oral route is not immediately viable, pharmaceutical companies will often invest resources in making it viable, rather than plumping for an alternative delivery method.

In a presentation last year, John Lynch, Chief Operating Officer of Merrion Pharmaceuticals said that the oral drugs market generated US\$26 billion sales in 2004 and would experience 16% growth up to 2008. He added that orally delivered products accounted for 84% of the sales of the top 50 selling drugs worldwide.

Oral products go from strength to strength, but the oral drug delivery sector is by no means an easy one to succeed in. In fact it has to some extent become a victim of this popular delivery route's success. Firstly, drug discovery efforts are directed at generating compounds that are readily orally deliverable and have the right pharmacokinetic/pharmacodynamic profile without the need for any specialised delivery technology. Secondly, when an oral drug delivery technology is needed, it is common for pharma companies to develop them in-house. It's worth the effort because the technology is likely to be useful to them in the future since the majority of products in the pipeline are administered orally. Thirdly, the potentially large rewards of developing a successful oral delivery system have meant that the market is now awash with hundreds, if not thousands, of undifferentiated oral drug delivery companies with equally undifferentiated technologies.

For pharma companies requiring a third party technology to deliver their compounds, it is difficult to find the right partner. For the delivery companies hoping to enter, although the sheer size of the oral delivery technology market could to some extent improve the chances and potential degree of success, things are significantly more difficult than they might initially seem.

The message that pharmaceutical companies usually send to would-be oral technology partners is: only those with technologies that are highly differentiated, fulfil needs that are near impossible to meet elsewhere, and are proven in the market place, need apply.

Nevertheless, although the environment is tough, success is possible. Indeed, a thriving oral drug delivery sector does exist and it is populated by innovative companies involved in fruitful collaborations with pharma and biotech partners. I will divide these successful oral drug delivery technologies into two broad categories:

1. technologies which represent the *crème de la crème* among many available systems addressing a common delivery need (such as modified-release or orally disintegrating tablets)
2. highly specialised technologies meeting a niche demand or a need with a high technological barrier to entry (for example, oral delivery of fragile macromolecules, or precision release at specific locations within the GI tract)

In this issue we are delighted to present articles from six of the leading names in oral drug delivery. It is of course up to the reader to decide into which, if either, of the two categories above the technologies described might fall.

Various aspects of oral drug delivery are covered including: oral controlled-release; orally disintegrating tablets (ODTs); fixed-dose combination capsules; oral macromolecular delivery; and the move to a specialty pharma business model.

Three of the articles in this issue are contributed by companies discussing their ODT systems. Side by side, these provide an insightful comparison of competing technologies, and taken together the papers provide a detailed overview of the latest developments, current issues and trends within this rapidly growing sub-sector of oral drug delivery.

The contribution from Penwest Pharmaceuticals discusses the recent approval and launch of Opana ER and the first definitive step in its strategy to leverage its oral drug delivery expertise in the transformation from a technology provider to a specialty pharmaceutical company focused on neurology.

The increasing number of oral fixed-dose combinations reaching the market and their growing acceptance by the medical and regulatory communities is highlighted by InnerCap Technologies. The company's multiphase, compartmentalised capsule technology, NovaCaps, both meets the existing needs for developing oral combinations, and expands the potential application of combinations into areas not previously considered possible.

Finally, we are pleased to include here a piece from Emisphere Technologies. Its *eligen* drug carrier technology for delivering fragile macromolecules via the oral route has the potential to bring the Holy Grail, oral drug delivery, within the reach of biologics companies and others for whom oral delivery has traditionally been viewed as out of the question. With a remarkable claim such as this, the company has met with scepticism and even derision over the years. Having made significant progress and generated robust data despite its critics, here it presents encouraging evidence that *eligen* does indeed fulfil its promise.

The primary purpose of this publication is to provide a platform from which companies can describe their oral drug delivery systems and outline their merits using scientific data and study results. However, during the process of choosing a drug delivery partner it is important not to underestimate the significance of "soft factors" – essentially the factors such as company culture, business practices and individual employees' personalities, which decide whether a good day-to-day working relationship between two organisations will be possible. This is especially important when considering a shortlist of similar technologies fulfilling similar functions.

In addition to enabling those readers seeking partnerships for oral drug delivery systems to learn about the technologies described in terms of science, specifications and compatibility with their own needs, it is my intention that this publication should also allow the reader, through the written word of the authors, to get to know the companies themselves a little in terms of their business strategy, manner and style.

Guy Furness
Publisher



CardinalHealth

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GROWING SALES AND NEW OPPORTUNITIES FOR ORAL FAST DISSOLVE

ORAL FAST DISSOLVE TECHNOLOGY IS OFTEN EMPLOYED WITH SUCCESS AS PART OF PRODUCT LIFECYCLE MANAGEMENT STRATEGIES, AND IS POPULAR IN THE OTC AND PRESCRIPTION ONLY MARKETS. HERE, DR IAN MUIR, VICE-PRESIDENT OF OPERATIONS AT CARDINAL HEALTH, EUROPE, GIVES AN OVERVIEW OF THE CURRENT TECHNOLOGY LANDSCAPE, DISCUSSES STRENGTHS AND LIMITATIONS, AND LOOKS AT HOW THE MARKET WILL DEVELOP IN THE FUTURE.

The drug delivery sector of fast dissolve products has grown rapidly from sales in 2002 of about \$850 million to 2005 where estimated sales were around \$1.4 billion (IMS Data). Despite this success there is no agreed regulatory definition of what constitutes a true fast dissolve product. It is generally accepted that products fall into this field if they dissolve in the mouth in less than 30 seconds, which is what distinguishes them from traditional effervescent, chewable or immediate release tablets.

There are some class characteristics, which all fast dissolve products have in common (see table 1). In fact the market has really been defined by the success of the various proprietary fast dissolve delivery systems and their ability to meet the needs of the patient, formulators and marketing groups.

The use of drug delivery technology in the product management lifecycle is well known to all in the pharmaceutical sector. Key to the success of a drug delivery-based application is that there is a clear unmet need or benefit to the use of the chosen system. A technology selection process is most successful when considering the market, patient and clinical requirements and increasingly the reimbursement environment for the product. Bringing these four factors together significantly enhances the chances of market acceptance. Some examples of considerations in each area are listed in table 2.

FAST DISSOLVE TECHNOLOGIES

For ease of description, fast-dissolve technologies can be divided into three broad groups: lyophilised systems, compressed tablet-based systems, and thin film strips.

The lyophilised systems have been by far the most successful among them in terms of sales value, sales volume and number of worldwide product approvals. The technology around these systems involves taking a suspension or solution of drug with other structural excipients and, through the use of a mould or blister pack, forming tablet-shaped units. The units or tablets are then frozen and lyophilised in the pack or mould. The resulting units have a very high porosity (see figure 1), which allows rapid water or saliva penetration and very rapid disintegration. Figure 2 shows an orodispersible tablet (ODT) produced using Cardinal Health's Zydis technology, disintegrating over three seconds.

Dose-handling capability for these systems differs depending on whether the active ingredients are soluble or insoluble drugs, with the dose capability being slightly lower for the former than for some tablet based systems. The units are capable of incorporating a range of taste-masked materials and have more rapid disintegration than tablet-based systems (table 3).

Compressed tablet-based systems are produced using standard tablet technology by direct compression of excipients. Depending on the method of manufacture, the tablet technologies have different levels of hardness and friability. This results in varying disintegration performance (see table 3) and packaging needs, which can range from standard HDPE bottles or blisters through to more specialist pack designs for product protection – CIMA Labs', PackSolv, for example.

The speed of disintegration for fast-dissolve tablets compared with a standard tablet is



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achieved by formulating using water soluble excipients, or super-disintegrant or effervescent components, to allow rapid penetration of water into the core of the tablet. The one exception to this approach for tablets is Biovail's Fuisz technology. It uses the proprietary Shearform system to produce a drug-loaded candy floss, which is then used for tableting with other excipients.

These systems can theoretically accommodate relatively high doses of drug material, including taste-masked coated particles. The potential disadvantage is that they take longer to disintegrate than the thin-film or lyophilised dosage forms. The loose compression tablet approach has increasingly been used by some technology houses, branded companies and generic pharmaceutical companies, for in-house development of line extension and generic fast-dissolve dosage forms

ORAL FILMS

Although oral film systems, the third class, have been in existence for a number of years, they have recently become the new area of interest in fast-dissolve pharmaceutical drug delivery. This is largely as a result of the success of the consumer breath freshener products such as Listerine PocketPaks in the US consumer market.

Such systems use a variety of hydrophilic polymers to produce a 50-200 mm film of material. This film can reportedly incorporate soluble, insoluble or taste-masked drug substances. The film is manufactured as a large sheet and then cut into individual dosage units for packaging in a range of pharmaceutically acceptable formats.

There remain a number of technical limitations with the use of film strips. The volume of the dosage unit is clearly proportional to the size of the dose, which means these extremely thin dosage forms are best suited to lower-dose products. As an example of this, Labtec claim that the RapidFilm technology can accommodate doses of up to 30 mg. This clearly limits the range of compatible drug products. The other technical challenge with these dosage forms is achieving dose uniformity and unit dose packaging, which is an area for differentiation in the technology providers such as LTS and Cardinal's DelStrip.

The much-heralded advent of major branded products in this area still seems some way off. This may be partly due to the technical difficulties of taste masking and dose loading, but also the fact that there appears to be fewer commercial barriers to entry into this field.

In 2001 and 2002 it was reported that many significant therapeutic products would launch using this technology over the next two or three years. Whilst there has been a five-fold increase worldwide in the number of thin film strips since 2002, very few if any such products have

Product Characteristics
Rapid and complete disintegration in less than 30 seconds
Dispersion of the dosage form in the mouth without water
Oral solid delivery system
Packaging which provides a safe and stable marketed product

Table 1: Key characteristics of orally disintegrating systems

Market	Patient	Clinical	Payer
Patent protection	Ease of use	Alternative route of administration	Cost effectiveness
Market exclusivity	Possibility of greater compliance	Reduced side effects	Application in clinical subset with unmet need
Stable manufacturing platform	Application in clinical subset with unmet need	Reduced dose	Compliance linked to clinical outcome.
Cost-effective manufacture	Palatable product	Bioequivalence	Price <i>versus</i> convenience for OTC
Stable device or packaging	Cost effectiveness	-	-
Proven regulatory & market track record.	-	-	-

Table 2: Key considerations in technology platform evaluation

entered the ethical prescription market.

In contrast the market for thin film strips is mainly in the consumer vitamins, minerals and supplements (VMS) and OTC areas. Active ingredients which appear to be suitable are vitamins, supplements such as melatonin and CoQ10, and some OTC ingredients. An example of the type of developments in this area are the deals between Bioenvelop and NutriCorp, who have approval for a range of products in Canada including benzocaine, caffeine and menthol. To give another example, Leiner Health Products have an exclusive deal to sell MonoSol film strips for OTC products, the first of which is reported as a melatonin supplement.

RATE OF DISINTEGRATION

One question, often asked, is whether the relative speed of disintegration is important in the selection between fast-dissolve products. At a general level there are various reports in the scientific literature and from consumer preference studies, which show patient preference for fast dissolve over a standard tablet if they are given the choice. This preference is usually linked



Figure 1: Magnified cross section of a lyophilised ODT, showing the highly porous structure

with novelty and ease of use. On a clinical level this can translate into better compliance.

For some drugs capable of being absorbed via the pre-gastric route, the use of a fast-dissolve system can result in the drug being absorbed more quickly and more reproducibly, compared with a standard tablet. In these specific cases the speed of dispersion, and therefore the relative amounts of drug retained in the mouth or the proportion of the dosage form swallowed before dispersing, could make a difference to the pharmacokinetic profile.

