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E: guy.furness@ondrugdelivery.com

MAILING ADDRESS:

Frederick Furness Publishing

48, Albany Villas, Hove, East Sussex, BN3 2RW

United Kingdom

PRODUCTION/DESIGN:

Mark Frost

www.frostmark.co.uk

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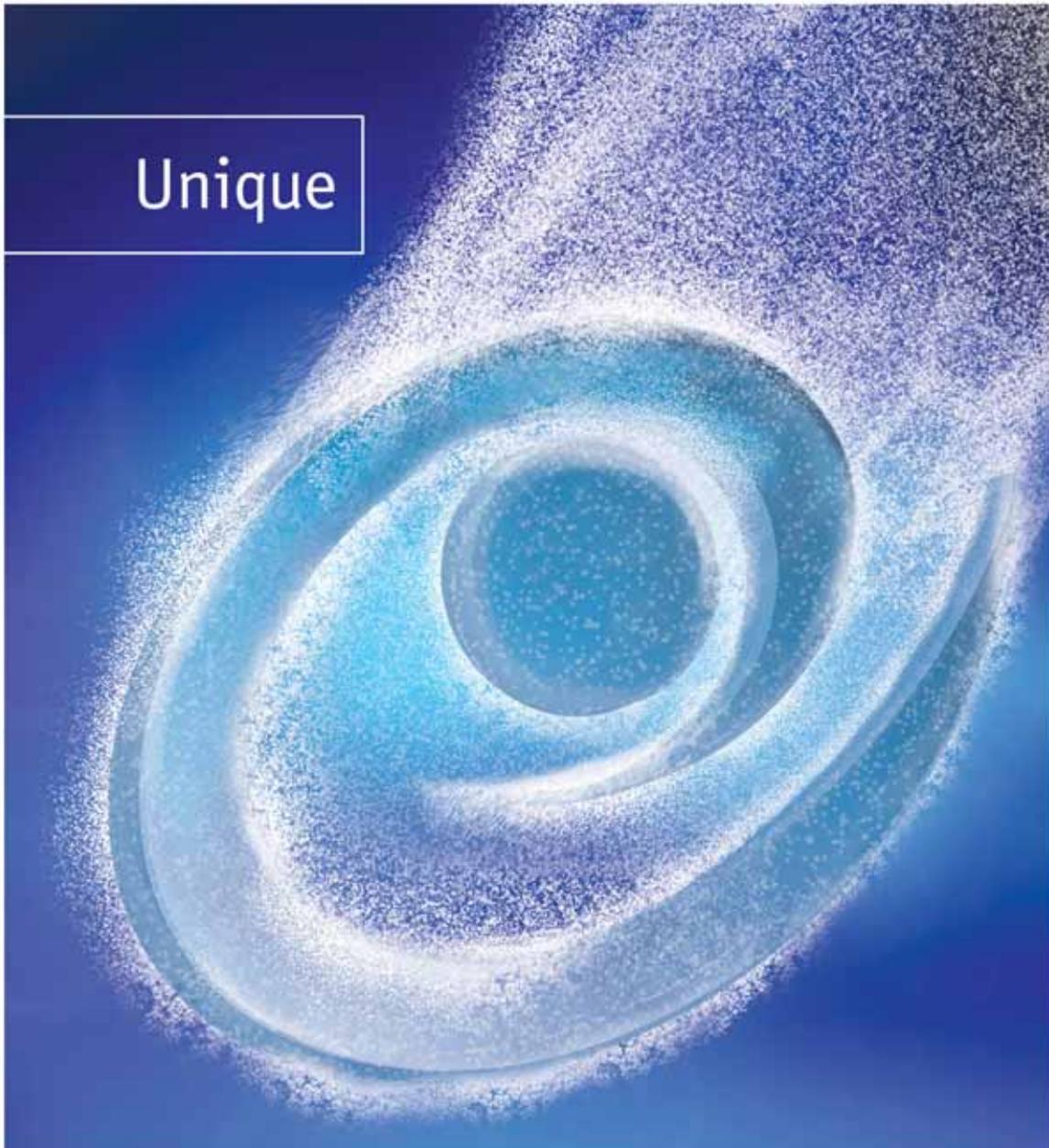
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ORAL DRUG DELIVERY: THE NUMBERS BEHIND THE BUSINESS

For the pharmaceutical industry, extended release oral dosage forms provide multiple commercial benefits. Reduced dosing frequency improves compliance, which translates into higher unit sales. And better therapeutic outcomes due to improved efficacy and improved tolerability can lead to fewer medication switches and greater physician loyalty. New formulations can also extend market exclusivity.

With oral drug delivery becoming an increasingly mature technology it's worth looking at some of the numbers and parameters that impact the business of oral drug delivery. What was once a novel and high value technology has increasingly become a commodity platform. Is there still value to be found in developing novel oral drug delivery platforms? Perhaps the numbers can give us a sense of the past, present and future.

BACKGROUND

The numbers in this article focus on the US market. The US represents the largest global market controlled by a single, remarkably transparent, regulatory process. This permits trends and values to be more easily analysed.

"COMPANIES PROVIDING ORAL DRUG DELIVERY TECHNOLOGIES WILL NEED TO EVOLVE THEIR OFFERINGS AND BENEFITS IF THEY HOPE TO AVOID COMPETING IN A COMMODITY MARKET"

And what happens in the US doesn't just stay in the US; products and ideas often move overseas. While there are great oral drug delivery ideas coming from Europe and Asia, companies almost always look to the US as the most important market.

We will define "drug delivery" for the purpose of this article as a formulation technology that enables and/or enhances the use of a

pharmaceutical active. The acronym (DDEP) refers to these drug delivery enhanced and/or enabled products. Our definition will not include commonly available formulations considered to be part of a standard toolbox. This includes simple enteric coated products such as proton pump inhibitors. Extended release pseudoephedrine, ephedrine and antihistamines are also excluded because of the formulation toolbox nature of the technologies. All other oral sustained release and quick dissolve technology products are included.

ORAL DRUG DELIVERY PRODUCTS SALES

Table 1 provides a summary of the annual sales of oral drug delivery products in the US for the years 2000 to 2008. This list is limited to prescription oral drug delivery products (oral DDEPs) that were among the Top 200 Retail Products in terms of sales. These Top 200 products accounted for about 85% of all retail sales in the US.

Overall, oral DDEPs accounted for between six and 11% of the sales of all pharmaceutical products in the Top 200. The sharp increase in sales of oral DDEPs between 2000 and 2003 is accounted for by the strong growth of new sustained release formulations of antidepressant, incontinence and ADHD medications. Oral sustained-release (SR) product sales accounted for 96.6% of all oral DDEP sales, with ODT formulations accounting for 2.2% and Liquid SR the remaining 1.2%.

The top-selling oral DDEPs are all SR formulations with Effexor XR (venlafaxine; Wyeth/Pfizer) holding the number one spot with peak sales of almost \$2.7 billion in 2008. The second-place product was OxyContin (oxycodone; Purdue) with reported sales of \$2.5 billion in 2008. Other top products included: Wellbutrin SR (bupropion; GlaxoSmithKline), which had sales of \$1.7 billion in 2003; Wellbutrin XL (bupropion; Biovail/GlaxoSmithKline), with \$1.7 bil-

lion sales in 2006; Toprol XL (metoprolol; AstraZeneca) with \$1.5 billion sales in 2006; and Adderall XR (mixed amphetamines; Shire) which had \$1.4 billion of sales in 2008.

It is worth noting that the majority of these products address chronic central nervous system indications. All of these top selling oral DDEPs are reformulations of previously approved, and very successful, immediate-release products.

The top products in terms of peak annual sales are all reformulations of previously approved and marketed actives. Only when you get to the 29th product, Invega (paliperidone; J&J), do you find a new molecular oral DDEP. Sales of Invega were reported as \$246 million in 2008.

The top selling non-SR oral DDEP was Claritin RediTabs (loratidine; Schering-Plough/Merck) at the 17th position with sales of \$383 million in 2002. Other notable ODT formulation products include: Zofran ODT (ondansetron; GlaxoSmithKline) with sales of \$214 million in 2005; and Maxalt MLT (rizatriptan; Merck & Co) with sales of \$192 million in 2008. Tussionex (hydrocodone/chlorpheniramine; UCB), a liquid SR product for the treatment of cough, was in at the 28th position with sales of \$247 million in 2008.

ORAL DRUG DELIVERY PRODUCT DEVELOPMENT PARAMETERS

What about the development parameters associated with oral DDEP? How long does it take to develop these formulations? What are the expected success rates?

The figures from the recent Bionumbers report, *DD09 – Drug Delivery Product Success Rates, Development Times, Costs and Marketing Exclusivity*, provide a good idea of development parameters for oral DDEP. The report looked at DDEP developed and approved over the last 13 years in the US. These numbers should be considered optimistic; products developed and approved in the last few years require longer development times and have lower success rates. The report provides detailed guidance on these trends.

For the period 1996 to 2008, it has taken on average 5.8 years to move a DDEP through

clinical development and approval. This is exclusive of any earlier formulation or preclinical activities. The average clinical development success rate for this period is 34% (see table 2). These figures now stand close to 6.2 years and 24% respectively.