Drug molecules which are likely to be suitable for delivery via this pre-gastric route are generally soluble in saliva and have a high partition coefficient ($\log P > 1$) – characteristics often associated with CNS active compounds. A good

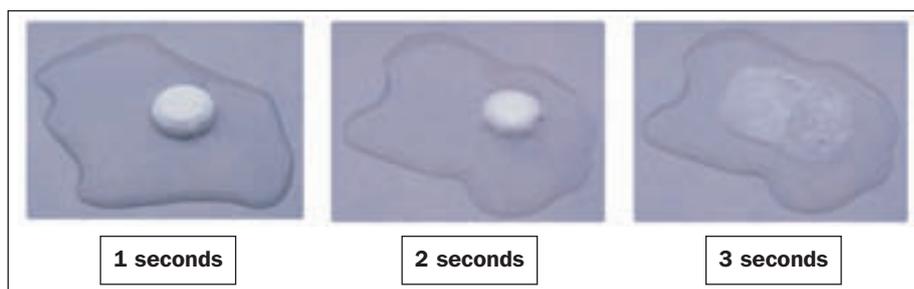


Figure 2: Rapid disintegration of a lyophilised Zydys tablet in minimal volume of water

Product	Technology	Diameter (mm)	Start (seconds)	End (seconds)
Alavert 10mg	CIMA	10.0	22.7	32.8
Benadryl Fast Melt	-	11.2	10.9	15.7
Claritin Reditabs	Zydis	11.1	0	3.8
Excedrin Quicktabs	-	17.5	11.8	25.8
Maxalt MLT	Zydis	11.0	0	1.8
NuLev	CIMA	14.0	7.9	13.9
Remeron Soltab	Quicksolv	9.7	22.3	56.6
Xilopar 1.25mg	Zydis	11.0	0	2.8
Zofran Zydis	Zydis	9.0	0	2.2

Table 3: Disintegration times for marketed fast dissolve products (Source: Bohnacker R et al, Pharm Ind 2005, Vol 67(3), pp 327-335)

Product	Technology
Zyprexa – Eli Lilly	Zydis – Cardinal Health
Claritin Reditab – Schering Plough	Zydis – Cardinal Health
Zomig ZMT – Astra Zeneca	Orasolv – Cima (Cephalon)
Maxalt MLT – Merck	Zydis – Cardinal Health
Zofran ODT – GSK	Zydis – Cardinal Health
Prevacid Solutab - TAP	Unknown
Risperdal – Janssen	Quicksolv – Janssen

Table 4: Top ODT products ranked by sales

Product	Technology provider
Mirtazapine	Teva
Mirtazapine	Barr
Mirtazapine	Actavis
Mirtazapine	Aurobindo
Clonazepam	Kali
Tramadol	Biovail
Citalopram	Biovail
Tramadol	Ethypharm

Table 5: Fast-dissolve generics

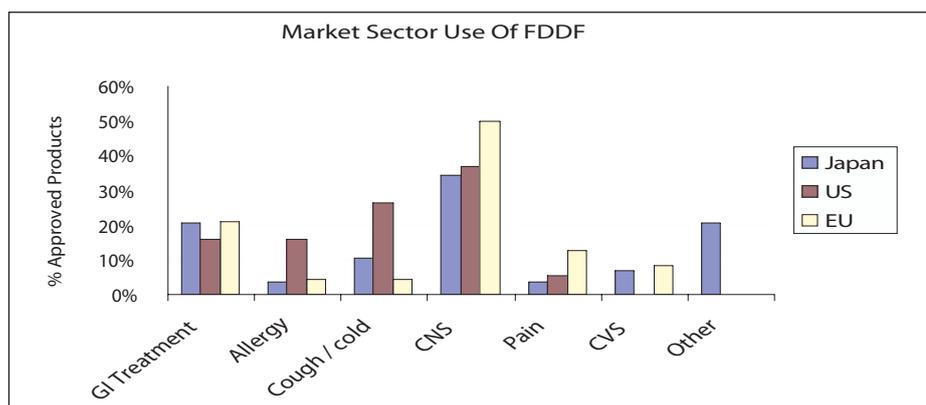


Figure 2: Proportion of fast-disintegrating systems approved, by therapeutic use

example where this route of administration has been used to commercial and clinical advantage is the Zydis based selegiline product, Zelepar. The ODT version provides equivalent therapeutic plasma levels to the 10 mg standard oral tablet with doses of only 1.25 mg and a resulting reduction in the metabolite associated side effects.

Currently, products developed and manufactured using Cardinal Health's Zydis, CIMA Lab's Orasolve and Janssen's in-house Quicksolv technologies account for more than 75% of US sales of fast-dissolve products (see table 4).

... TO THE FUTURE

Not surprisingly, with a large market and significant brands, there have been a number of generic filings in the fast-dissolve area, some of which have entered the market and others are awaiting the resolution of patent or regulatory reviews. Table 5 shows just some of the reported examples of fast dissolve-based generic applications.

Within the patient population, fast-dissolve has applications in some increasingly important demographic groups, such as elderly and junior age groups.

The switch of products from the prescription-only to OTC markets in the US and EU will also drive increasing interest in more consumer-orientated and differentiated dosage forms. This is where consumer-orientated products may start to have a greater role in the pharmaceutical arena, and a number of the thin-film technology and other fast-dissolve products could clearly have applications in the OTC area.

One area that is, as yet, under developed is the delivery of biological molecules via the oral route. Many of these molecules are unstable during processing and unstable in the acid of the stomach and so parenteral administration is the only option.

Some fast-dissolve technologies could be used to produce stable freeze-dried solid tablets and deliver these pre-gastrically in a form that allows rapid dissolution in the mouth. The recent European approval of GRAZAX the fast-dissolve formulation of a purified grass pollen product for the treatment of allergic rhinitis shows that delivering a stable form of the protein for local effect can be sufficient to achieve therapeutic outcomes in a more patient orientated dosage form.

Figure 3 shows the proportion of approved fast-dissolve products by therapeutic area and geographic region. CNS applications are clearly the most popular in all three regions. The capacity of fast-dissolve technology to increase compliance means that pain management products and treatments for Parkinson's disease, depression, schizophrenia, Alzheimer's disease and other CNS conditions will continue to be strong areas for development within the fast dissolve field.



FROM ORAL DRUG DELIVERY TECHNOLOGY TO PROPRIETARY PRODUCT DEVELOPMENT

Penwest Pharmaceuticals is implementing a strategy to make the change from being a drug delivery technology provider to a specialty pharma company. This article outlines how Penwest (Danbury, Connecticut, US) is currently implementing this change. By drawing on its reputation for technical excellence in oral controlled release, and choosing its product development targets intelligently, Penwest is moving forward to attain its goal of becoming a specialty pharma company, marketing its own portfolio of neurology products.

Prepared by ONdrugDelivery on behalf of Penwest Pharmaceuticals

Penwest's business has been built on developing sophisticated yet simple oral controlled-release systems. In the late 1990s, Mylan Pharmaceutcial's Nifedipine XL was the first generic controlled release nifedipine to be approved, and utilised the proprietary TIMERx® technology. The product demonstrated scientific excellence by meeting the challenge of mimicking the release profile of Alza/Pfizer's Procardia® XL. Its release was followed by sev-

is indicated for chronic moderate-to-severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time. Opana ER is well protected from competition by several barriers to entry. The FDA has granted three-year exclusivity, and the product benefits from a strong, multilayered IP estate strategy. Other barriers to generic entry include: limited availability of the active compound; the substantial technical challenge of avoiding (partial or complete) disintegration of the formulation when coming into contact with alcohol, something that could lead to dose dumping (which TIMERx overcomes but which is an issue with some other technologies); and compliance with FDA risk-management strategies.

Beyond the US launch, Endo and Penwest are also evaluating the international opportunity for Opana ER. Opana ER's forecasted revenue stream is an important component in funding Penwest's growth over the years ahead.

The product is the result of a long-standing collaboration with Endo Pharmaceuticals, which already marketed an i.v. version and was looking for an experienced drug delivery company that could provide a controlled-release technology for an oral formulation.

Development costs were shared equally (50/50). Endo took responsibility for clinical trials and the regulatory process, manufacturing and marketing. Penwest brought the technology

PENWEST IS ACTIVELY LOOKING TO BROADEN ITS EARLY STAGE DRUG DEVELOPMENT PIPELINE BY INVESTIGATING IN-LICENSING NCES IN SELECTED AREAS OF NEUROLOGICAL THERAPEUTICS

eral other proprietary oral delivery systems – including Geminex® and SyncroDose™ - and a gastro-retentive technology (see figure 1 for more details of these technologies).

Penwest's transformation started with the 2003 sale of its excipients business to the German firm Josef Rettenmaier Holding GMBH and Co. KG, which demonstrated Penwest's commitment to pursuing drug development. This was followed by Penwest's partner Endo Pharmaceuticals submitting an NDA to the US FDA for Opana® ER, the oral controlled-release formulation of the opioid analgesic oxomorphone, which utilises the TIMERx technology.

Opana® ER was approved on June 22, 2006 and is available in 5, 10, 20 and 40 mg tablets. It



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Figure 1: Opana® ER. FDA approved June 22 2006, August 14 2006, launched by Endo's sales force August 14, 2006

(TIMERx), product formulation and IP, and receives a royalty on profits.

Opana ER enters a market for long-acting strong opioid analgesics valued at US\$3.2 billion (2005), and the timing of its launch may be fortuitous for several reasons. First, physician hesitancy over long-acting opioids is waning, and a recent WHO guideline supports the use of round-the-clock analgesia.

Secondly, the opioid prescriber market is under covered giving Endo the opportunity to achieve good penetration. The company has significantly expanded its sales team to support Opana ER, adding some 220 new reps to create a total sales force of about 600.

Among long-acting pure oral opioids, oxycodone (Oxycontin®) is currently the most prescribed. However, there is clearly room for an alternative. Although Opana ER and Oxycontin both interact on the μ -opiate receptor, patients respond differently to different compounds within this class, meaning that the choice of an alternative improves treatment options. Additionally, in long-term treatment, opiate rotation (switching from one opioid to another similar product) overcomes the reduced efficacy that is often seen when one product is used over an extended period.

Of perhaps more interest, is that Opana ER is a new, differentiated entrant. Oxycontin may be an extended-release product, but marketing data indicates that in a substantial number of patients, it is being used three times per day despite being indicated for twice-daily adminis-

tration. In contrast, Opana ER appears to be a true twice-daily formulation.

In a 12-week, randomised, double-blind, placebo-controlled study, 250 opioid-experienced patients with chronic low back pain, entered the study with a pain score of 70 out of a possible 100, indicating moderate to severe pain, despite receiving treatment with another opioid. Patient ratings of Opana ER were more favourable than their ratings of their previous opioid or of a placebo.

Opana ER has also been studied in opioid-naïve patients with chronic pain. In first time users, side effects can be unpleasant enough to make the patient discontinue opiate therapy, and it was important to know how this group of patients would tolerate Opana ER. In a multi-center, randomized, double-blind, parallel group trial, the safety and efficacy of Opana ER were compared with a placebo in 205 opioid-naïve patients with moderate-to-severe chronic low back pain. Opana ER demonstrated a statistically significant ($p < 0.0001$) difference in pain scores between oxymorphone ER and a placebo over a 12-week treatment period, during which the drug was administered twice daily. After titration to an effective and tolerated dose of Opana ER, adverse events incidence was remarkably low over the 12 week double blind treatment period, with some of the common opioid effects occurring but in a low frequency.

The FDA's final approval of Opana ER was a key milestone for Penwest and represented a major step in advancing the company's strategy of building a specialty pharmaceutical company with a focus on developing compounds targeted

at disorders of the nervous system. Opana ER will be a significant asset as Penwest continues to develop its product portfolio.

CNS FOCUSED PORTFOLIO

Two factors have driven the company's specialisation in the therapeutic field of neurology. The first is the excellent fit of neurology with Penwest's technologies. Neurological disorders usually require chronic/ongoing therapy, Dr Baichwal, Penwest's Chief Scientific Officer, states, often self administered in non-clinical settings. This points clearly to the use of long-acting oral dosage forms. Maintaining constant plasma levels of an active compound while minimising dosing frequency is also beneficial in neurology therapies, again pointing to long-acting formulations. "Penwest's controlled-release technologies can help with compliance and safety by delivering a steady stream of medicine," he notes.

The second addresses product sales and marketing. Prescriptions for neurological products are typically written by neurologists – a relatively small and identifiable group. Penwest has recognised that the type and size of sales force needed to address this market fits with the specialty pharma model and can be achieved more quickly than that required to reach, for example, the large number of primary care practitioners.

Dr Baichwal details that the company has adopted a three point strategy. Each aspect of this strategy is characterised by progressing experience and strengths.

Product Name	Indication	Development Status	2007	2008
Opana® ER (oxycodone)	Chronic Pain	approved and launched		-
Nalbuphine ER	Pain	Phase I	Phase II	Pivotal Trial
Torsemide ER	Edema/CHF	Phase I	Multiple Phase II	Pivotal Trial
PW4110	Epilepsy	Formulation Development/POP	Pivotal trial	-
PW4150	Epilepsy	Formulation Development	POP / Phase I	-
PW4153	Parkinson's Disease	Formulation Development/POP	POP / Phase I	-
PW4158	Parkinson's Disease	Formulation Development/POP	POP / Phase I	-

Figure 2: Product pipeline showing current development status, and expected status for 2007 and 2008

The initial strategy has been to develop existing compounds that can be improved using Penwest's technologies. Penwest currently has two named products in its portfolio that demonstrate this approach: Nalbuphine ER and Torsemide ER.

Nalbuphine ER is a controlled release formulation of nalbuphine hydrochloride and incorporates Penwest's drug delivery technology. Nalbuphine ER is designed to be taken as a twice-daily tablet. This formulation will have plasma kinetics derived from both immediate release and controlled release components. Nalbuphine hydrochloride is a synthetic opioid agonist-antagonist analgesic of the phenanthrene series and is currently only available as a sterile solution suitable for subcutaneous, intramuscular, or intravenous injection under the brand name NUBAIN® and as a generic. Annual sales of this product are approximately US\$10 million - constrained by the currently available formulations and indications. If approved, Penwest expects that oral Nalbuphine ER, which has successfully completed Phase IIa trials, will compete in the moderate to moderately severe pain market with drugs such as Tramadol®.