The corresponding 1996 to 2008 average development time for oral DDEPs is 4.9 years, with an average of 2.7 years for ODT formulations and 5.6 years for oral SR products. These can be compared with the 5.8 year average noted in the previous paragraph (see table 2). It is reasonable to expect that these times have increased by at least 10% in the past few years.

The overall development and approval success rate for oral DDEPs is 43%, with a 47% success rate for oral SR DDEPs (table 2). This is about a third higher than the overall rate for DDEPs (34%). Current success rates for oral DDEPs are probably lower, but most likely above 33% (1 in 3).

It is interesting to speculate why the development and approval times for oral DDEPs are shorter than the average for all DDEPs and why the success rate is higher. The reason may be that oral DDEPs are targeted to enhance convenience. SR provides once-a-day dosing versus thrice daily, for example. And ODT gives the convenience of 'melt in the mouth' tablets. These product benefits often require little more than demonstrating bioequivalence with currently approved immediate-release products. Even if efficacy endpoints are required, the development program is often quite simple. And if the drug delivery platform is validated, the regulatory review period can be short.

MARKET EXCLUSIVITY

The attractive development parameters associated with oral DDEPs are offset to some extent by the relatively short market exclusivity periods for these products. The US FDA provides regulatory exclusivity of three or five years depending on whether a product incorporates a previously approved active (three years) or a new molecular entity (five years). This regulatory exclusivity is with regard to generic products approved solely on the basis of bioequivalence data (the ANDA process) and exclusivity runs in parallel with any patent exclusivity the product may possess.

In the case of products incorporating previously approved actives, the three year exclusivity provides no protection from functionally equivalent DDEPs. These functionally equivalent DDEPs incorporate the same active, but use a non-patent infringing drug delivery system. These products are approved on the basis of their own clinical data.

In the marketplace this means DDEPs enjoy market exclusivity from generics for the longer of the two FDA exclusivity periods, or any patent protection existing for the pharmaceutical active. But this does not prevent the introduction of functionally equivalent DDEPs where there are numerous technologies available and there is no parent molecule patent protection.

In the generic scenario a good example of the three year exclusivity period is seen

The third approach to securing exclusivity involves developing novel delivery systems that cannot be duplicated. This is difficult with oral drug delivery systems. As is the case within the electronic products market (computers, smart phones, televisions), once a company introduces a new technology competitors are quick to offer a comparable technology that does not infringe the originator company patents.

Year	Top 200 Product Sales (US\$ billions)	Top 200 Oral Drug Delivery Product Sales (US\$ billions)	Proportion of Oral Drug Delivery Products (%)
2000	90.0	5.5	6.1%
2001	103.2	7.3	7.1%
2002	111.0	9.9	9.0%
2003	117.5	12.2	10.4%
2004	117.3	12.3	10.5%
2005	119.7	11.6	9.7%
2006	126.4	12.9	10.2%
2007	130.6	13.6	10.1%
2008	133.2	14.5	10.9%

Source: SDI/Verispan

Table 1: Top 200 Retail Product Sales – US

with Wellbutrin XL. A once-daily formulation of bupropion, this product was developed by Biovail and licensed to GlaxoSmithKline. With the underlying active having lost its patent protection long ago, the first generics appeared a little over three years after the approval of Wellbutrin XL, despite Biovail having issued patents that extended through 2018.

In the functional-equivalent scenario, there are two approved oral SR formulations of Tramadol, each of which was approved on the basis of its own technologies and studies.

There are at least three strategies for securing extended market exclusivity with oral drug delivery products. The first, as noted earlier, relates to having a patent on the underlying pharmaceutical active. This is often the basis for the exclusivity enjoyed by big pharma's products and for which oral drug delivery formulations represent a lifecycle strategy.

The second strategy involves securing patent protection on non technology-related performance parameters of the DDEPs; for example, drug plasma levels. This strategy has been used effectively by Purdue Pharma with their OxyContin product line. First approved in 1995, this product enjoys market exclusivity until at least 2011, solely on the basis of patents related to serum levels of the active. Attempts to invalidate these patents, while initially successful, have failed and OxyContin continues to generate sales of more than \$2 billion annually.

In general one can expect to have no more than three to five years' exclusivity with a new oral drug delivery product unless one also has patent protection on the underlying pharmaceutical active, has defined a unique product profile, or has a unique technology.

FUTURE OF ORAL DRUG DELIVERY PRODUCTS

There remains an important therapeutic role for sustained-release and quick-dissolve drug delivery products. Unfortunately commercial benefits are more limited than has been seen in the past with billion dollar products like Procardia XL, OxyContin, Wellbutrin XL and Effexor XR. Product exclusivity is limited and pricing flexibility will be limited.

Nonetheless there remain pressing oral delivery needs that can be exploited therapeutically and commercially. The first of these, sustained release liquids, is poorly served by current technologies. While products based on UCB's Pennkinetic delivery system have been available for more than two decades, the delivery technology is crude and unlikely to meet current FDA standards for new products. However, the promise of new liquid SR platforms is starting to be realised with the recent approval of an extended release liquid formulation of clonidine by Tris Pharma.

Product Type	Average Development Time* (years)	Average Success Rate
DDEP	5.8	34%
Oral DDEP	4.9	43%
Oral SR DDEP	5.6	47%
ODT DDEP	2.7	data not available

* time from initiation of clinical development to approval

Source: *Bionumbers*

Table 2: Comparison of average development times and success rates for DDEPs, Oral DDEPs, Oral SR DDEPs and ODT DDEPs for the period 1996-2008.

The most exciting oral drug delivery opportunity may be in the area of abuse deterrent formulations for opioids and stimulants. There exists in the US a significant regulatory interest in reducing the levels of misuse and abuse of these products.

Embeda, from King Pharmaceuticals, is the first of the abuse deterrent formulations to be approved by the FDA. An oral SR morphine combined with naltrexone, Embeda provides sustained-release analgesia when taken orally as directed. But when crushed, the narcotic antagonist naltrexone is released antagonising both pain relief and opioid high. This should limit successful attempts to get a rapid high by crushing and swallowing, injecting or insufflating the product.

Additional abuse-deterrent strategies are in development ranging from the use of narcotic antagonists, to the inclusion of aversive agents, to the use of physical methods to make crushing and solubilisation difficult. If these technologies can match the efficacy and safety of current opioids and stimulants, but with little abuse potential, they will find significant market acceptance.

REFLECTIONS

Companies providing oral drug delivery technologies will need to evolve their offerings and benefits if they hope to avoid competing in a commodity market. The same

principles that make today's computer or mobile phone obsolete within a couple of years applies to drug delivery technologies. While these technologies are still useful and pharmaceutically valuable, they do not support the attractive margins they used to command even a few years ago.

An important test for the drug delivery industry will be whether it can rise to the challenge of true innovation. The numbers suggest oral drug delivery remains as relevant today as it did a decade ago. Who will lead the way to new technologies and products?

Josef Bossart PhD
Managing Director, Pharmanumbers, LLC
(jb@bionumbers.com)

The report, *DD09 - Drug Delivery Product Success Rates, Development Times, Costs and Marketing Exclusivity*, is available from Bionumbers.

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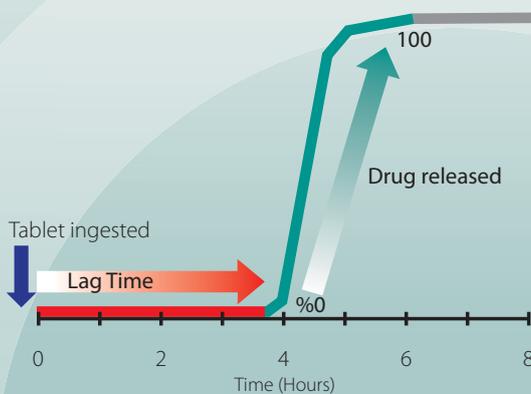
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SPECIALISED TECHNIQUES FOR DEVELOPING ODT DOSAGE FORMS

Orally disintegrating tablets (ODTs) are unique dosage forms that facilitate improved patient convenience and compliance. However, they also come with unique formulation and manufacturing challenges, requiring specialised expertise, in order to create a product that appeals to customers while improving on disintegration and dissolution rates. Eurand employs a proprietary external lubrication tableting system to manufacture its AdvaTab® ODT. This is often used in combination with its Microcaps® technology for masking the bitter drug taste and rapidly dispersing microgranule technology. In this article, Dr Michelle Papp, Formulation Scientist, Dr Gopi Venkatesh, R&D Director, and Troy Harmon, Vice-President Business Development, all of Eurand, describe how, by removing lubricants from within the tablet formulation, an AdvaTab ODT provides important patient advantages through increased dissolution and disintegration rates. External lubrication also creates manufacturing advantages for partners, such as decreased overall production time and harder, more robust tablets that can be packaged in bottles or blisters. Eurand's recent commercialised AdvaTab products include Lamictal® ODT with GlaxoSmithKline and Unisom® SleepMelts with Chattem.