The one non-neurological product in Penwest's pipeline is Torsemide ER. This is a controlled-release formulation of the loop-diuretic torsemide, and is currently marketed as an immediate release oral formulation branded Demadex®, for the treatment of congestive heart failure (CHF). Torsemide ER has been

developed as a once daily tablet using Penwest's Geminex. It provides extended release of the drug during the waking hours when CHF patients need protection from absorbing dietary salt.

Chronically treated CHF patients typically need to excrete between 150 mEq and 200 mEq of sodium per day to prevent water retention weight gain that can lead to cardiac decompensation. The current formulations of loop diuretics have short periods of action during which most of the sodium excretion takes place. Short durations can both leave the patient unprotected for long periods during the day, when sodium retention is occurring via food, and create the potential for large urinary volume diuresis after drug ingestion, resulting in unpleasant side effects endangering compliance.

Commenting on clinical trial results released at the end of 2005, Dr Thomas Sciascia said that the company was "encouraged that the data supports the conclusion that torsemide can be formulated and administered once daily in a manner that can result in a longer duration of action than that provided by currently marketed brands of the drug. This difference could be significant to congestive heart failure patients in a real world situation in which dietary sodium intake is large and sodium intake occurs throughout the waking hours."

Retaining Torsemide ER when Penwest has decided to concentrate on neurologicals perhaps raises some questions, but the rationale is sim-

ple - Torsemide ER offers great development potential. This fits with Penwest's philosophy of creating differentiated products. Torsemide ER is a clear demonstration of the benefit that its technology can bring to an existing compound. In contrast to Nalbuphine ER, which Penwest plans, if approved, to market itself, Torsemide ER, if approved, will be marketed by a partner.

Clinical indications and development timelines of these products, together with several other neurological compounds in Penwest's pipeline, are summarised in figure 2.

The second thread of Penwest's strategy is the development of external technology-based products and the broadening of its technology profile. The company is developing products and accessing a portfolio of differentiated technologies with specific applications in the neurology field. Importantly, this part of the strategy is not limited to Penwest's traditional field of oral delivery. Feasibility studies are currently underway with several pioneering non-oral delivery systems, the company has revealed.

The final piece of the three-part strategy is the establishment of a proprietary portfolio of neurological NCEs. Penwest is actively looking to broaden its early stage drug development pipeline by investigating in-licensing NCEs in selected areas of neurological therapeutics. Areas of interest include niche neurological diseases, where small molecule drug development is still needed to treat conditions that are not adequately addressed with available medi-



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cations. Penwest's goal is to commercialize these products, if approved, by building a specialty sales force of its own or through out-licensing arrangements.

BUILDING THE MANAGEMENT TEAM

The refocused Penwest has built an optimal management team, making several key appointments to progress the business. Jennifer Good was appointed to Chief Executive Officer in June of 2006. With nine years of experience at the company, Jennifer brings the necessary expertise, vision and energy to move Penwest forward in its strategy. The appointment of Benjamin Palleiko, a former investment banker, to Senior Vice President, Corporate Development and Chief Financial Officer has

ensured optimal relations with Wall Street and will further support in driving the business.

The scientific team is also stronger. Amy O'Donnell, MD, has been appointed to the new position of Senior Director of Clinical Development joining Chief Medical Officer Thomas Sciascia, MD, and concentrating the company's focus on therapeutic product development.

Penwest has also preserved its drug delivery heritage. Dr Anand Baichwal, co-inventor of TIMERx and subsequent oral delivery technologies, is the Company's Chief Scientific Officer and Senior Vice-President of Licensing.

Commenting on the company's positive outlook he says: "By late 2009, Penwest's goal is to be a true development-focused specialty pharmaceutical company, selling and marketing its own portfolio of neurology products."

CONCLUSION

Penwest is not alone in evolving from a technology provider to a drug development company, attracted by the growth that can be achieved via the specialty pharma business model. Companies such as Biovail and Alza have achieved success in transforming themselves into high growth, value added pharmaceutical companies developing important medicines that have a positive impact on patients. Penwest plans to capitalise on the opportunities that lie ahead of them with their experienced management team, their expertise in drug delivery technologies and their knowledge in drug development. Penwest has built on its past achievements, combining them with its current strength and expertise, and is poised for a new level of growth through a diverse portfolio of drugs primarily targeted at treating diseases of the nervous system.

PENWEST'S TECHNOLOGY PORTFOLIO



Oral controlled release technology based on a natural gum matrix.

TIMERx achieves a variety of release profiles (First order, Zero order, Burst CR, etc) for a wide range of drugs, accomodating even the most difficult actives.

TIMERx can be used in:

- Low to high dose drugs
- Insoluble to highly-soluble drugs
- Drugs with short half-life and/or narrow therapeutic window.

The technology is based on acustomised, agglomerated hydrophilic complex that forms a controlled-releasematrix upon compression.

The matrix consists of two polysaccharides, xanthan and locust bean gum. Interactions between these components in an aqueous environment form a tight gel with a slowly-eroding core.



Dual-delivery system which can release drugs or isomers at two different rates.

To achieve the unique release profiles different custom granulations are made for each drug component. The two drugs are then compressed on a standard bi-layer press.

Geminex offers:

- Rapid development times which can result in a speed-to-market advantage.
- Custom formulations are made for each drug component to ensure maximum therapeutic benefits.
- Special equipment is not required; a standard bi-layer press is all that is required.
- Geminex-based products are more cost-effective than combination drug products that are based on the application of multiparticulate technologies.

Geminex can deliver a medication that is therapeutically superior to its individual components.



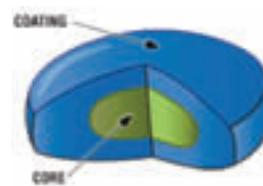
Schematic of Geminex bilayer tablet



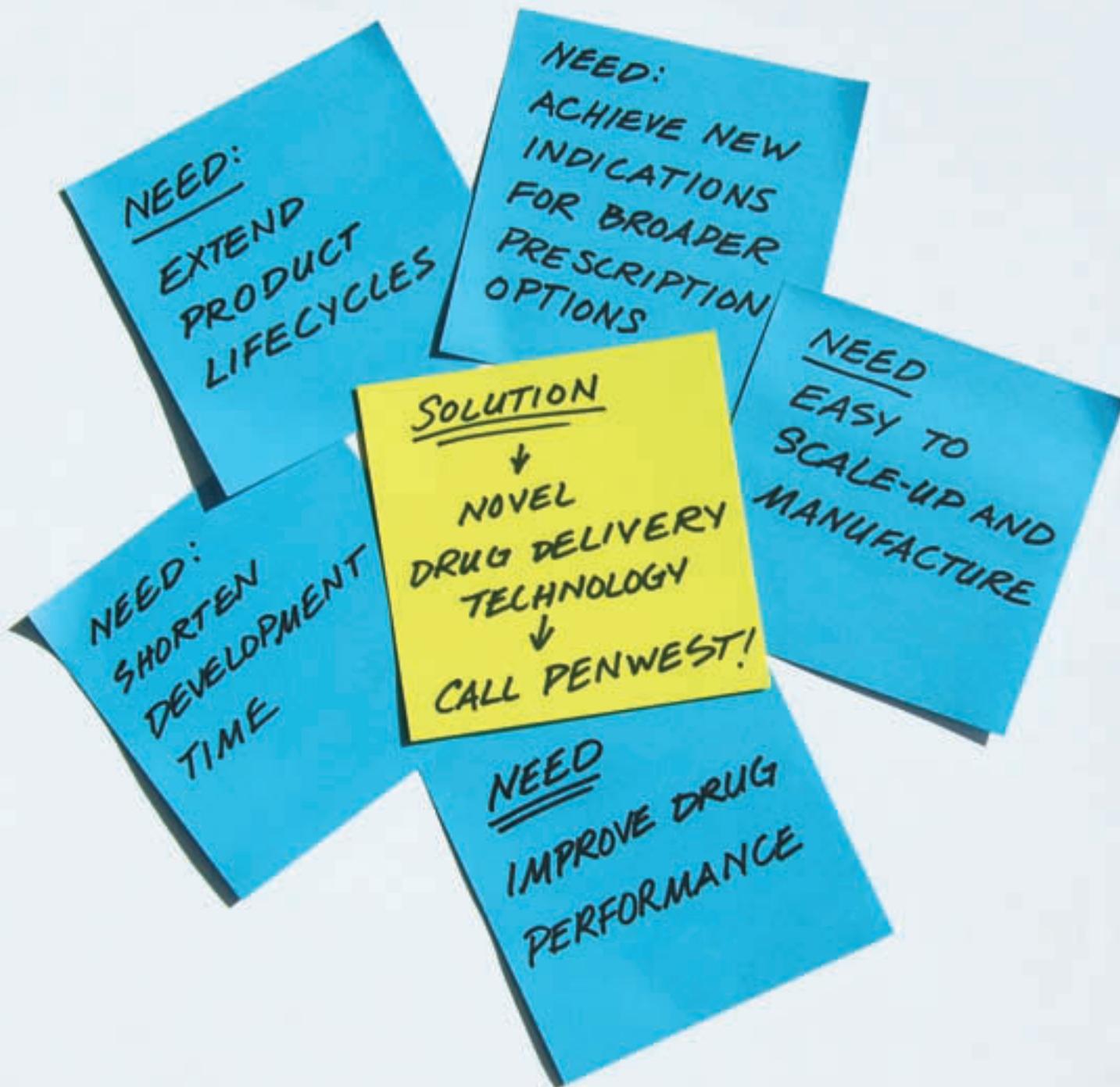
Releases drug at the desired time and site in the body to coincide with the body's circadian rhythm pattern or to allow drugs to be delivered to different sites within the GI tract.

By administering drug at the optimal time after ingestion, SyncroDose can potentially improve the therapeutic benefit of drugs or reduce the dose needed to provide a given therapeutic effect. If a reduction in dose occurs, the side effects of the drug may also be reduced or lessened in severity.

A SyncroDose tablet consists of an inner core of drug and a surrounding compression coating containing TIMERx® based materials (see below). Lag time is controlled by variations in the two polysaccharides, xanthan gum and locust bean gum, found in the TIMERx coating.



Schematic of a SyncroDose tablet showing core and coating



Achieve your drug's optimum performance with Penwest's drug delivery technologies:

- **TIMERx[®]** for controlled release
- **Geminex[®]** for dual drug delivery
- **SyncroDose[™]** for site and time specific delivery
- **Gastroretentive Technology** for maximum drug absorption in the upper GI tract.

For information about these solid dose technologies and partnering opportunities with Penwest:

- ☎ 1.877.PENWEST
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COMBINATION ORAL PRODUCTS: THE TIME IS NOW!

In years gone by, the pharmaceutical industry has overlooked or dismissed combination products, save but a few of the most obvious, straightforward applications. In this article, Fred Miller, CEO of InnerCap Technologies, outlines why the climate is now right for the full potential of combination product development across the spectrum of therapeutic categories to be realised, and how the technology to make this possible and commercially viable is now available.

Prepared by ONdrugDelivery on behalf of InnerCap Technologies

Up until almost the very end of last century, combination products essentially remained on the periphery of pharmaceutical development. There was no wholesale argument against the concept of fixed-dose combinations. It was more the case that there was nothing much motivating the sector towards their development.

There were a few exceptions where a fixed-dose combination was the obvious (or only) approach, such as the combinations of hormones in oral contraceptive pills, and levodopa combined with a dopa decarboxylase inhibitor for Parkinson's disease. Otherwise, however, industry focus was squarely on producing as many blockbuster NMEs as possible.

The regulatory authorities were not against, but there were some questions about inflexible dosing regimens and identifying the source of adverse events arising from combination medicines, so neither were they actively pro combination products. Physicians were similarly ambivalent. Most were certainly not crying out for combination products to be made available to them, but they had no serious grievance with the idea of combination products *per se*.

In recent years, however, the tide has begun to change quite sharply. The number of combination products reaching the market has begun to accelerate, and several high profile combination brands are generating formidable revenues for their developers. Indeed, there are now at least twelve combination drug products amongst the top-200 selling pharmaceuticals.

Such combination products have only achieved success because they work. That is, they have shown significant therapeutic benefit

and proven popular with patients. As a result, physicians are becoming more accepting. Furthermore, there is a positive feedback effect whereby, as combination products become more common, physicians are more familiar with their benefits, more comfortable with using them, and therefore increasingly likely to prescribe them. Indeed, as the merits of combination products are revealed, groups of specialist medical professionals are now calling for the development of combinations in certain applications within their field.

We have also seen definitive signs of regulatory acceptance of combination products of late. As stated above, regulators, while not actively against combination, used to be rather passive. Nowadays they too are identifying applications where combinations are appropriate, and are actively promoting the development of combinations as the preferred option. For example, in May 2004 the US FDA published a draft guidance document entitled: *Fixed Dose Combination and Co-Packaged Drug Products for Treatment of HIV*. Its opening sentence reads, "This guidance is intended to encourage sponsors to submit applications to the FDA for approval of fixed-dose combination and co-packaged versions of previously approved antiretroviral therapies for the treatment of HIV." We will return to discuss this particular guidance in more detail later on in the article, but the point to note here is that the regulators have taken a position on fixed-dose combinations, and its is unequivocally in favour of their continued development.

So, it is clear that the trend is now well established, but why have combinations gained



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acceptance, and why now? What has changed?

In fact a variety of factors all pointing to fixed-dose combinations have converged, including a growing awareness of both the therapeutic and commercial advantages. Initially, it is likely that the pharmaceutical industry began seriously looking at combination product development more out of necessity. In short, they were having difficulty filling their pipelines with the NMEs on which they had previously relied.

Pharma's pipeline productivity problems gave it cause to pay combination products the attention they deserved. And once pharma companies took a closer look, everything fell into place. A formidable window of opportunity that they had all but overlooked, was opened.

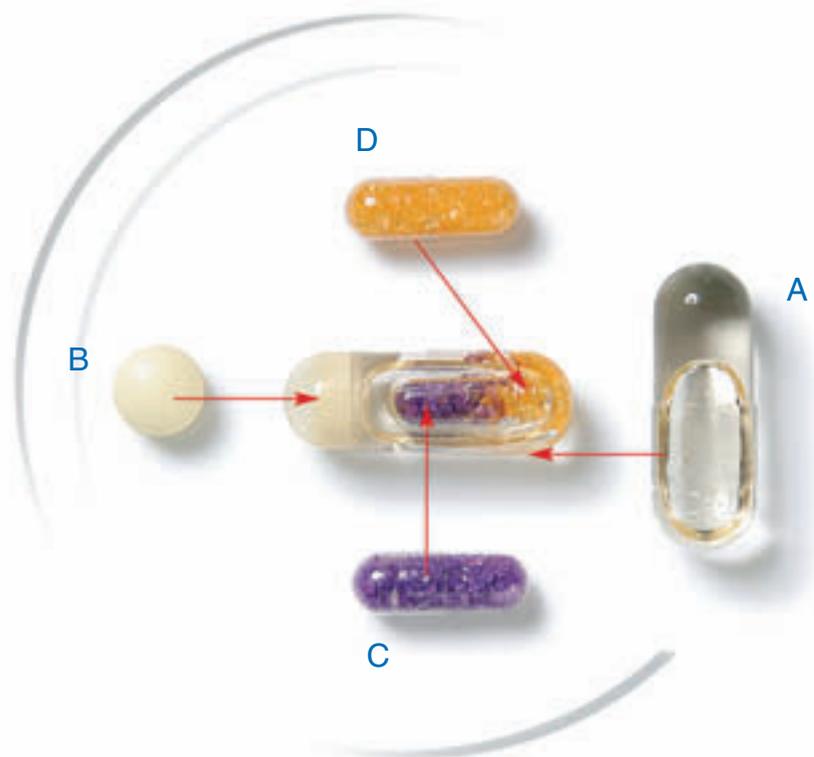
POSITIVE OTC EXPERIENCE

To a certain extent, it was the OTC sector which took the lead in getting significant numbers of combination products onto the market. Companies producing OTC medicines must of course be in very close touch with consumers' wants and needs, and so the fact that pharmacy shelves are stocked full of OTC combination products indicates that consumers like them. It is easy to understand why. If one, for example, is suffering from the high temperature, aching joints and nasal congestion caused by 'flu, one tablet that tackles all of the symptoms together is obviously very welcome.

It is too generalist and simplistic to say that because combination OTC products are successful, combination prescription-only medicines (POMs) will therefore automatically enjoy similar success. However, several comparisons can be drawn. The OTC experience has shown that patients like combinations, and patient opinion has undoubtedly become an increasingly important consideration in POMs. Furthermore, the argument that combination products offer a more convenient alternative to taking two, three or four separate medications, applies equally in the POM and OTC settings.

COMMERCIAL BENEFITS

Combination products bring several commercial benefits to their developers. As touched upon previously, the development of a novel formulation combining two or more existing com-



- A:** high-potency insoluble active compound in a lipid emulsion
- B:** sustained-release tablet
- C/D:** cocktail of two crystalline active materials

Figure 1: NovaCaps capsule showing the four different components it incorporates

pounds is an excellent lifecycle management strategy for revitalising product pipelines. A combination of existing compounds is faster, less expensive and less risky to develop than an NME, and the product can be patent protected from generic competition. Fixed-dose combinations also strengthen brand identity and are clearly differentiated from other products with only one active ingredient.

THERAPEUTIC EFFICACY

Patient popularity and profit potential are of course important. However, by far the most powerful factor driving the market for fixed-dose combinations is their significant positive impact on therapeutic outcomes. Indeed the therapeutic efficacy of a product is one of the most important determinants of both patient popularity and commercial success.

Study after study has demonstrated the benefits of using fixed-dose combinations in all manner of clinical indications.

For example, an August 2006 review of treatment options for Type 2 diabetes advocated the use of metformin combined with a thiazolidinedione in most cases, since the combination achieved very low HbA1c levels

and, unlike thiazolidinedione alone, did not result in rapid weight gain. More generally, the article cited the advantages of fixed-dose combinations as: "lower cost, improved efficacy, better compliance, and fewer side effects".

It went on specifically to describe why a fixed dose combination was preferable to administering the active ingredients separately. "The advantages of fixed-dose oral antidiabetic combinations, compared with their components taken separately, are lower cost and better compliance.

"In most situations, the cost of combination therapy is less than the cost of the individual components, and in some cases the price is similar to that of one of the drugs in the combination so that the second drug is 'free'. In addition, one co-pay rather than two co-pays can be economically advantageous. In some situations, the number of nongeneric drugs that are covered by a third-party payer is limited, and if an oral combination is classified as one rather than two nongeneric drugs, the patient will be allowed an additional, often much needed, nongeneric drug."¹

An editorial by Dr Clifford Bailey in *Diabetes and Vascular Disease Research* stat-



Figure 2: Example of a biphasic, compartmentalised capsule, containing liquid and solid components

ed: “It is widely acknowledged that increasing the number of daily medications is associated with decreased adherence. For example, in the Diabetes Audit and Research in Tayside Scotland (DARTS) study, adherence of patients on two agents was less than half that of patients on one agent. Preliminary evidence indicates that switching from two separate tablets to a single fixed-dose combination can improve adherence.”

He also described the efficacy of combination therapies both in hypertension and for lipid lowering products, and went further still, suggesting that it could be advantageous to combine diabetes treatments with those for the related cardiovascular conditions. “A case can be made for fixed-dose combination tablets to facilitate intensive therapy and to bridge the boundaries of diabetes, dyslipidaemia and hypertension,” he wrote.²

There is strong evidence for the use of combinations in the treatment of hypertension alone. To give one of many examples yielded by a cursory literature search, a paper published earlier last year in the *American Journal of Cardiovascular Drugs* reviewed the blood-pressure lowering efficacy of two fixed-dose combinations: olmesartan medoxomil + hydrochlorothiazide and amlodipine besylate + benazepril. It found that “both combinations significantly improve both systolic and diastolic blood pressure compared with monotherapy, with the individual agents, or placebo”.³

In tuberculosis, a paper in last September’s *Respiratory Research* highlighted the problem of low rifampicin bioavailability in existing combinations. Calling for additional development efforts to overcome this technological barrier, the authors wrote: “The fabrication of a polymeric once-daily oral multiparticulate fixed-dose combination of the principal anti-tuberculosis drugs, which attains segregated delivery of rifampicin and isoniazid for improved rifampicin bioavailability, could be a step in the right direction in addressing issues of treatment failure due to patient non-compliance.”⁴

In the management of pain, some well-known combinations have been available for many years, such as paracetamol combined with weak opioids. It seems that in the new pro-combinations era, analgesic combinations are being looked at again. One potential opening for combinations was referred to in a recent supplement to *Clinical Rheumatology*. The article highlighted concerns with NSAIDs, including the cardiovascular side-effects of selective (and indeed non-selective) COX-2 inhibitors. Author Dr R Landford argued: “These concerns and warnings have left physicians seeking safe alternatives to anti-inflammatory drugs for both short- and long-term uses in many patients ... Amongst the possible strategies, combinations of drugs that provide analgesic efficacy at reduced individual doses may confer the optimal risk-benefit ratio for pain management in the long term or in patients at increased cardiovascular risk.”⁵

In the treatment of HIV/AIDS, it is widely accepted that combination therapy is essential for treatment – usually three or more different compounds from two classes. It is also well known that the complex dosing regimens and high pill burdens imposed on HIV patients contribute to non-adherence and therefore can negatively impact both treatment outcomes and quality of life. Combining the various active ingredients in the smallest number of tablets per day – ideally just one – is the obvious solution to this serious problem.

The May 2004 FDA Guidance covering fixed-dose combinations in HIV notes that there were more than 20 unique anti-retrovirals approved in the US yet only a handful of fixed-dose combinations had been approved. Some compounds are not compatible because of overlapping toxicities and potential viral antagonism. However the FDA makes it clear that where safety and efficacy is in evidence, the regulatory path for approval of new fixed-dose combinations (FDCs) is clear and straightforward, and that it will “act swiftly” to evaluate such products on submission.

It provides a list of possible double and triple combinations for which it expects development “could be accomplished without conducting new clinical efficacy and safety studies”. The FDA guidance adds: “Combinations of two or more active antiretroviral drugs like those listed ... are not the only type of FDC product suitable for combinations. For example, Kaletra (lopinavir/ritonavir), an approved FDC, is an antiretroviral combined with a metabolic booster; a low dose of ritonavir (an inhibitor of cytochrome p450 3A) is used to increase plasma concentrations of lopinavir, the component responsible for the antiviral efficacy. Other HIV protease inhibitors are often administered with low doses of ritonavir and may be suitable for co-packaging or co-formulation. FDA encourages sponsors to develop FDCs for this type of drug combination to help in simplifying regimens.”

Additionally, it is worth noting that the Guidance points out that although it is focused on HIV/AIDS, many of the principles relating to combinations are more generally applicable in different diseases such as malaria and tuberculosis.

In summary, across the spectrum of diseases, we can see that the advantages of fixed-dose oral combinations are being highlighted by experts. Robust scientific evidence that combinations are popular; improve adherence, compliance, therapeutic outcomes and rate of recovery; and reduce side-effects, adverse events and costs, is in abundance.

FORMULATION OPTIONS

The tide has changed, and not only is the case for the development of new fixed-dose oral combinations now clear, but there are calls for their development from various quarters.

Looking to the R&D process, in pharmaceutical companies once the decision to proceed with the development of a specific combination for a particular indication has been made, it is time to start considering the formulation option.

Where it is possible and appropriate, a simple combination in a standard compressed tablet, or layered tablet, might be the best course of action. However, there are a variety of reasons why other approaches could be preferable. As an increasing number of active compounds come up as candidates for combinations, more formulation issues begin to arise. Combining two insoluble compounds or a soluble compound with an insoluble one, for example, presents a considerable technical barrier to the development of a standard tablet form. Similarly, when the active ingredients are chemically incompatible, a conventional tablet is not likely to be appropriate.

InnerCap has developed an elegant approach which overcomes technological barriers such as these, providing a simple and cost-effective development process for a wide variety of combinations. Its NovaCaps platform comprises a range of multi-phased, multi-compartmental capsule-based delivery systems.

The principle of NovaCaps is shown by the photo in figure 1 (page 13), which shows how four individual compounds are combined into one single NovaCaps dosage form. The combination example consists of a high-potency insoluble active compound in a lipid emulsion, a sustained-release tablet and a cocktail of two crystalline active materials. A combination of release profiles can be incorporated in the system.

In the development of combinations of one soluble and one insoluble compound, capsules containing substances in different physical phases can be utilised (see figure 2). NovaCaps can combine incompatible and compatible drugs utilizing different physical phases. Each compartment is sealed to prevent the medicaments from escaping and coming into contact with one another. If a compound is currently stable within a capsule, stability problems are precluded in a multi-capsule application.

As with any new combination drug project, a combination drug may not work in a specific dosage form due to incompatibility or other formulation issues and an alternative delivery system will have to be identified. For instance, both bi-layer tablets and multi-compartment capsules have specific benefits associated with the dosage form. If the combination product will contain incompatible or multi-phase compounds, multi-compartment capsules can make a project possible that may otherwise fail in a bi-layer tablet. This new development may allow projects that have failed in the past to become viable projects and dramatically increases the possibilities when working with different combinations.