Tablets are still the pharmaceutical dosage form of choice for oral administration. During their manufacture, an extensive amount of friction between the tablet and the surfaces of the die and punch is generated as the tablet is ejected. This can impart considerable amounts of strain and shear to a tablet resulting in tablet defects such as sticking, capping and lamination.¹⁻³

The tablet defects arising as a consequence of these adhesion and frictional forces are generally reduced by the incorporation of a hydrophobic lubricant such as magnesium stearate, stearic acid, or sodium stearyl fumarate (Pruv®) in the final blending step prior to tableting. However, this internal lubrication process imparts a hydrophobic film on the surface of the powdered or granulated formulation which can negatively impact the performance properties of the resultant tablets.

Depending on the formulation, choice of lubricant and its concentration, this method may result in a longer disintegration time (DT) and slower dissolution due to reduced water penetration rate, as well as lower tablet strengths due to decreased interparticulate bonding. These negative effects from internally incorporated lubricants can become problematic, especially in the case of orally

disintegrating tablets, which are required to disintegrate within 30 seconds when tested for DT by United States Pharmacopeia (USP) Disintegration Test Method <701>.

To reduce the negative aspects, a new approach has been developed that localises the application of lubricants to the interface between tablet and tooling. This method is known as external lubrication.

There are different techniques for applying an external lubricant during tableting. Manual application methods, such as gentle blending of the tooling with the powdered lubricant⁴ or swabbing the lubricant in suspension onto the punches and die wall⁵, have long been known and are still used in compaction studies utilising a single station tablet press or a compaction simulator. Although useful for small-scale studies, this method is not practical for production scale. Therefore, a second automated method involves the direct application of lubricant powders to tooling on rotary presses. Recent demonstrations⁵⁻¹⁶ highlighting the advantages of external lubrication by automated systems have stimulated interest in its use and a variety of equipment is available.

Kyowa Hakko Kogyo (Tokyo, Japan) has developed a powder material spraying device



Michelle K. Papp, PhD
Formulation Scientist



Gopi Venkatesh, PhD
R&D Director



Troy Harmon, MS, MBA
Vice President Business Development

Contact:
Dr Michelle Papp
Formulation Scientist
T: +1 937 415 0433
F: +1 937 898 9529
E: michelle.papp@eurand.com

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Vandalia, OH 45377
United States

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for use in combination with an industrial-scale rotary tablet press called the ExLub system. It is extensively used by both Kyowa Hakko Kogyo and Eurand for the development and commercialisation of several ODT products.

A second system, the Fette Tablet Press-PKB-1 (Press-Kammer-Beschichtung) external lubrication system manufactured by Fette GmbH (Schwarzenbek, Germany), was first described by Gruber *et al.*⁶ Currently, PKB-1, -2, and -3 external lubrication systems are available from Fette and magnesium stearate and sodium stearyl fumarate as external lubricants on this system have been evaluated.^{6,10}

A Kikusui (Yokohama, Japan) tablet press equipped with an external lubrication system, ELS-P1 or P2^{14,15,16} has also been described in the literature for the external application of magnesium stearate. Other external lubrication systems^{17,18,19} exist, such as Die Wall Lubrication System and Punch Face Lubrication System offered by GEA Pharma Systems (Courtoy; Halle, Belgium) and Lubrication System offered by Sejong Pharmatech Co Limited (Incheon, South Korea), which uses a US FDA-approved edible oil as the lubricant. However these are not described in the literature. Bayer Aktiengesellschaft (Leverkusen, Germany) has an approved US patent (US6,079,968) for an external lubrication system.

The above external lubrication systems involve the spraying of the lubricant by an air nozzle directly onto a tablet tooling similar to that represented in figure 1. However, the individual systems differ in the details of achieving/monitoring the lubricant spray rate and its adherence to the punches and die wall. For example, the ExLub system has a penetrating aperture and a dispersion chamber with a pulsating vibration air supply to control the spray rate precisely. For the ELS-P1 or ELS-P2 the use of the electrostatic charge function on the spray nozzle improves the adherence and hence increases the amount of the lubricant deposited on the punch surfaces and die wall.

In all cases, these external lubrication methods concentrate the lubricant at the interface between the formulation and the stainless steel tooling where friction is at a maximum. The main advantage is that it leaves the powder surfaces on the interior of the tablet lubricant free.

With traditional dry-blended lubricants, the surface morphology of the excipients can become hydrophobic³ potentially compromising the strength of the compacts. This necessitates additional energy, in the form of higher compaction forces, in order to fracture lubricated particles to create the clean,

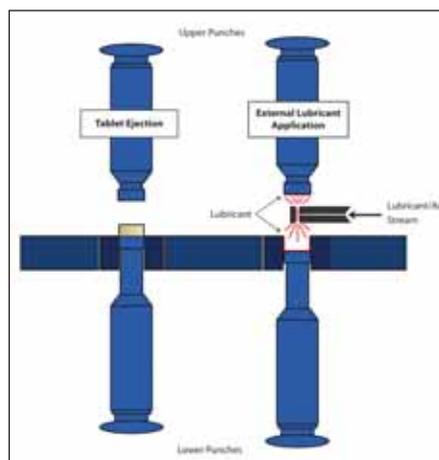


Figure 1: Schematic of external lubrication system showing lubricant application to tablet tooling system surface

unlubricated surfaces needed for the formation of strong intermolecular bonds.

With external lubrication, lubricants are not coating the particles to be compressed, instead the lubricant is directed to the tooling. Therefore the generation of new surfaces is not necessary. External lubrication methods require less force to produce tablets of comparable strength, in contrast to those formulated with internal lubricants.^{4,5} In some cases, tablets are 10-30% stronger at comparable compression forces when external lubrication is employed.⁴

Surprisingly, the increased tablet strengths associated with externally lubricated tablets, compared with internal lubricants, does not result in an increased disintegration time nor

decreased dissolution. The use of an external lubricant for the tableting of calcium hydrogen phosphate/starch granules showed a 20-second faster dissolution compared with the same granules blended with magnesium stearate.⁶

Otsuka *et al* reported the immediate release of trypsin (100% in approximately seven minutes) when tableted using external lubrication, compared with less than 20% release of the drug in 20 minutes when an internal lubricant was used. In this case, the disintegration of the external lubricated tablets was immediate whereas the internally lubricated tablets failed to disintegrate.⁴ This was attributed to the external lubricant method producing a tablet with higher porosity and increased wettability.

The advantage of increased dissolution and disintegration without impacting negatively on tablet strength makes external lubrication an ideal choice for ODT development. Figure 2 provides a summary of ODT products manufactured by Eurand for commercialisation or to support phase III clinical development.

All of these products take advantage of the benefits provided by utilising external lubrication in their manufacture. For example, diphenhydramine HCl, an antihistamine, the active ingredient in the OTC brand product, Unisom[®] is indicated to induce sleep, typically taken at bedtime. The ODT product comprising Diffucaps[®] beads taste-masked using Eurand's Microcaps[®] technology, AdvaTab[®] microgranules (rapidly dispersing microgranules), shows superior oral disintegration results as well as better taste/flavour results, while providing a robust dosage form.

Although it is desirable to optimise and control the quantity of the lubricant sprayed onto die wall and punch surfaces during the production of such ODTs, Jahn and Steffens, and Yamamura *et al*, make the following observations regarding such:

- Lubricant spray rate is optimised by determining the threshold lubricant concentration on the tablet or the spray rate that is characterised by the lowest ejection force observed during tablet ejection.⁹
- Higher spray rates above the optimised level had no significant enhancement but lubricant concentration on the tablet continued to increase.⁹
- Based on the compaction data for lactose, mannitol, sorbitol and pregelatinised starch, a nearly linear dependency between spray rate and lubricant (magnesium stearate) concentration of tablet was evident.⁹

ODT Product ²⁰⁻²⁴	Available Strengths	Corresponding Tablet Diameter and Weight*
Lamictal [®] ODT	25 mg	7.0 mm, 100 mg
	50 mg	9.0 mm, 200 mg
	100 mg	11.0 mm, 400 mg
	200 mg	14.0 mm, 800 mg
Temazepam ODT	7.5 mg	7.0 mm, 125 mg
	15 mg	9.0 mm, 250 mg
	22.5 mg	10.0 mm, 375 mg
	30 mg	11.0 mm, 500 mg
Undisclosed ODT	25 mg	9 mm, 250 mg
	50 mg	11 mm, 500 mg
	75 mg	13 mm, 750 mg
Paracetamol ODT	250 mg	13 mm, 700 mg
	500 mg	17 mm, 1400 mg
Ranitidine HCl ODT	150 mg	15 mm, 1100 mg
	75 mg	11 mm, 550 mg
APAP/HCB ODT	300/10 mg	15 mm, 1100 mg
	500/5 mg	17 mm, 1400 mg
Unisom [®] (Diphenhydramine HCl ODT)	25 mg	11 mm, 450 mg
Undisclosed ODT CR	10 mg	8.0 mm, 200 mg
	25 mg	12.0 mm, 500 mg
	50 mg	15.0 mm, 1000 mg

Figure 2: Summary table of products using Eurand's AdvaTab[®] technology

- Tensile strength has been observed to be nearly constant, despite the lubricant concentration increased up to ten-fold from 0.12% to 1.27%⁹ in contrast with conventional internal lubrication, where variations in the lubricant concentration or modifications in the blending dynamics of the lubricant prior to compression cause significant variations in the resultant tablet tensile strengths, thereby necessitating continued optimisation whenever the blending dynamics of the lubricant change due to changes in the composition, equipment, or both.
- Evaluation by scanning electron microscope (SEM) observation by focused ion beam showed the thickness of the magnesium stearate layer on the central part of the tablets be relatively uniform and thinner than at the edges for two different spray rates.¹⁶

As an added benefit, external lubrication has been shown to increase the stability of certain APIs, such as those that are incompatible with magnesium stearate. Eprazinone hydrochloride is one such compound. Compressed tablets of eprazinone hydrochloride with 0.12% external magnesium stearate had a higher percentage of the API remaining after four weeks at 40°C and 75% RH compared with the internally lubricated formulation containing 1.06% magnesium stearate. The lower amount of magnesium stearate required by the formulation utilising external lubrication resulted in the increased stability of eprazinone hydrochloride.¹⁶

Increased stability of the enzymatic drug trypsin has also been reported from an external lubrication technique.¹ In this case, the lower compression forces required to produce a tablet of corresponding strength to that of internally included magnesium stearate resulted in exposing the API to less heat or pressure. As a result, less loss of activity of the API was reported.

CONCLUSION

Although the advantage of a stronger tablet with faster dissolution and disintegration times might not be obvious for a conventional tablet, it can provide a critical advantage in the development of orally disintegrating tablets. Likewise, utilisation of this technology can eliminate an additional manufacturing step, decreasing the overall production time.

Taken as a whole, external lubrication techniques can provide many benefits over traditional tablet manufacturing methods that incorporate a lubricant in the blend.

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Nanotechnologies for Personalized Medicine

Raju Kucherlapati, Harvard University, U.S.A.
Genetics and Genomics in Clinical Medicine

Hiroshi Maeda, Sojo University, Japan
*The Enhanced Permeability and Retention Effect in Cancer and
Inflammation for More Selective Drug Delivery: Past, Present,
and Future Outlook*

Ramin Najafi, NovaBay Pharmaceuticals, U.S.A.
*Creating and Growing an Innovative Company without
VC Funding*

Nicholas Peppas, The University of Texas-Austin, U.S.A.
*Controlled Release 50 Years Later: Responsive Intelligence and
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COMPANY PROFILE - MAYNE PHARMA INTERNATIONAL



A leading pharmaceutical organisation, built on a heritage of 160 years of industry excellence, Mayne Pharma International is a technology-driven, drug delivery, contract development and manufacturing company for oral and topical pharmaceutical products.

Mayne Pharma International has comprehensive experience in the solid oral Drug Delivery System (DDS) market, encompassing development and manufacture of these products.

The company has:

- more than 30 years' experience in successfully developing DDS products for the global market
- a dedicated product development facility which meets cGMP standards, and includes pilot-scale plant equipment. This allows a scale-up pathway from small clinical trial batches to full commercial manufacture
- proven ability to develop and successfully transfer manufactured product and technology to other sites around the world
- formulation capabilities to help with product life cycle management.

Mayne Pharma International has been granted, or applied for, patents that protect its various drug delivery technologies. The in-market sales of products developed at the Salisbury, Australia facility using its technologies are in excess of US\$500 million per year.

DRUG DELIVERY SYSTEMS

Mayne Pharma International's drug delivery systems include:

Technology to control drug release

To enable pulsed release; sustained release; modified release; and delayed release profiles (pellet/bead formulations produced using extrusion and marumerisation, or spheronisation processes).

Technology to improve oral bioavailability

Particularly for insoluble drugs (SUBA™ technology).

Technology to taste mask liquids and tablets

To improve palatability and aid swallowing (Cleantaste™ technology).

TECHNOLOGY TO CONTROL DRUG RELEASE

Pellet (or bead) technology allows a variety of different drug delivery profiles to be achieved by coating drug and excipient with various polymers. The drug cores are generally spheroidal in shape and have a diameter in the range of 300-1,700 µm.

Two types of process are used to generate the spheroidal particles (see diagram):

- The first of these processes, which allows potencies up to 90%, utilises extrusion and marumerisation to form a drug core with a polymer coat.
- The second process is known as spheronisation, where the drug particles are fixed

to the outside of a seed core (typically a sugar sphere). This process provides a very tight size distribution of pellets. Drug potencies up to 60% are possible.

For both of the processes above, the desired drug release profile is achieved by coating particles with the appropriate polymer.

SUBA™

SUBA™ is a novel technology for enhancing the bioavailability of poorly water soluble drugs utilising a solid dispersion of drug in polymers having acidic functional groups.

SUBA™ has been shown to increase the oral bioavailability of itraconazole (our lead candidate) when compared with the innovator product (Sporanox®).

CLEANTASTE™

Cleantaste™ technology allows a polymer coat to be applied to produce particles (25-150 µm diameter) to improve taste. It is also possible to use this technology to improve stability or to deliver sustained release characteristics. The fine, non-gritty texture of product produced by this technology lends itself to being used in orally dispersible tablet and liquid formulations, as well as encapsulated products. Cleantaste™ acetaminophen (paracetamol) and ambroxol have been commercialised and launched in Australia, the USA and Japan.

SERVICES SUMMARY

Mayne Pharma International can develop and manufacture oral and topical formulations for clinical trials and has the ability to deliver to sites anywhere in the world. Mayne Pharma International can provide:

- **Tablets** (immediate, modified, sustained, delayed or pulse release and taste masked)
- **Capsules** (powder, pellets/beads)
- **Liquids and Creams**

Placebo formulations can be provided to match client specifications or innovator product. Packaging and labelling to suit customer requirements.



Pellet technology used for controlled release formulations

In addition to its drug delivery technologies, Mayne Pharma International offers a number of specialty services:

• **Formulation Development**

Provide solutions to a range of common formulation challenges such as poor solubility, poor bioavailability, short half life, low Cmax, poor powder flow, non-uniform crystal size and scale-up issues.

- **Analytical Services**
- **Regulatory Services**

ABOUT MAYNE PHARMA

Mayne Pharma International competes in the oral drug delivery, branded, generic and value-added API markets. The oral pharmaceutical business at Salisbury, Australia, is a GMP facility.

Annual production capacity:

- Approximately 2,500 million capsules and tablets
- 100 tonnes of bulk product
- 16 million units of liquids and creams

The site is approved by major regulatory authorities:

- FDA: United States
- MHRA: UK
- TGA: Australia
- TPD: Canada

Mayne Pharma International has generated a substantial worldwide patent estate in the drug delivery field, comprising:

- 11 patent families
- 38 pending applications
- 76 granted

Mayne Pharma International is located in Salisbury, South Australia, approximately 19 km from the capital city of Adelaide on a 19-hectare site. There is 12,000 m² of manufacturing space located on the site.

Mayne Pharma International is a wholly owned subsidiary of HalcyGen Ltd, an Australian public company listed on the ASX.

Mayne Pharma International
PO Box 700
Salisbury
South Australia 5108,
Australia

T: +61 8 8209 2604
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Mayne Pharma International has over three decades of experience developing complex products for oral drug delivery using a range of technologies. Our capabilities include:

Drug Delivery Technologies

- Sustained release - deliver steady levels of drug over 12 to 24 hours following a single dose.
- Pulsed release - deliver pulses of drug over 12 to 24 hours following a single dose.
- Modified release - immediate release of some drug and delayed release of the balance.
- Delayed release- target drug to a specific site particularly avoiding release in the stomach via enteric coating.
- Taste mask liquids & tablets - make drugs more palatable or easier to swallow.
- Improve oral bioavailability - particularly for insoluble drugs.

Mayne Pharma International has been granted, or has applied for patents that protect our oral drug delivery technologies.

We use a range of technologies at laboratory scale, pilot scale and commercial scale including:

- Granulation - fluid bed, extrusion and high shear.
- Fluid bed coating - top, bottom & tangential spray coating.
- Spray drying.
- Tableting and encapsulation.

Facility features include:

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- Licensed to handle schedule products to S8 (CII to CIV).
- Licensed to use solvents including methylene chloride.
- Labelling and packaging services.
- Finished goods either FOB or CIP.

Mayne Pharma International*
1538 Main North Road Salisbury South
South Australia 5106, Australia
P +61 8 8209 2604
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Elan
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ADVANCES IN SOLID DOSE ORAL DRUG DELIVERY

Oral drug delivery still remains the preferred route of drug administration by physicians and patients alike. Here, Gurvinder Singh Rekhi, PhD, Senior Director, Oral Controlled Release Product Development at Elan Drug Technologies, describes novel technologies which provide improved performance, patient compliance and enhanced delivery. These technologies will advance further differentiation in the oral delivery market.

Oral delivery continues to be the most popular route of administration due to its versatility, ease of administration and probably most importantly patient compliance. In a recent New England Healthcare Institute report, the cost of non-compliance in the US alone was estimated to be as much as \$290 billion, or 13% of total annual health care expenditure.¹ Providing patients with simplified, convenient

systems some 60% of the market.³ The introduction of widely prescribed proprietary medicines in new oral controlled-release forms will be the driver of market gains.

Generally, controlled-release medicines can be categorised into two groups based on actions. Extended-release formulations deliver a portion of the total dose shortly after ingestion and the remainder over an extended time frame. For

example, Avinza[®] is a once-daily, rapid-onset, extended-release morphine product. Delayed-release systems provide steady dosing after passage through the stomach, such as with Bayer Healthcare's Safety Coated Bayer Aspirin product.