Also, multi-compartment capsules can accelerate the development of a combination product and proceed to clinical trials by minimising the formulation development of a combination tablet project. This allows a combination product to enter clinical trials and accelerate the process to determine if the new product achieves the desired therapeutic effects in the trial group. This approach can save millions of dollars in development costs, and a first-to-market advantage can be the factor that decides the success or failure of a multi-million dollar product in the marketplace.

Novacaps offers extensive advantages and opens up a variety of opportunities in the development of novel combinations. These include:

- **The ability to incorporate multi-phased materials**

Solids, powders, granules, crystals, hot melts, pastes, gels, liquids, coated materials, lipids, enrobed, softgels, nanomolecules, beadlets, micro-encapsulated, encochleates, suspensions, emulsions and gases in a single dosage form.

- **Incompatible drugs in a single dosage**

Wider selection of drugs to work within single dosage form

- **Multiple capsule shell materials**

Multiple shell materials can be used in single dosage form.

- **Multiple release profiles**

Combine different release profiles such as immediate, delayed, enteric, sustained and timed.

- **Single Indication**

Drugs combined to target one disease state or side effects.

- **Multiple indications**

Drugs combined to target separate disease states or organ systems.

- **Ease of scale-up**

Modified existing equipment can be used to manufacture products.

- **Fewer excipients**

Different phases can reduce number of excipients in dosage.

- **Increased bioavailability through absorption**

Materials to increase bioavailability can be included in formulation. Poorly water soluble drugs can be significantly enhanced.

- **Increased stability**

Reduced oxidation through use of antioxidants protecting actives. Reduced moisture sensitivity by use of lipophilic matrix.

Furthermore, products presented in this delivery system can help pharmaceutical marketing teams build a compelling case for an attractive solution. Some of the aspects of the NovaCaps-enabled product's profile that could be included are summarised here:

- Fewer pills to be administered.
- Reduces number of drugs prescribed by physician.
- Reduces liability issues relating to prescribing physician.
- Drugs are administered in correct sequence.
- Timing of regimen correctly adhered to by provider.
- Greater consumer appeal.
- Aid in drug identification and product differentiation.
- Create positive psychological response through colour and visual product appeal.
- Simplicity of regimen reduces mistakes.

- Smaller number of bottles to maintain.
- Less odour and unacceptable taste.
- Capsules are preferred dosage form by most patients.
- Capsules are easier for most patients to swallow.
- Non-gelatin capsules.

CONCLUSION

The time for combination products has now come, and an effective formulation solution is now in demand. Not only can the NovaCaps technology be applied to solve problems in the development of standard oral combinations, but it enables the rapid and cost-effective development of advanced, highly differentiated, innovative products.

InnerCap is now actively engaged in seeking partners with which to develop products and bring them to market. The company will consider a range of transaction structures including product licensing, co-promotions, distribution arrangements, royalty-based transactions and partnership arrangements.

InnerCap's philosophy is built around providing solutions to patients, healthcare providers, physicians, and its R&D partners through the development of combination drug therapies. We offer partners the benefit of a strong intellectual property position, in relation to the InnerCap delivery system and a range of delivery targets.

REFERENCES

1. Bell D, Wyne K: "Symposium on diabetes: use of fixed-dose oral combinations." *Postgraduate Medicine*, 2006, Vol 119, No 2
2. Bailey C: "Whence and whither the fixed-dose combination?" *Diabetes and Vascular Disease Research*, 2005, Vol 2, Issue 2, pp 51-53
3. Quan A, Chavanu K, Merkel J: "A review of the efficacy of fixed-dose combinations olmesartan medoxomil/hydrochlorothiazide and amlodipine besylate/benzazepril in factorial design studies." *American Journal of Cardiovascular Drugs*, 2006, Vol 6, No 2, pp 103-113
4. du Toit LC, Pillay V, Danckwerts MP: "Tuberculosis chemotherapy: current drug delivery approaches." *Respiratory Research*, 2006, Vol 7, No 1, p 118
5. Langford RM: "Pain management today-what have we learned?" *Clinical Rheumatology*, 2006, Vol 25, Supplement 7, pp 2-8



COMBINING TECHNOLOGIES WITHOUT COMPROMISE:

TASTE MASKING + ODT + MODIFIED RELEASE

Incorporated into 130 marketed products generating an estimated US\$2 billion in sales annually by 2004, the first generation of orally dissolving tablet technologies is well established in the global pharmaceutical market. Here, Steve Ellul, Business Development Director at Eurand, explains how second-generation ODT technologies, which overcome technical challenges and address needs not met by the first generation, are now poised to enter the global market, and Eurand's Advatab is in the prime position.

Prepared by ONdrugDelivery on behalf of Eurand

"We are delighted that GSK has chosen Eurand for this important project. We believe it further confirms our market leading position in the fields of taste-masking and oral disintegrating tablets.

"The combination of our Microcaps™ and Advatab® technologies has received an enthusiastic reception from industry leaders such as GSK and we are currently in advanced negotiations with companies in Japan, Europe and the USA for a range of different products."

This was Gearóid Faherty, Eurand's Chief Executive Officer commenting just last October on the news that GlaxoSmithKline had entered into a development and licensing agreement to use Eurand's Microcaps taste-masking system and Advatab oral disintegrating tablet (ODT) technology for the development of a new formulation of a GSK compound.

The question is: why Advatab and why Eurand? What exactly did Eurand bring to the table that others did not? It is of course impossible to answer this in a single sentence or even a paragraph, but there are several distinct reasons why pharmaceutical companies might well wish to make Eurand their partner; and these are set out in detail throughout the remainder of this article.

Let's begin by examining the market briefly. ODTs provide: convenient dosing; inconspicuous drug administration without the need for water; enhanced compliance and enhanced efficacy. There is a wealth of data which suggests that a significant demand for ODTs exists as a

result of these benefits. A few key facts and figures are summarised here as examples:

- More than half of all medicines are given orally, yet 30% of patients find swallowing difficult; in particular children and the elderly.
- Some medical conditions cause dysphagia.
- In one survey, 88% of patients indicated that they would prefer ODT formulations over traditional oral dosage forms.
- In a study in 4,000 depressed patients, conducted by Organon and presented at the American Psychiatric Association, two thirds preferred the ODT formulation of Remeron to the conventional tablet formulation, and half said that they were more likely to comply with the ODT product.
- A 2003 poll conducted by Harris International and sponsored by Schwarz Pharma suggested that 40% of American adults have experienced difficulty swallowing pills. As a result, 14% delayed taking their medication, 8% skipped doses and 4% discontinued treatment. Less than 25% discussed the swallowing difficulty with their doctor.

Yet the advantages of ODT formulations are not only for patients. The suitability of ODT technology for application in lifecycle management, market expansion and product differentiation means that pharmaceutical companies that choose to develop ODT versions of their products can derive considerable commercial benefit.



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This is by no means merely conjecture. Such is the market pull for ODT technology that it has enjoyed continually growing success since it first became available in the 1980s. In its 2005 report on the segment, Technology Catalysts said that the ODT/fast dissolve market was “certainly one of the fastest growing segments in the >US\$30 billion oral drug delivery industry in 2004. The current market consists of over 130 launched branded products for 82 molecules, collectively generating revenues in excess of US\$2 billion in 2004 – an increase of 20% over 2003”.

Nonetheless, this first generation of ODT technologies leaves in its wake several unmet needs. The core requirements for an ODT system are as follows:

- Pleasant taste and mouth-feel without grittiness
- Adequate speed of disintegration (less than 30 seconds)
- Good drug-loading capacity
- Mechanical strength of tablet that allows standard packaging
- Ability to manufacture the tablet on standard lines with minimal involvement of expensive specialised equipment

It is of course possible to identify first-generation technologies that meet the needs above – but the difficulty is finding a single technology that ticks all of these boxes. When it came to choosing a first-generation ODT technology, pharmaceutical companies had to make their selection on the basis that any single ODT would satisfy perhaps one or two requirements, but at the expense of others.

One simple example of how one characteristic had to be played off against the other is that of disintegration time and drug loading. Rapid disintegration was often achieved by making the tablet highly porous. However it is clear that as porosity (the proportion of the dosage form that comprises nothing more than air) increases, the amount of space in the tablet remaining for the active drug substance and excipients decreases accordingly. Furthermore, increased porosity can make the tablet mechanically weaker and more friable, to the extent that additional specialised packaging such as peel-off blister packaging is required.

Taste-masking provides another example of how difficult it is to tick all the boxes. Ineffective taste-masking technology means that the dose of bitter active ingredient has to be kept small, limiting the application of the technology to low-dose products. The obvious way of ensuring effective taste-masking is to use a thicker coating, but this often results in poor dissolution in the stomach.

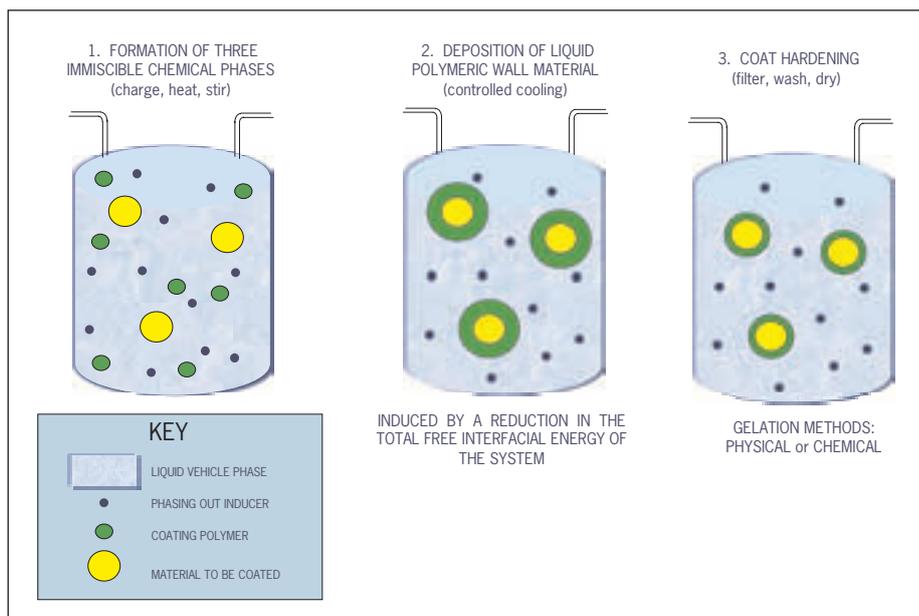


Figure 1: The Microcaps® coacervation process – microencapsulation by phase separation

In first-generation ODT development, compromise was the name of the game. When discussing and assessing a second-generation ODT, it is important to look at how it measures up against the various requirements together, rather than analysing their performance against each criterion in isolation. The remit for the next generation of ODT systems is for a single technology to meet all of the requirements upon it.

AdvaTab is that technology. It has already reached the market in Japan, and AdvaTab products are due to be launched in 2007 in the US, and in Europe in 2008.

Taste-masking ability, although not the only important quality of an ODT, is certainly at the crux of the issue. Firstly, the proper engineering of the taste-masked drug particle is the first step in the creation of an ODT product. Secondly, developing an effective approach to taste-masking that does not impinge on the other characteristics of the tablet has presented a huge technical challenge in ODT R&D. Third, although first-generation ODT development was all about compromise, the taste-masking element provides the least wiggle room. If patients can't bear even to put the tablet in their mouths because it is so face-twistingly bitter, the technology has surely fallen at the first hurdle – especially since ODTs are a means of improving the patient experience in order to make a product more attractive and increase compliance.

Eurand has a strong heritage in the provision of first-class taste-masking technology. There are two broad approaches to masking the bitter taste of a drug. Organoleptic methods typically employ strong flavours and/or sweeteners to overpower the drug's taste. The second

approach, physical barrier methods, include spray drying, fluid bed coating and coacervation. These techniques coat particles of the active compound so that they do not come into direct contact with the taste receptors on the tongue.

Eurand's Microcaps taste-masking technology uses coacervation, a versatile, precise coating technique that encapsulates individual drug particles, completely enveloping them to achieve superior taste-masking properties. The coacervation process, which is outlined schematically in figure 1, places a uniform coating of polymeric membranes of varying thicknesses and degrees of porosity directly onto the dry crystals or granules, creating particles, typically 150-300 microns in size, suitable for incorporation into an ODT.

Microcaps has been used to taste-mask a wide range of extremely poor-tasting drugs, including zolpidem for insomnia, sumatriptan for migraine, ranitidine for GERD, and cetirizine for allergic rhinitis, as well as theophylline, ibuprofen, acetaminophen and pseudoephedrine. Eurand's taste-masked actives are incorporated into products such as Novartis's Triamcinic Softchews®, Whitehall Robins' Children's Chewable Advil®, Rulid® (roxithromycin), and the Benadryl® line of products from Pfizer.

Microcaps goes further than simply the provision of effective taste-masking. As anyone involved in drug development will know, the real challenges only become apparent once work on a specific product begins, and so the true superiority of Microcaps is best highlighted by an example of its application in a real-world product development scenario.

ODT property	AdvaTab® capability
Incorporate microcapsules	Yes, without grittiness or fracture
Taste & mouthfeel	Excellent - smooth and pleasant
Disintegration time	around 15-30 seconds *
Dose capacity	up to ~ 750 mg **
Manufacturing process	Efficient
Moisture sensitivity	No special requirements
Packaging	Bottles or push-through blisters

* Dependent upon total dose

** Dependent upon total tablet weight

Figure 2: Summary of the key characteristics of Advatab – a second-generation ODT

Ceterizine, the active ingredient of Pfizer’s anti-histamine product, Zyrtec, is a particularly bitter compound, the taste of which it is not possible to mask using standard methods. An additional difficulty is that ceterizine is chemically incompatible with many standard excipients, ruling out several conventional tableting techniques. Furthermore, many of the most obvious technical solutions to these two problems affect pharmacokinetics/dynamics, making it difficult to develop a product that is bioequivalent to the original.

The versatility of Microcaps meant that it was able to surmount this challenge. Firstly, Microcaps avoids the use of incompatible excipients within the particles, thereby making for a stable formulation. Secondly, Eurand was able to apply sufficiently thick coating to achieve good taste masking without compromising on the pharmacokinetic requirements. Once in the mouth this coating provides an inert, mouth-insoluble barrier between the drug and the taste buds, thus shielding the latter from the bitter chemical. When it reaches the stomach, the system allows rapid dissolution and diffusion of the active compound across the coating.

The creation of Microcaps-coated particles is the first part of the process. The key to AdvaTab’s other properties lies in the further processing of the Microcaps particles into the finished AdvaTab ODT.

This process is responsible for imparting the excellent mouth-feel to AdvaTab tablets because AdvaTab uses small particles of excipients which (unlike microcrystalline cellulose and calcium phosphate, which are chalky) disintegrate rapidly in the mouth to form a smooth, creamy, sweet-tasting suspension.

Eurand uses a patented modified direct com-

pression tableting system and an external tablet lubrication system. Crucially, in terms of the equipment used and the cost, they are essentially standard production processes.

The lubrication system is particularly interesting. AdvaTab tablets are produced using an external lubrication system while traditional tablets are produced using an internal lubrication system. The internal lubrication system used with conventional tablets disperses lubricant on the inside and on the surface of the tablets. However, this method can decrease the hardness of a tablet by reducing the binding action of drug particles.

AdvaTab is produced using a proprietary system that uses 10-30 times less hydrophobic lubricant than conventional tablet production and can be 30-40% stronger than conventional tablets. As a result the tablets are both hard and durable (friability is typically less than 0.5%) yet do not impede liquid entry upon contact with saliva as the tablet does not contain water-insensitive cohesive bonds between particles to hinder disintegration. Furthermore, due to the fact that AdvaTab only has lubrication on the surface of the tablet, drug content can be increased, thereby allowing for higher drug load.

A summary of AdvaTab’s key characteristics is provided in figure 2.

GOING FURTHER

So far we have discussed how a one system, AdvaTab, comfortably meets all of the demands that no single technology amongst the first generation of ODTs could. But this is really just the first part of the answer to the original question, “Why AdvaTab and why Eurand?”

Some time has passed since the first generation ODTs first reached the market, and in the interim, the pharmaceutical industry has changed considerably and its expectations of ODT technology have grown accordingly. The second part of the answer to the question “Why AdvaTab and why Eurand?” is about how AdvaTab meets the additional demands of today’s and tomorrow’s pharmaceutical industry.

AdvaTab can be readily combined with modified-release technology, to produce modified-release, orally-disintegrating tablets, without compromising other aspects of the tablets’ performance. This was not previously possible since most ODT systems were conceived with only rapid oral disintegration in mind.

It is very easy to understate the significance of being able to combine these two technologies within one product, but consider the following. A blockbuster product whose lifecycle to date has included the launch of a conventional IR tablet followed by the launch of an ODT reformulation can now be reformulated a second time as a CR/ODT. Similarly, a product whose lifecycle to date has included the launch of a conventional IR tablet followed by the launch of a CR reformulation can now be reformulated a second time as a CR/ODT.

What an attractive prospect this is, in an industry crying out for more clearly differentiated products, but experiencing an NME drought combined with a sustained wave of patent expirations; a market where convenience and compliance are increasingly valuable attributes, and the provision of a pleasant patient experience is more important than ever before.

TECHNICAL CHALLENGE = BARRIER TO ENTRY

The apparent contradiction between the terms “fast-dissolve” and “controlled-release” gives us a good idea about how difficult it might be to incorporate these two ostensibly opposed characteristics into a single tablet. In fact what is asked of the technology is for it to enable the tablet to disintegrate totally in the mouth but without releasing any of the active compound until after it reaches the stomach, and when it does release the active compound, to do so at a specified rate. It is a very tall order, but there is a bright side to this, especially for those who have access to the technology that makes it possible.

Currently, one potential threat to established players in the ODT market, including Eurand, is that there are few barriers to entry. Indeed Technology Catalysts says that the ODT tablet market is “one of the easiest drug delivery market segments to enter for either brand companies or

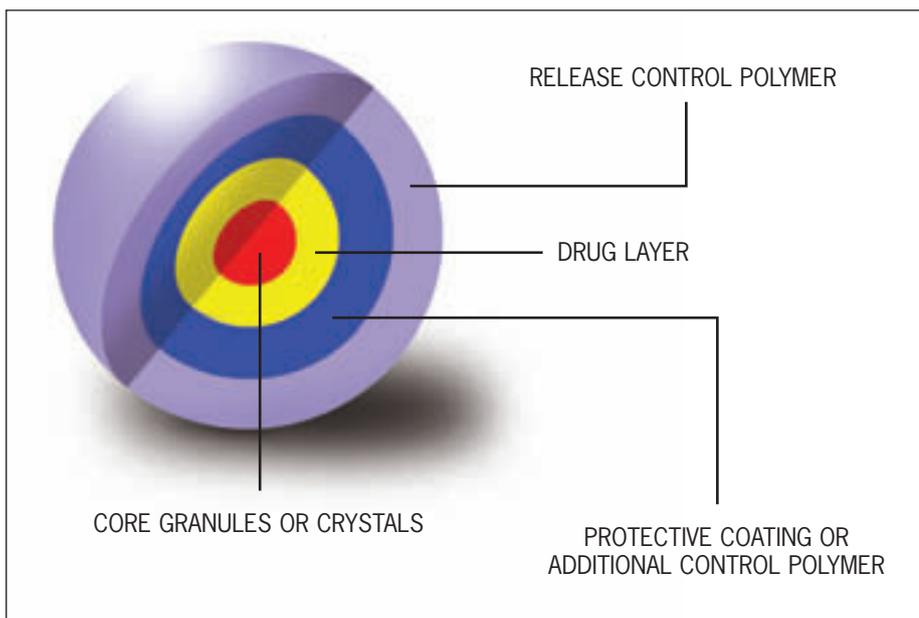


Figure 3: Schematic of a particulate produced using Diffucaps® customised release technology

generic companies”. AdvaTab is protected by a robust patent estate, and its versatility and performance already provide a formidable barrier to competition. However, successfully accomplishing ODT and MR technology combination represents another extremely high barrier to entry both in terms of the sheer difficulty in meeting the technological challenge and of course through the creation of new, strong patent protection.

Eurand’s established and well-known sustained-release technology, Diffucaps®, enables the development of sustained-release products for absorption throughout the gastrointestinal tract. The drug cores, coated with functional polymers by Eurand’s coacervation and fluid-bed coating processes, provide drug particles that are flexible enough for compression without breakage (or loss of modified-release properties), and small enough to achieve good mouth feel in an ODT with sustained-release profiles over one to 12 hours. The process can achieve various dissolution profiles by altering the composition and thickness of the coating polymers.

Diffucaps can be used to develop ODTs with sustained release, time-delayed release, and pulsatile release profiles, as well as combinations of these profiles. In figure 3, the technology has been used to layer active compound onto a neutral core, followed by one or more rate-controlling, functional membranes, allowing up to six hours of delayed release. Eurand has achieved ODT beads of less than 500 µm in very robust tablets. Figure 4 shows a sustained-release ODT formulation of potassium chloride (KCl) maintaining its rate of release up to 12 hours, compared with a standard non-ODT sustained-release KCl.

Optimum release profiles in vivo can be achieved by incorporating bead populations with different release profiles into the dosage form. For example, the technology can release the drug as either a burst or sustained-release profile with a lag time of at least four hours. The lag time between administration and drug release can be prolonged up to about ten hours. Two or more bead populations, with different release profiles or different actives or both, can readily be combined into a single dosage form for maximum flexibility, unique pharmacokinetic profiles and combination products.

CONCLUSION

For pharmaceutical companies, the (often rather bleak) reality they usually face when they peer into the world of oral drug delivery technology is that the space is populated by a vast number of pretty similar technologies offered by an similarly substantial number of undifferentiated companies.

How refreshing it is then to discover Eurand which, as we have shown here, is markedly different and way ahead of the curve. Without question its ODT technology exceeds the standards set in early ODT products. Eurand’s portfolio of oral delivery technologies are market leaders when considered individually. Critically, as discussed here, they can easily be combined into one product, hence setting the standard for future ODT products. This unique ability to combine technologies provides enormous and much needed potential for fresh approaches in lifecycle management, revitalising pipelines, extending the patent lives of blockbuster brands and erecting significant technical barriers to entry for generic and other competition.

Added to this technological edge is the fact that Eurand has a long history of technological excellence in ODT and taste-masking, a global presence with around 500 employees at five sites worldwide, an established and expanding network of leading pharma and biotech partners, an array of proprietary, market-proven oral delivery technologies, and a growing pipeline of its own products. It soon becomes clear that when we ask the question “Why AdvaTab and why Eurand?” a variety of rather compelling answers readily come forth.

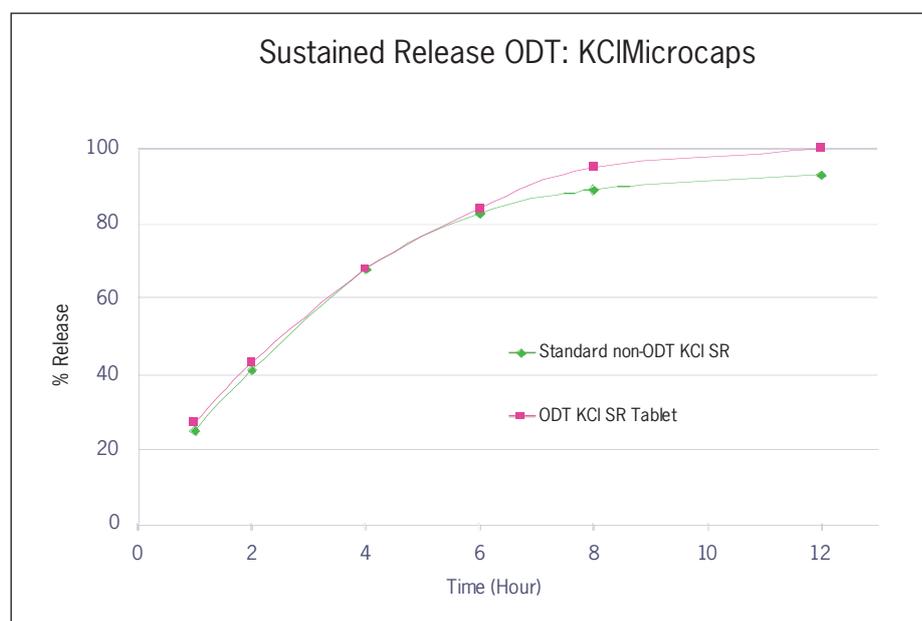


Figure 4: Release profile of KCl from a MicroCaps SR ODT compared with release from a standard SR tablet

ORAL DRUG DELIVERY: THE HOLY GRAIL

One of the most difficult technical challenges in drug delivery is the successful development of large-molecule and protein therapeutics as orally administered formulations. It also promises some of the richest rewards. Here, Emisphere Technologies' Director of Corporate Development, Ms. Bavani Shankar, shows that Emisphere is closing in fast on drug delivery's true Holy Grail.

There is no doubt that oral administration of drugs is the "Holy Grail" sought after by the pharmaceutical industry. This method of administration is patient friendly and improves patient compliance. However, this route is not available to large molecules and proteins, thereby limiting their potential for a wide range of therapeutic indications. Some of the major challenges to delivering these molecules are:

- Degradation of drugs by the high acid content and digestive enzymes
- Poor absorption of drugs through epithelial membrane
- Transition of some drugs to an insoluble form at physiological pH levels, effectively slowing the absorption rate.

The drug delivery industry is comprised of companies seeking novel methods to deliver large molecules orally and improving oral absorption of small molecules including, but not limited to: the pro-drug concept, where the drug is chemically modified; lipid based systems; and other novel delivery systems. This article will focus on the oral delivery of therapeutic molecules utilising Emisphere's novel drug delivery technology, *eligen*[®].