Two of the most widely commercialised controlled-release technologies are OROS[®] (developed by J&J's Alza), and the SODAS[®] technology developed by Elan Drug Technologies (see

figure 1). Other successfully commercialised technologies include SkyePharma's Geomatrix[®], Eurand's Diffucaps[®] and Flamel's Micropump[®].

"ADVANCES IN NANOTECHNOLOGY HAVE IN RECENT TIMES PROVIDED ONE OF THE MOST SIGNIFICANT OPPORTUNITIES FOR GROWTH, ADDRESSING THE ESTIMATED 40% OF DRUGS LEAVING THE CLINIC THAT HAVE POOR WATER SOLUBILITY ISSUES"

oral medications that improve compliance and thus result in more effective treatment has been one of the major drivers of innovation in the oral drug delivery market.

Within the oral drug delivery market, controlled-release tablets and capsules will continue to create the largest demand. Adaptations of these technologies, including chewable, orally disintegrating, nanoparticle and combined technology formulations, are expected to broaden applications and revenues. The total market for oral medications adapted to delivery systems is forecast to reach \$56.7 billion in 2012, up 7.1% annually from 2007² for the US alone. Oral products represent about 70% of the value of pharmaceutical sales and among drug delivery

RECENT DEVELOPMENTS

Since the development of those technologies described above, both they and other technologies have evolved to address specific therapeutic needs such as in the treatment of pain and blood pressure. A number of companies are engaged in the development of pulsatile release systems where drug is released in pulses, separated by defined time intervals. Ritalin[®] LA and Focalin[®] XR, both used to treat Attention Deficit Hyperactivity Disorder (ADHD), mimic the twice-daily dos-

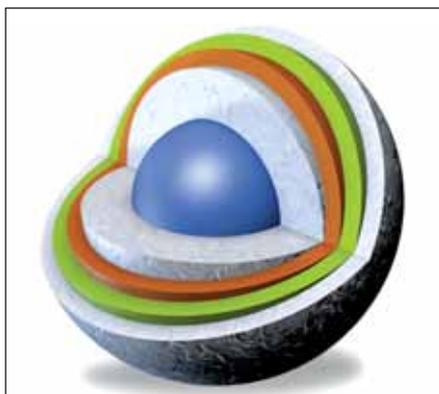


Gurvinder Singh Rekhi, PhD
Senior Director, Oral Controlled Release Product Development
T: +1 770 538 6321
F: +1 770 538 6421
E: gsingh.rekhi@elan.com

Elan Drug Technologies
1300 Gould Drive
Gainesville
GA 30504
United States

General Contact details:
T: +353 1 709 4068 (Europe & ROW)
T: +1 610 313 7045 (US)
E: edtbusdev@elan.com

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SODAS® (Spheroidal Oral Drug Absorption System) is Elan Drug Technologies' multiparticulate drug delivery system. Based on the production of controlled-release beads, the SODAS® technology is characterised by its inherent flexibility, enabling the production of customised dosage forms that respond directly to individual drug candidates' needs.

Figure 1: Pictorial representation of Elan Drug Technologies' SODAS® technology

ing of a conventional immediate release tablet. These once-daily pulsed profiles offer the patient efficacy throughout the day negating the need for children to take a second dose during school hours. Ritalin® LA and Focalin® XR both utilise Elan's SODAS® technology.

Further manipulation of delivery systems has led to the development of chronotherapeutic systems, where release enables a drug to take advantage of the natural biorhythms of the human body. Cardiovascular products such as Biovail's Cardizem® XL and UCB's Verelan® PM provide therapeutic concentrations to correlate with normal circadian rises in blood pressure when patients are most at risk from hypertension and a possible heart attack.

Orally disintegrating tablets (ODTs) are evolving into an important delivery system for drugs that treat medical conditions vulnerable to a sudden onset of symptoms. Such conditions include allergies, nausea, migraine headaches and schizophrenia. Among the available ODT technologies are Catalent Pharma Solutions' Zydys®, CIMA Labs' (Cephalon) Durasolv® and Orasolv®, and SPI Pharma's Pharmafreeze™ systems. Catalent's Zydys® technology has been the most commercially successful, and has numerous products launched through licensees.

Eli Lilly's Zyprexa® is one of the most widely prescribed drugs that have been adapted to ODT delivery. GSK's Lamictal® ODT product is the most recently approved by the FDA in this class of products. It used Eurand's technology, and is the first antiepileptic treatment available in an orally disintegrating formulation.

While there are a number of other delivery systems being developed, such as chewables and transmucosals, advances in nanotechnology have in recent times provided one of the most significant opportunities for growth, addressing the estimated 40% of drugs leaving the clinic that have poor water solubility issues.⁴ Elan Drug Technologies' NanoCrystal® technology is seen as leader in this area and recently received the Technology Innovation Award at the 14th Annual Drug Delivery Partnership Meeting in Orlando, Florida, USA.^{5,6}

Figure 2 summarises some of the most common problems encountered in the development of poorly soluble products. Oral formulations developed using the NanoCrystal® technology, compared with conventional forms, can overcome many of these obstacles. Specifically, NanoCrystal® can enhance bioavailability and thereby reduce dose and size of dosage form, provide for rapid absorption and hence rapid onset, extend the range of dose proportionality allowing for more drug to be delivered to the body, and reduce fed/fasted variability thereby enhancing safety and efficacy.

Several of these benefits are embodied in marketed solid oral products including Abbott's TriCor® 145mg, Merck's Emend® and Pfizer's

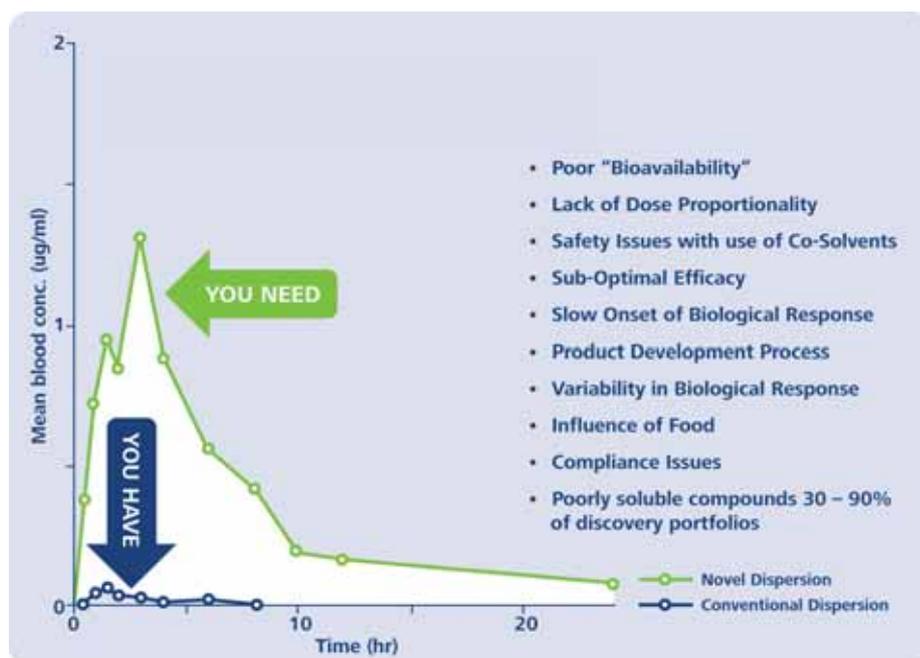
Rapamune®. In-market sales for these three products in 2008 were over US\$1.8 billion. Other technologies designed to overcome problems associated with poor water solubility include Skyepharma's IDD® solubilisation technology which has been used to launch Triglide® (Shionogi Pharma Inc), and LifeCycle Pharma's Meldose® technology which was used in Fenoglide® (also marketed by Shionogi in the US). Over the coming years, many more poorly water soluble products are expected to be launched aided by these and similar technologies.

FUTURE OPPORTUNITIES

While oral bioavailability is now considered an important feature of optimising the drug³ there are many more advances underway that will provide even further opportunity.

Mini-tablets in one system for greater flexibility

The launch of new drugs which incorporate a number of mini-tablets provides a very flexible oral dosage option which can incorporate different mini-tablets, each one formulated individually and designed to release drug at different sites so that higher dose loading is



A significant percentage of active pharmaceutical ingredients identified through discovery screening programs are poorly soluble in water. These molecules are difficult to formulate using conventional approaches, and are associated with innumerable formulation-related performance issues: poor oral bioavailability; lack of dose proportionality; and slow onset of action.

Figure 2: Delivery of poorly soluble drugs: the problem



Programmable Oral Drug Absorption System (PRODAS® technology) is Elan Drug Technologies' multiparticulate tablet technology, which combines the benefits of tableting technology within a capsule.

Figure 3: Pictorial representation of Elan Drug Technologies' PRODAS® technology

possible within the gastro-intestinal tract. It is also possible to incorporate mini-tablets of different sizes so that high drug loading is possible. The Trilipix® fenofibrate product launched by Abbott in January 2009 is comprised of a number of mini-tablets. Another technology using a similar approach is the PRODAS® delivery system by Elan Drug Technologies.⁷ A PRODAS® capsule is shown in figure 3.

Abuse-resistant delivery systems

At present there are a number of initiatives to minimise the risk associated with abuse of drugs; in particular strong pain medications. A record 36 million Americans have abused prescription drugs at least once in their lifetime, a US government study found.⁸ Pain Therapeutics was considered the front runner with its abuse-resistant formulation of oxycodone, which was formulated with DURECT's sustained-release gel-cap ORADUR® technology. In December 2008, Pain Therapeutics received a complete response letter from the US FDA for its NDA (submitted in June 2008) for REMOXY®. To date, REMOXY® has not been approved for marketing, with the FDA believing additional non-clinical data will be required to support its approval.⁹

Alpharma's morphine-based abuse-resistant opioid, Embeda™, which was licensed to King Pharmaceuticals, has become the first product of its type to gain approval. It contains morphine and a sequestered naltrexone core in an extended-release formulation. Launched in mid September 2009, a black box warning and a REMS program were conditions of the approval. In February 2010, analysts Cowen and Company estimated 2009 sales of \$15 million and expect the product to achieve sales of \$250 million by 2012.

Other drug delivery programs such as Remoxy and Acura's Acurox™ are still not approved by the FDA.¹⁰ The most recent expectation is that Acurox™ will be launched in the third quarter of 2010, with Remoxy® following in 2011. It is estimated that the market for abuse-resistant products, which will be driven by oxycodone and morphine abuse-resistant formulations, will be worth \$1.2 billion by 2017.¹¹

Alcohol dose dumping

Another challenge for the controlled release market is that of alcohol dose dumping. In 2005, Palladone® capsules were withdrawn from the market in the US and Canada due to dose-dumping when co-ingested with alcohol. Work to resolve this problem is being addressed by a significant number of companies including Flamel with its Trigger-Lock® Micropump technology. The Trigger-lock® formulation of an opioid analgesic is being studied in two clinical trials.

Egalet's key technology is an oral drug delivery system of capsules comprising a coat and a drug release matrix. The drug is distributed throughout the drug release matrix, and is released over time as the coat and matrix are eroded within the gastrointestinal tract. Egalet's technology claims to be abuse resistant (neither crushable nor injectable, resistant to fast extraction) and does not experience alcohol-induced dumping.

Other technologies designed to avoid/reduce alcohol dose dumping include Durect's

SABER™ technology, SOLIQS' Meltrex® technology and Banner's Versatrol™ controlled release softgel technology.

Combination approaches

Advances in the oral controlled release (OCR) market have seen companies looking to combine products and/or technologies to achieve better therapeutic effects. The development of drug combinations designed to help improve patient compliance has been a significant driver of the pharmaceutical industry for many years. The combination of approaches to overcome delivery problems of certain drug candidates will become more prevalent as companies push further the limits of their technologies. Combining the NanoCrystal® technology with its Oral Controlled Release Platform, Elan Drug Technologies seeks to overcome problems associated with poorly water soluble candidates, while applying any one of its OCR technology platforms to offer the additional benefits of modified or controlled release properties and allow the drug to be processed into a solid oral dosage form.

Other delivery approaches with potential

Other approaches that also have significant potential include the targeting of drug directly to the colon and also the stomach.^{12,13} Colonic drug delivery has attracted interest primarily for local delivery in diseases of the colon such as Crohn's disease, ulcerative colitis and colorectal cancer. Furthermore, it has been proposed that the colon is a better site than the small intestine to promote oral macromolecule uptake. The colon is also typically a site of drug absorption from extended-release preparations where a substantial portion of the drug is delivered to the colon.

One approach is XenoPort's proprietary Transported Prodrug™ technology, which utilises the body's natural mechanisms for actively transporting nutrients through cellular barriers to gain efficient absorption into the bloodstream. XenoPort's approach typically relies on a drug's ability to diffuse passively through the intestinal wall to enter the bloodstream and reach the targeted tissue. Its most advanced project is currently in Phase III clinical trials. Other approaches being investigated include Alizyme's Colal delivery system (also in Phase III) and Cosmo's MMX technology, which is in Phase II.

Research around gastro-retentive delivery, where dosage forms are retained in the stomach to achieve a prolonged and predictable drug delivery profile in the GI tract continues. One example is Depomed's AcuForm® – a multi-hour, gastro-retentive, controlled-release drug delivery system, which allows for targeted, controlled delivery of pharmaceuticals to the upper GI tract.

Year	Reformulations	NCEs	Total
2002	55	17	72
2003	49	21	70
2004	69	31	100
2005	64	18	82
2006	77	18	95
2007	50	16	66
2008	73	25	98
2009	75	26	101

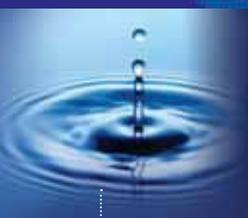
Source: Compiled by Elan Drug Technologies using US FDA website (www.fda.gov).

Figure 4: FDA approvals 2002-2009: reformulations and NCEs



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Reviewing the number of US FDA approvals over the past years, new chemical entities have accounted for only 25% of all products approved, with the majority of approvals being reformulations or combinations of previously approved products (see figure 4).¹⁴ With a new formulation costing approximately \$40 million¹⁵ and taking four to five years to develop compared with the average cost of a next-generation product (in the region of \$330 million¹⁶), the potential of reformulation using OCR technologies cannot be emphasised enough. Moreover, the development of an NCE has been estimated to cost between US\$1.3-1.7 billion.¹⁷

In the face of financial pressures, it is not surprising that more pharmaceutical companies are turning to drug delivery companies to optimise their marketed products. Analysts at PricewaterhouseCoopers believe that an extra five years’ of patent life could generate 50-100% more revenue for a product.¹⁸

There are now many drug delivery companies that offer a range of OCR solutions, plenty of which have been validated by product launches. Ongoing developments as noted here will ensure the OCR market will continue to grow in order to satisfy demand of pharmaceutical companies and patients alike.

**ABOUT THE AUTHOR AND ELAN
DRUG TECHNOLOGIES:**

Dr Gurvinder Singh Rekhi is based at Elan Drug Technologies’ Gainesville, Georgia facility. He has been instrumental in the development of a number of products that have since been commercialised – both in the US and internationally.

Elan Drug Technologies is a world leading drug delivery company which has provided oral controlled release solutions for dozens of products which have been subsequently launched worldwide. Over 1,900 patents/patent applications support its technologies.

Since 2001, 11 oral drug delivery products have been launched through licensees/partners in the US alone, making Elan the most successful drug delivery service provider worldwide over that period. Elan’s most recent oral controlled release product approval in the US uses its internally developed MXDAS™ technology. This technology was used in the development of Ampyra™ (dalfampridine), which received US FDA approval in January 2010 and was subsequently launched in March 2010.

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March 23, 2010, Saint Petersburg, Florida USA, INNERCAP Technologies, Inc., an international drug delivery and specialty pharmaceutical company, recently announced the grant of US Patent No. 7,670,612 entitled "Multi-Phase, Multi-Compartment

Capsular Delivery Apparatus and Methods for Using Same." The delivery system has uses for bio-pharmaceutical,

pharmaceutical, medical foods and nutraceutical products. In addition to the existing New Zealand patent, this patent covers the

company's multiphase multi-compartment delivery system used to

enable the development of multicompartment, multi-phase delivery forms (two piece capsule based) of combination products that have compatibility, formulation or targeted delivery obstacles.

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

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

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

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United States Patent No. 7,670,612
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THE RIGHT FORMULATION – AND HOW TO GET THERE

The objective of drug formulation is to develop a product with the correct amount of drug in the right form, and to maintain its chemical and biological integrity for delivery at or over the proper time, at the proper rate, and in the desired location. SRI International's approach to drug formulation is customised according to the client's needs and the stage of development. This article by Gita Shankar, PhD, Director of Formulations R&D, Pharmaceutical Sciences at SRI, describes the strategy that the company uses to develop an appropriate formulation.

Formulators start their task by gaining an understanding of the bulk drug's physical and chemical properties. Once the pharmaceutical profile of the drug has been determined, the appropriate route of administration can be identified and designed. Next we develop preclinical formulations, which overcome the drug's innate deficiencies. For example, a poorly soluble drug might require solubilising additives, and a poorly bioavailable drug might require a permeability enhancer.

Additional excipients are selected to overcome potential problems in processing, manufacturing and stability. Bench studies are performed on pilot batches to establish the efficacy, manufacturability and stability of dosage forms. The final formulation design is optimised to take into account the pharmacokinetic properties of absorption, distribution, metabolism, and excretion.

These steps in the drug development process are common to all routes of administration. However, this article covers only the development of oral dosage formulations.

Oral formulation has been the preferred and most common route of delivery around the globe owing to its ease of administration and good patient compliance. And from a drug development and manufacturing perspective, an oral formulation offers superior stability compared with intravenous formulations. Developing an oral formulation is by no means an easy task because each drug substance is a different entity with different characteristics.