THE ELIGEN[®] TECHNOLOGY

The *eligen*[®] technology, developed by Emisphere Technologies Inc, is a platform technology based on the use of a library of over 4000 synthetic, proprietary chemicals known as "carriers" or "delivery agents". These delivery agents enable or enhance the absorption of therapeutic agents across biological membranes, such as those of the GI tract, thereby allowing these molecules to enter into the systemic circulation. The delivery

agents have no known pharmacological activity themselves at the intended clinical dose levels.

The unique feature of this technology is that it facilitates oral delivery without chemical modification of the drug. The interaction between the EMISPHERE[®] delivery agents and the drug molecule is non-covalent.

Although the mechanism of action has not been fully elucidated, studies conducted to date show that these delivery agents transiently alter the physicochemical properties of the drug molecules (e.g. hydrophobicity), allowing the drug molecule to be more readily transported across the GI, along with the delivery agent. Once the molecules cross the epithelial cells, the delivery agent disassociates from the drug molecule, returning the molecule to its therapeutically active state. Figure 1 summarises a proposed mechanism for the delivery agents.

Additional studies conducted on the pathway of absorption have shown that the transport is by passive transcellular diffusion and maintains cell integrity.

The *eligen*[®] technology does not disrupt the tight junctions between the cells, as is the case with classic penetration enhancers.

A TECHNOLOGICAL PERSPECTIVE:

The technology is broadly applicable for different types of molecules varying in molecular size (up to 100,000 Daltons) and structure. Using this technology, Emisphere Technologies has shown the delivery of therapeutic molecules in several clinical studies, some of which are described below.

Small Molecules: The pharmacokinetic profile of molecules orally delivered using the *eligen*[®] technology is typically characterised by a rapid onset of action. This feature has been used



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HEPARIN DELIVERED ORALLY UTILISING EMISPHERE'S ELIGEN® DRUG DELIVERY TECHNOLOGY, IS BOTH BIOLOGICALLY AND CHEMICALLY IDENTICAL TO HEPARIN DELIVERED BY EITHER THE SUBCUTANEOUS OR INTRAVENOUS ROUTES OF ADMINISTRATION

to obtain more desirable formulations of several small molecules (Cromolyn, Acyclovir) that are poorly bio-available on their own. In one case, the bioavailability of a therapeutic molecule was increased nearly five-fold utilising one of the EMISPHERE® delivery agents.

Heparin: Heparin is a polysaccharide used in the prevention and treatment of deep vein thrombosis (DVT's) in patients undergoing orthopaedic surgeries. In a large Phase III clinical study, Emisphere has shown that an oral heparin formulation with an EMISPHERE® delivery agent exhibited a biological effect comparable with an injectable heparin in patients undergoing hip replacement surgery. More recently, Emisphere has conducted studies showing that heparin delivered orally utilising Emisphere's *eligen*® drug delivery technology, is both biologically and chemically identical to heparin delivered by either the subcutaneous or intravenous routes of administration.

Insulin: Insulin is an essential hormone for the regulation of carbohydrate metabolism and is used in the treatment of both Type I and Type II diabetes. Emisphere has successfully demonstrated in clinical studies, absorption of insulin from the GI tract with concomitant reductions in blood glucose levels following administration of an oral formulation containing an EMISPHERE® delivery agent in combination with insulin as a tablet dosage form. Beyond the mere convenience of an oral dosage form (instead of an injection), there are other physiological advantages. For example, oral insulin mimics the physiological path of natural insulin secretion. It is absorbed through the mesenteric veins, travels to the portal vein and thus the liver where it modulates hepatic glucose secretion.

Recombinant Human Growth Hormone (rHGH): Human growth hormone is a protein drug, with a molecular weight of 22000 Dalton, used in the treatment of growth disorders caused by the inadequate secretion of endogenous growth hormone. Novartis Pharma AG, in a new Phase I study, showed data indicating that recombinant human growth hormone (rHGH) can be absorbed

with elevated level of IGF-I when given to growth hormone-deficient (GHD) patients in an oral formulation using Emisphere's *eligen*® technology. This is the largest protein that has been delivered orally in humans to date.

A BUSINESS PERSPECTIVE:

With the progress in the synthesis of recombinant proteins and peptides, it is now possible to make commercial quantities of pure proteins at a reasonable cost. This has generated a demand for more patient friendly means of administration, as evidenced by the alternate delivery products that are in development or have been approved in the past few years.

Emisphere's *eligen*® technology meets the most important criteria required to make it commercially viable – efficacy (10 products tested in humans with positive data), safety (over 140,000 human dosings without any serious adverse events attributed to the technology), cost-effective, convenient (tablets and capsules; no cumbersome devices) and stable (room temperature stable for up to two years).

With many pharmaceutical companies facing serious gaps in their R&D pipelines and the patent expirations of their blockbuster drugs, these companies have turned to lifecycle management to drive more profits. Emisphere's strategy of applying for patent protection on all aspects of its proprietary technology also adds

value by providing patent life extension in the form of a new and improved product.

CONCLUSION

The need for a convenient method of drug delivery is evident. Emisphere Technologies has shown that its *eligen*® oral drug delivery technology has a number of competitive advantages including delivery agents that are effective across a broad range of molecules; do not rely upon the addition of other agents that can have an adverse effect on gastro-intestinal membranes or the digestion process; can be formulated in a variety of dosage forms (for example, suspension, tablets and capsules); can be produced in commercial quantities and are stable at room temperatures for a required period of time.

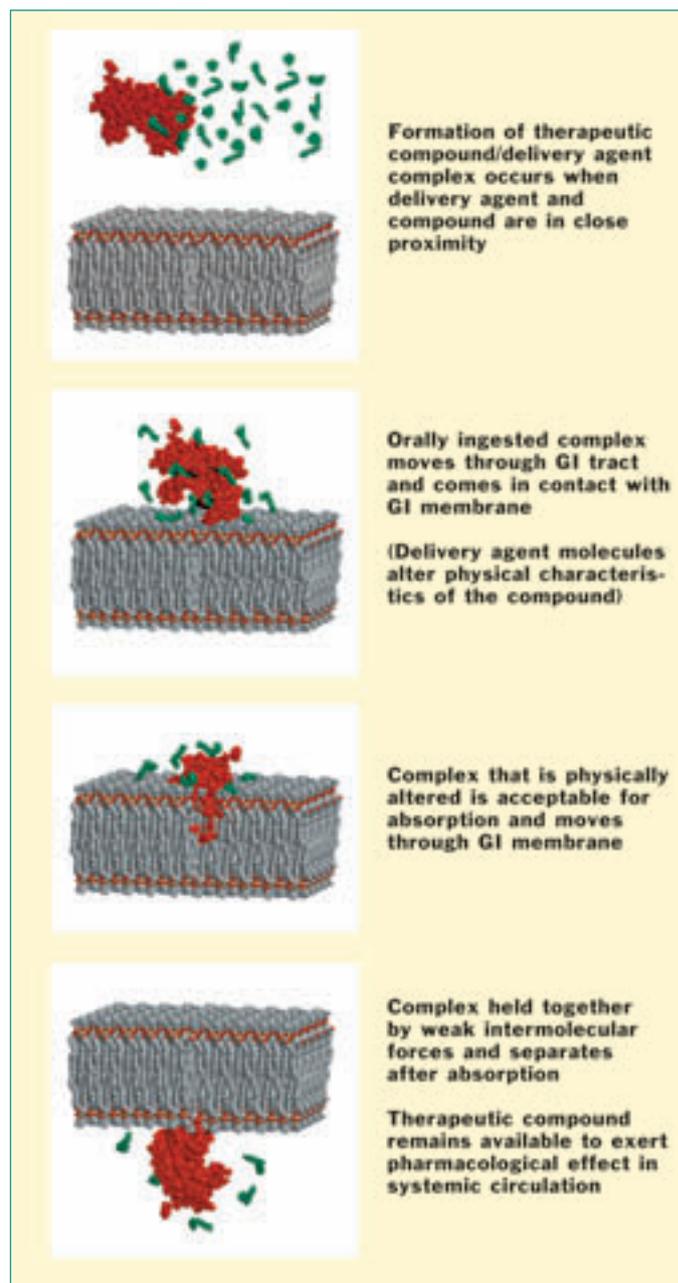


Figure 1: Proposed delivery agent mechanism

MORE THAN JUST FAST-DISSOLVE: CIMA'S BROAD ORAL DELIVERY TECHNOLOGY OFFERING

In a drug delivery industry where marketed products and a broad technology platform are crucial, CIMA LABS INC today is in an excellent position. Some time ago, it was a company that simply provided orally disintegrating tablet technology. Today CIMA offers a range of oral drug delivery systems the majority of which, being utilised in commercially available products, are thoroughly market-proven.

Prepared by ONdrugDelivery on behalf of CIMA LABS INC

Products are everything in drug delivery today; and rightly so. For a delivery technology is essentially valueless without a pharmaceutical product application. It is therefore appropriate that in this article, we describe CIMA's drug delivery technology offering in the context of the many products in which they have been applied.

In September 2006, Cephalon, CIMA's parent company, announced the US FDA approval of Fentora®, its buccal tablet formulation of fentanyl, which uses CIMA's OraVescent® technology. Fentora is the first and only buccal tablet indicated for the management of breakthrough pain in opioid-tolerant cancer patients.

Thanks to the unique delivery system, Fentora is protected by a robust patent estate until 2019. Yet the benefits that OraVescent brings to the product are more than just commercial. The therapeutic efficacy of Fentora is rooted in the way it is delivered.

Breakthrough pain, a common component of chronic pain, is characterised by its rapid onset, intensity, and relatively short duration. Conventional short-acting oral opioids, which are swallowed and absorbed in the gastrointestinal tract, can take up to 30-45 minutes to take effect. With Fentora, thanks to OraVescent, approximately half of the medicine is absorbed directly across buccal mucosa, and into the bloodstream more quickly than if it were swallowed and broken down by the liver in the gastrointestinal tract.

The sugar-free Fentora tablet is placed between the upper cheek and gum above a rear molar tooth. When it comes into contact with

saliva, Fentora's delivery system generates a reaction leading to the release of carbon dioxide. It is believed that transient pH changes accompanying this reaction may optimise how well the tablet dissolves and how quickly the medicine passes across the buccal mucosa.

In placebo-controlled clinical trials, patients treated with Fentora showed a statistically significant improvement on the primary end point, the Sum of Pain Intensity Differences (SPID30) ($p < 0.01$) and some patients experienced clinically significant decreases in pain intensity and greater pain relief within 15 minutes, the first time point measured. In addition, pharmacokinetic data indicate that systemic exposure to fentanyl occurred earlier and was approximately 30% greater with Fentora than with Cephalon's ACTIQ® (oral transmucosal fentanyl citrate).

ACTIQ is another example of a marketed product that incorporates CIMA's delivery systems. CIMA's Oral Transmucosal Delivery System (OTS®) – the "lozenge-on-a-stick" technology – allows easy patient control of the rate of drug delivery. The active ingredient is administered by rotating and dissolving it against the oral mucosa, thus providing a simple mechanism for the patient to dose to effect.

Fentora and ACTIQ have of course been developed inside the Cephalon family. However, CIMA's operations extend outside Cephalon. The company has a variety of collaborations with pharmaceutical partners. For example, in June 2006, the US FDA approved BioMarin and Alliant Pharmaceuticals' Orapred

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Pharmaceutical Partner	Product Name	Therapeutic area	Technology
Alliant	Orapred ODT	asthma	OraSolv
Avanir	FazaClo	schizophrenia	OraSolv
AstraZeneca	Zomig-ZMT/ Rapimelt	migraine	DuraSolv
Bristol-Myers Squibb	Tempra FirsTabs	paediatric pain	OraSolv
Cephalon	FENTORA	breakthrough cancer pain	OraVescent
Cephalon	ACTIQ	breakthrough cancer pain	Transmucosal Delivery System (OTS)
Novartis	Triaminic Softchews	paediatric cough / cold	OraSolv
Organon	Remeron SolTab	depression	OraSolv
Schering-Plough	Clarinx Reditabs	allergy	OraSolv
Schwarz Pharma	NuLev	gastrointestinal	DuraSolv
Schwarz Pharma	Parcopa	Parkinson's disease	DuraSolv
Schwarz Pharma	Niravam	anxiety	DuraSolv
Cephalon	Spasfon-Lyoc	muscle spasm	Lyoc
Cephalon	Paralyoc	pain	Lyoc
Cephalon	Loperamide-Lyoc	diarrhoea	Lyoc
Wyeth	Alavert	allergy	DuraSolv

Figure 1: Marketed products that use CIMA's oral delivery technologies

ODT for the treatment of exacerbations of asthma and eczema in children. It is the first orally disintegrating tablet formulation of prednisolone to be made available in the US.

The product uses CIMA's OraSolv® ODT technology and its approval brought to 11 the total number of approved pharmaceutical products utilising CIMA ODT systems. Another OraSolv product, again developed with a partner, is Schering-Plough's Clarinx Reditabs, an ODT version of the company's antihistamine desloratidine. This was approved in the US in July 2005.