To standardise oral formulation development, the US FDA published the biopharmaceutical classification system (BCS) guidance in 2000, which formed the basis of the scientific framework used for classifying drug

substances based on their aqueous solubility and intestinal permeability.¹

The biopharmaceutical classification system was developed primarily in the context of immediate release (IR) solid oral dosage forms. It is a drug development tool that allows estimation of the contributions of three major factors – dissolution, solubility and intestinal permeability – that affect oral drug absorption from IR solid oral dosage forms. The classification is associated with a drug dissolution and absorption model that identifies the key parameters controlling drug absorption as a set of dimensionless numbers: the absorption number, the dissolution number and the dose number.

According to the BCS, there are four classes of drug substances based solely on their solubility and intestinal permeability:

- Class I: High Solubility – High Permeability
- Class II: Low Solubility – High Permeability
- Class III: High Solubility – Low Permeability
- Class IV: Low Solubility – Low Permeability

Class I drugs exhibit a high absorption number and a high dissolution number. The rate-limiting step is drug dissolution; if dissolution is very rapid, then the gastric emptying rate becomes the rate-determining step. Metoprolol, diltiazem, verapamil, and propranolol are examples of Class I drugs.

Class II drugs have a high absorption number but a low dissolution number. *In vivo* drug dissolution is then a rate-limiting step for absorption except at a very high dose number. The absorption rate for Class II drugs is usually slower than the rate for Class I drugs and absorption occurs over a longer period. Phenytoin, danazol,



Figure 1: High Throughput Liquid Handling System.



Gita Shankar, PhD
Director of Formulations R&D,
Pharmaceutical Sciences
T: +1 650 859 2000
F: +1 650 859 3041
E: gita.shankar@sri.com

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Binary Combinations (1:1)		Ternary Combinations (1:1:1)	
Solvent Combination	Abbreviation	Solvent Combination	Abbreviation
Ethanol / Water	Eth Wat	Ethanol / Water / PEG400	Eth Wat PEG
Ethanol / PEG400	Eth PEG	Ethanol / Water / Propylene Glycol	Eth Wat PG
Ethanol / Propylene Glycol	Eth PG	Ethanol / Water / Tween80	Eth Wat Twe
Ethanol / Tween80	Eth Twe	Ethanol / Water / Glycerin	Eth Wat Gly
Ethanol / Glycerin	Eth Gly	Ethanol / PEG400 / Propylene Glycol	Eth PEG PG
Water / PEG400	Wat PEG	Ethanol / PEG400 / Tween80	Eth PEG Twe
Water / Propylene Glycol	Wat PG	Ethanol / PEG400 / Glycerin	Eth PEG Gly
Water / Tween80	Wat Twe	Ethanol / Propylene Glycol / Tween80	Eth PG Twe
Water / Glycerin	Wat Gly	Ethanol / Propylene Glycol / Glycerin	Eth PG Gly
PEG400 / Propylene Glycol	PEG PG	Ethanol / Tween80 / Glycerin	Eth Twe Gly
PEG400 / Tween80	PEG Twe	Water / PEG400 / Propylene Glycol	Wat PEG PG
PEG400 / Glycerin	PEG Gly	Water / PEG400 / Tween80	Wat PEG Twe
Propylene / Glycol / Tween80	PG Twe	Water / PEG400 / Glycerin	Wat PEG Gly
Propylene Glycol / Glycerin	PG Gly	Water / Propylene Glycol / Tween80	Wat PG Twe
Tween80 / Glycerin	Twe Gly	Water / Propylene Glycol / Glycerin	Wat PG Gly
		Water / Tween80 / Glycerin	Wat Twe Gly
		PEG400 / Propylene Glycol / Tween80	PEG PG Twe
		PEG400 / Propylene Glycol / Glycerin	PEG PG Gly
		PEG400 / Tween80 / Glycerin	PEG Twe Gly
		Propylene Glycol / Tween80 / Glycerin	PG Twe Gly

Figure 2: Solvent combinations (SRI's Level 1 screen) used for the paclitaxel solubility study. (Concentrations: ethanol X%v/v in water; water 100%; PEG400 100%; propylene glycol Y%v/v in water; Tween80 Z%v/v in water, and glycerin A%v/v in water).

ketoconazole, mefenamic acid, and nifedipine are examples of Class II drugs. *In vitro-in vivo* correlation (IVIVC) is usually expected for Class I and Class II drugs.

For Class III drugs, permeability is the rate-limiting step for drug absorption. These drugs exhibit a high variation in the rate and extent of drug absorption. Cimetidine, acyclovir, neomycin B and captopril are examples of Class III drugs.

Class IV drugs exhibit a many characteristics that are problematic for effective oral administration. A decade back, extreme examples of Class

IV compounds were an exception rather than the rule, yet today about 10% of the drug candidates under development fall into this category. A well-known example of a Class IV drug is paclitaxel.

PROPRIETARY HIGH-THROUGHPUT SOLUBILITY SCREENING SYSTEM

In recent years, there has been an increase in the drugs that fall into BCS Classes II, III and IV. Of these, Class II and IV pertain to drugs that are poorly water soluble. Currently, more than

one-third of the drugs listed in the US Pharmacopoeia are poorly water soluble. Poor solubility leads to significant hurdles in the oral absorption and bioavailability of the drug candidate by decreasing its dissolution rate and membrane permeation.

SRI has developed its own proprietary solvent screening system, which is both economical and fast. This system, which we call the High-Throughput Solubility Screening (HTSS) system, uses minimal drug quantities, since in its early development stages, availability of the drug is limited.

Our proprietary screening system is based on a High-Throughput Liquid Handling Instrument (see figure 1) which is used to prepare the excipient combinations. This instrument is programmed for aspirating and dispensing the solvents/excipients. A predetermined volume of the cosolvent combinations are dispensed into each well in a microtiter plate. After solvent addition, the plates are shaken in a controlled environment for an extended period. Levels of solubility are read using the baseline turbidity of the excipient.

A software program is used to control the solvent combinations and the analytical outputs. Different level screens of solvent combinations are available to address different formulation options. A stock solution of the drug is prepared either in absolute alcohol or DMSO and added into plates prefilled with the premixed cosolvent combinations. The plates are again shaken and analysed using the turbidity reader. Solubility is assessed by the change in turbidity before and after addition of the drug in the solvent system.

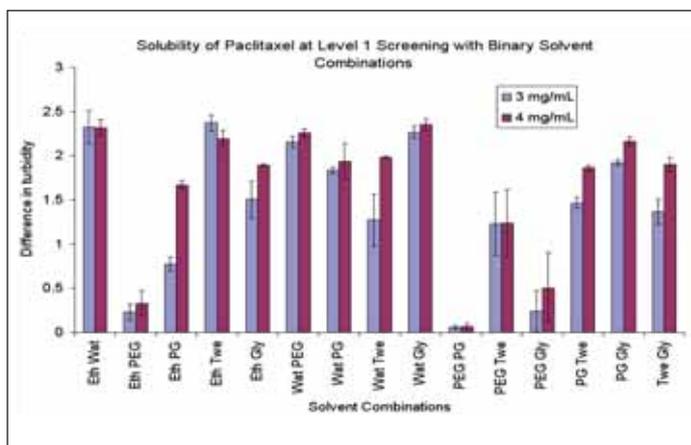


Figure 3: Solubility of paclitaxel (3 and 4mg/mL) with binary combinations of six solvents

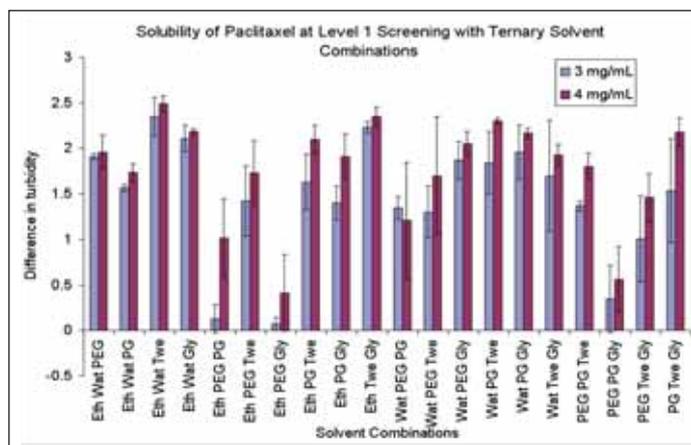


Figure 4: Solubility of paclitaxel (3 and 4 mg/mL) with ternary combinations of six solvents



Figure 5: Top: Ussing absorption unit; Bottom: Slider with the intestinal tissues being mounted between the side-by-side compartmental unit of the Ussing system.

The following is an example of the strategy employed in developing a formulation for a model drug substance, in this case, paclitaxel.

SRI EXAMPLE

A total of 35 solvent combinations (listed in figure 2) were generated by the software using the six solubilising excipients in binary and ternary combinations at a 1:1 and 1:1:1 ratio, respectively. Paclitaxel stock solutions were prepared in absolute ethanol and dispensed into each of the micro-titer plates containing solvent combinations to obtain the desired final concentrations of 3 and 4 mg/mL. Turbidity was measured using the plate reader.

Figures 3 and 4 show the solubility profiles of paclitaxel in both binary and ternary combinations as obtained from the HTSS. In these figures, the longer bars represent more turbidity in the formulation. Based on this analysis, we were able to narrow down a few cosolvent-based formulations options for paclitaxel, which were then tested in a pharmacokinetic study.