OraSolv is one of three ODT technologies that CIMA offers. It is a compressed tablet system that produces an ODT combining taste-masking with a low effervescence system. OraSolv tablets are produced using low compression forces and are presented in CIMA's patented light- and moisture-proof packaging system, PackSolv®. OraSolv is used in a total of six marketed partner products, details of which are given in figure 1.

CIMA's second compressed tablet ODT system, DuraSolv®, has been incorporated into five marketed products with three pharmaceutical partners, Schwarz Pharma, Wyeth and AstraZeneca (see figure 1 for details). DuraSolv uses greater compression forces during manufacture and therefore produces a more durable ODT compared with OraSolv. DuraSolv tablets, which contain taste-masked active ingredients

with or without a low effervescence system, offer greater packaging flexibility since they can be presented in blister packs or standard bottles. Both OraSolv and DuraSolv can be engraved.

A total of seven products utilising LyocTM, the third ODT system available from CIMA, have reached the market in France and various African nations. These products include Spasfon-Lyoc® (the anti-spasmodic, phloroglucinol), Paralyoc® (paracetamol), and Loperamide-Lyoc® (the anti-diarrhoea compound, loperamide).

Unlike OraSolv and DuraSolv, Lyoc ODTs are prepared by lyophilising an aqueous solution, suspension or emulsion of the active compound with excipients. Since the process is carried out under conditions that produce a stable product, no additives or preservatives are required. Lyoc tablets are more porous than those produced using CIMA's other systems, meaning that very short disintegration times can be achieved.

Criteria	DuraSolv	OraSolv	Lyoc
ODT Technology	compressed tablet	compressed tablet	lyophilised tablet
Taste-Masking	yes	yes	yes
Packaging	bottle or blister	blister	blister
Dose Range	125 mcg – 500 mg	1 mg – 750 mg	500 mcg – 500 mg
Disintegration Time	10- 50 seconds	10 - 40 seconds	2-20 seconds

Figure 2: Summary comparison of CIMA's three ODT technologies

The fourth oral delivery offering from CIMA is an oral powder delivery technology, which utilises CIMA's taste-masking expertise. The technology is comprised of taste-masked drug granules with or without flavour, packaged in a sachet. The granules can be administered with or without food. Oral powder technology can accommodate significantly higher doses compared with other solid dosage forms (>1 gram). The packaging sachet for the technology is unit dose, moisture impermeable, and has the flexibility to meet many child-resistant packaging requirements.

CONCLUSION

With Lyoc, OraSolv and DuraSolv, CIMA LABS INC is the only drug delivery company to offer both compressed and lyophilised ODT technologies which have been proven in the market place. Figure 2 gives an overview of the various characteristics and advantages of CIMA's ODT technologies

It is of course impossible to find a single ODT technology that is both compatible with every possible active pharmaceutical ingredient and able to address all clinical and commercial requirements. This means that being able to offer this range of ODT technologies – each offering different characteristics and benefits – puts CIMA in the strongest possible position – a position from which it is most likely to be able to meet the needs of those seeking an ODT system for their product.

In addition to its technology portfolio, CIMA brings 15 years experience of formulation and taste-masking, bringing both the technical development and manufacturing expertise required to produce successful commercial products which are able to reach the market quickly.

With the OraVescent buccal tablet technology, and the “lozenge-on-a-stick” Oral Transmucosal Delivery System (OTS®) described previously, CIMA's offering clearly reaches further than ODT. However, the same theme is seen across the entire technology portfolio. In every case, CIMA has demonstrated unequivocally its ability not only to talk about and hypothesize on the amazing things that its technologies could do, but rather to prove them by applying them in successful marketed pharmaceutical products.

THE ADVANTAGES

OF MULTI-PHASE, MULTI-COMPARTMENT CAPSULES ARE CLEAR

Deliver Incompatible Compounds

Deliver incompatible compounds in a single dosage form with different release profiles.

Multiple Release Profiles

Incorporate one or more release profiles into a single dosage form such as immediate, enteric, targeted, chronotherapy and pulsatile.

Higher Perceived Value

Consumers view multi-phase, multi-compartment capsules as having a higher perceived value than ordinary tablets, capsules and soft gels.

Choice of HPMC or Gelatin Capsules

With multi-phase, multi-compartment capsules you are not limited to just gelatin (animal-based product) but have the option of natural HPMC (hydroxypropyl methyl-cellulose) and alternative capsule materials.

Better Visual Appeal

Multi-phase, multi-compartment capsules have none of the dust and residue associated with powder capsules. Better visual product appearance translates to higher perceived value.

Increased Absorption and Bioavailability

Liquids naturally offer faster and increased absorption and availability of active ingredients.

Increased Profit Potential

Add up all the advantages. Expect higher sales...and high margins!



Multi-Phase System

Compounds can be delivered with the most advantageous pharmacokinetic profile such as liquids and solids

Faster Development

Multi-phase, multi-compartment capsules reduce the development time compared to bi-layer tablets to get a new product into clinical trials faster.

Smaller Capsules

Hard-shell capsules have thinner wall construction, allowing them to contain more ingredient in a smaller capsule versus thicker-shelled soft gel capsules.

Hard shells have faster and more complete dissolution than soft gels.

Less Odor and Less Irritation

Reduces unpleasant ingredient taste and odor commonly found with tablets and traditional capsules. And, liquids provide less irritation than traditional delivery methods.

Tamper Proof Sealing

Band sealing reduces tampering and provides a non-permeable barrier to retard oxidation and increase shelf-life.

Unique Appearance

This new delivery system stands apart from look-alike products that crowd retail shelves.

Compounds

Deliver Pharmaceutical, bio-pharmaceutical and nutraceuticals in a single dosage form.



Patent Pending US-2005-0008690-A1

COMPANY PROFILES



About SkyePharma

SkyePharma PLC (LSE: SKP; Nasdaq: SKYE) develops pharmaceutical products benefiting from world-leading drug delivery technologies that provide easier-to-use and more effective drug formulations. Combining this capability to formulate and manufacture drugs, both for clinical studies and post-marketing, with our established pre-clinical, clinical and regulatory expertise, we identify and develop new therapeutics for ourselves and for our partners. There are now eleven approved products incorporating SkyePharma's technologies in the areas of oral, inhaled, topical and injectable delivery, supported by enhanced solubilization capabilities. In early 2006 SkyePharma announced its intention of divesting the Injectables Unit, based in San Diego, USA.



Technologies

Oral

The GEOMATRIX™ tablet systems control the amount, timing and location of the release of drug compounds through the digestive tract. The combination of different chemical components in the core and barrier layers, each with different rates of swelling, gelling and erosion, allows the production of tablets with a wide range of release profiles. Development partners are GlaxoSmithKline and Sanofi-Aventis.

Approved products include Paxil CR™ (depression) and Xatral® OD/Uroxatral® (benign prostate hypertrophy).

Inhalation

SkyePharma's environmentally friendly inhalation technologies comprise both non-CFC propelled metered dose aerosol and dry powder inhalers.

Our multi-dose dry powder inhaler is fully breath-actuated, easy to use

and consistently delivers uniform doses. Novartis and AstraZeneca are among our partners. Novartis' Foradil® Certihaler™ incorporating SkyePharma's dry powder inhaler is now approved in 27 countries in Europe, the Middle East, Latin America, South Africa and New Zealand and has received FDA approval.

Enhanced Solubilization

SkyePharma has several complementary technologies that can make insoluble drugs more soluble. These technologies may be used either alone or in conjunction with SkyePharma's other drug delivery technologies. Partners include Sciele Pharma for Triglide™ (lipid disorders) and others.

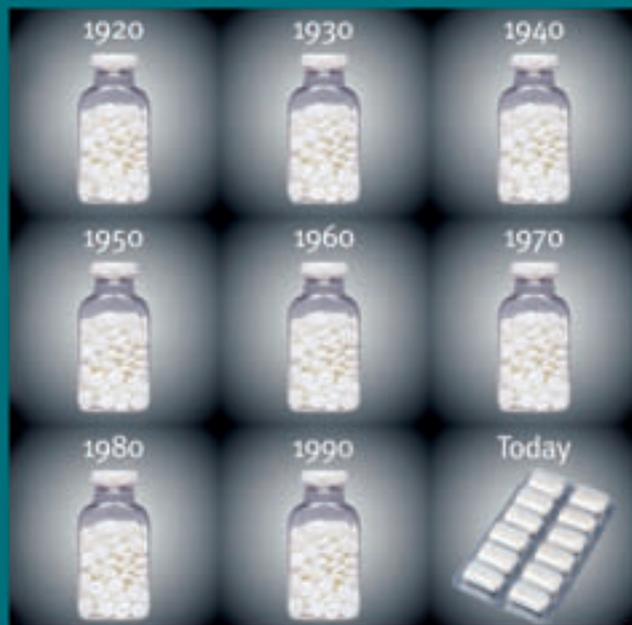
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- Challenges and progress in transitioning from drug delivery to specialty pharma
- Responding to and capitalizing on the generic drug market
- New approaches for biotech delivery and combination products
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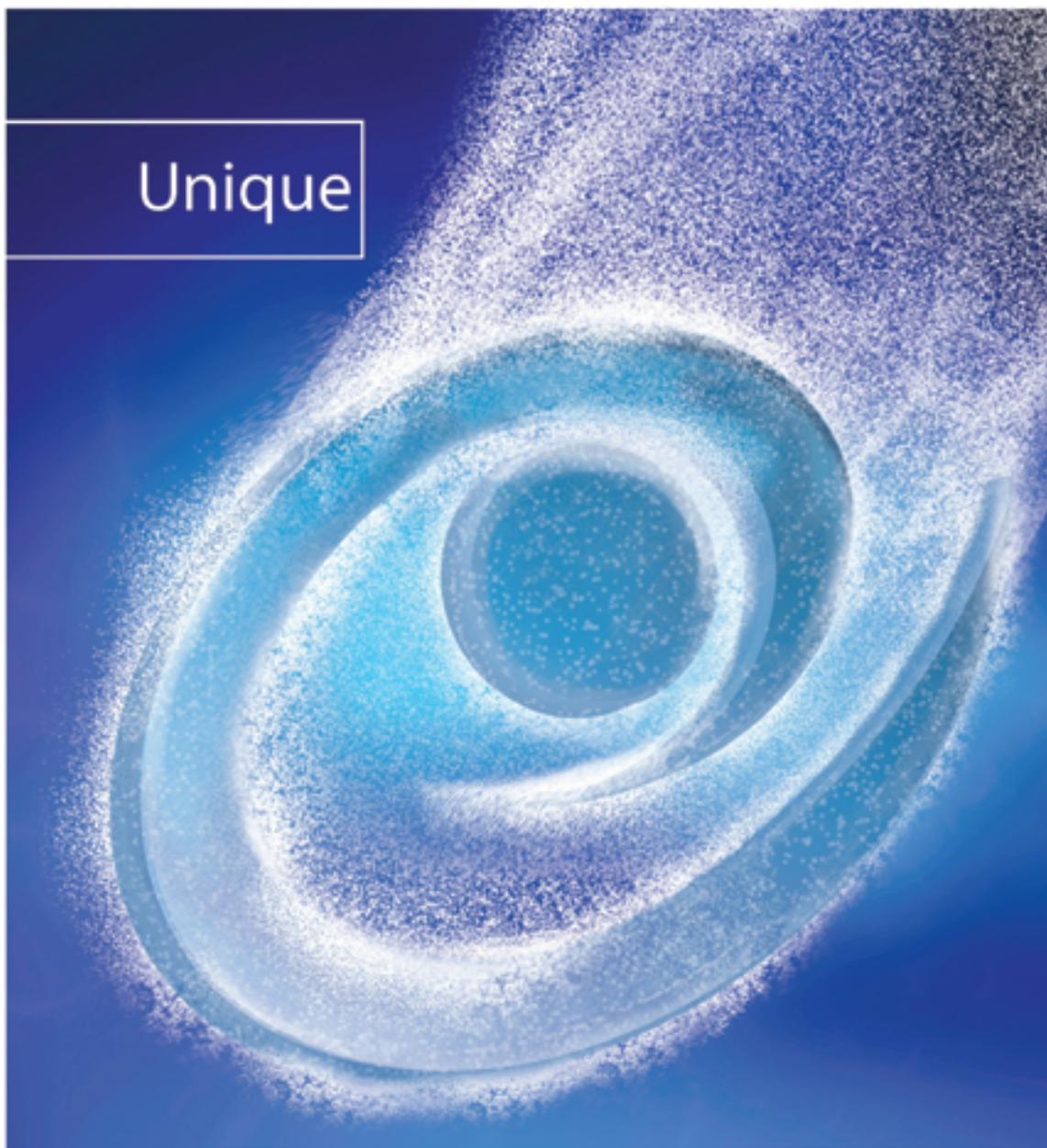
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Unique



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