PROPRIETARY *IN VITRO* PERMEATION SYSTEM

Although Class III and Class IV drugs are poorly absorbed substances, in recent times there has been an increase in drug products falling into these categories owing to newer formulation options. Class III compounds are drug substances that are sometimes highly water

soluble, but they do not have the appropriate hydrophobic-hydrophilic balance to be absorbed by the intestinal epithelium.

Developing an oral formulation for these compounds sometimes requires imparting the right hydrophobic-hydrophilic balance to improve the GI-permeation of the drug. In this step in the drug development process, SRI uses an *in vitro* screen known as the Ussing Permeation System to rank-order formulations on the basis of their permeability.

The system at SRI is a modified Ussing system (shown at the top of figure 5) that has multiple sets of side-by-side chambers and is used for *in vitro* studies. Each set consists of two side-by-side diffusion chambers, a heating block for temperature control, needle valves for gas flow adjustment and gas mixing, and Ag/AgCl voltage and current electrodes for measuring transepithelial voltage and for passing current.

Harvested segments of small intestine or colon are mounted on sliders placed between the two horizontal chambers of the modified Ussing system (bottom of figure 5). One of the chambers is exposed to the mucosal side of the intestinal segment and the other to the serosal side.

For drug transport across epithelial membranes of harvested rat small intestine and colon segments in the mucosal-to-serosal (M-to-S) direction, aliquots of buffer are added to both the mucosal and serosal chambers. The buffer in the mucosal chamber is replaced with a solution of the drug formulation. Aliquots of buffer solutions are removed periodically from the serosal chambers and are replaced with equal volumes of fresh warm buffer previously saturated with 100% O₂.

Changes in transepithelial short-circuit current (in micro-Amps) and membrane resistance (in Ohms) as a function of time are monitored continuously during *in vitro* studies to serve as indicators of tissue viability and drug permeability, respectively.

The buffer samples from the receptor chambers are analysed for drug content on a high pressure liquid chromatograph (HPLC). Owing to the expected variation for *in vitro* test conditions and harvested rat intestinal segments, four replicates are used per experimental condition.

Apparent Permeability Coefficient (P_{app})

Calculation:

To compare data obtained from different *in vitro* experiments, the apparent permeability coefficients are calculated using the equation:

$$P_{app} = \frac{dQ / dt}{C_0 \times A}$$

where dQ/dt is the linear appearance rate of mass in the receiver compartment, C₀ is the ini-

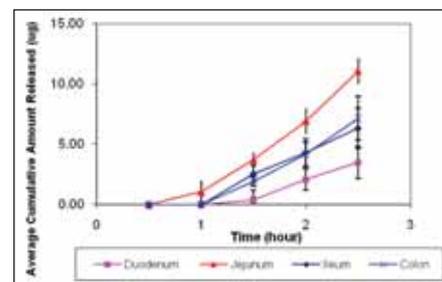


Figure 6: Drug transport in the mucosal-to-serosal direction, across different segments of rat intestine and colon, from buffer.

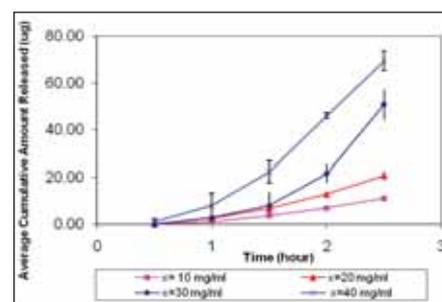


Figure 7: Effect of drug concentration on transport in the mucosal-to-serosal direction across rat jejunum, from buffer.

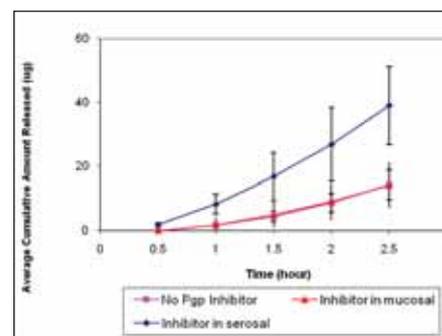


Figure 8: Effect of a known Pgp inhibitor on drug transport in the mucosal-to-serosal direction across rat jejunum.

tial solute concentration in the donor compartment, and A is the surface area.²

The following is an example of the strategy employed in developing a formulation for a model BCS Class III drug substance.

SRI EXAMPLE

Figures 6, 7 and 8 illustrate this strategy for a poorly permeable drug substance. The plot between the amount of drug transported through the different regions of the intestine from the mucosal to the serosal side for the drug at a given concentration and formulation is presented in figure 6.

The cumulative amount of drug transported through jejunum fragments of the intestine from the mucosal to the serosal side

at increasing drug dose concentrations (in the same formulation), is shown in figure 7.

Figure 8 presents data obtained from using a Pgp (permeability glycoprotein) inhibitor, which was placed either on the mucosal side or on the serosal side, compared with that without an inhibitor. In this figure, the dose, formulation, and kind of intestinal segment used are constant. Similar data compilation continues until all conditions and formulation options are covered.

Based on calculated P_{app} values (data not shown) obtained from *in vitro*

data, the rate of M-to-S transport of drug was found to be highest in jejunum, followed by colon and ileum, and lowest in duodenum (figure 6). Increasing the concentration of drug in the mucosal (donor) chamber increased M-to-S transport of drug in a dose-dependent manner (figure 7). Increased M-to-S transport of drug was observed *in vitro*, when a known Pgp inhibitor was added to the mucosal or serosal chambers. Addition of a known Pgp inhibitor to the serosal chamber caused a dramatic (three-fold) increase in M-to-S transport of drug. Addition of inhibitor to the mucosal chamber also increased M-to-S transport of drug, but to a lesser extent (figure 8).

The above observations are indicative of the significant role of presystemic elimination processes in poor permeation of drug across the GI tract. The secretory transporters involved may include Pgp, the family of multi-drug-resistance-associated proteins (MRP), and possibly other transporters operating across the GI tract.

SRI's strategy is to study the permeation properties of the drug substance *in vitro* with and without added permeation and solubility enhancers. Experiments are also conducted in the presence and absence of inhibitors of efflux proteins (glycoproteins that pump out the absorbed drugs through independent pathways, resulting in a net decrease in the amount of drug in the serosal side). If the drug substance is found to be influenced by the efflux proteins, the formulation strategy will include inhibition of those proteins.

IN SITU PHARMACOKINETIC DATA BY INTRA-DUODENAL ADMINISTRATION IN RATS

Once the *in vitro* permeation data has been obtained, we determine the pharmacokinetic parameters of the drug in the presence of various formulation additives/permeation enhancers upon intra-duodenal administration

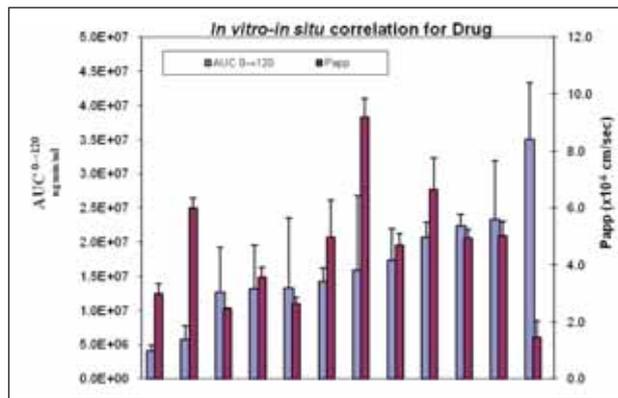


Figure 9: AUC versus P_{app} values obtained for different drug formulations

in rats. The *in situ* absorption of the drug in the presence of the various additives and enhancers and upon intra-intestinal administration is evaluated in healthy rats. The rats are fasted overnight and anaesthetised so that the abdomen can be opened for isolation of GI tract. Ligatures are placed above the mid-duodenum and below the mid-jejunum, and an intestinal dosing receptacle is created; the drug is then administered into the lumen of intestine by injecting formulation compositions at mid-duodenum level. Blood samples are collected pre- and post-dose, processed for collection of plasma, and analysed by LC-MS.

Selection of formulation additive combinations is based on the P_{app} values obtained from comparative *in vitro* studies. The absorption of the drug is determined by calculating the area under the plasma drug concentration versus time curve (AUC). Based on the results from *in vitro* and *in situ* studies, AUC values obtained are compared with the corresponding P_{app} values calculated using *in vitro* experimental data. Figure 9 is a bar graph comparing the AUC values with their corresponding P_{app} values for the different compositions studied.

In vitro studies using the Ussing system may be useful for determining the preferential site of drug absorption for BCS Class III/IV drugs, and for screening and selection of formulation additives as permeation enhancers. *In situ* studies would further facilitate optimising the concentrations and ratios of additives used, therefore reducing the cost and number of *in vivo* evaluations for formulation optimisation. *In vitro-in situ* correlations performed in our laboratories have indicated that it is difficult to predict the *in vivo* performance of different formulation additives solely based on *in vitro* transport studies using isolated intestinal segments at higher concentrations of permeation enhancers or when paracellular transport is the mode of drug absorption.

CONCLUSION

Now is the time for integrating high-throughput experimental techniques into the preformulation and formulation steps in the drug discovery process. Companies are screening larger numbers of drug candidates than ever before, and the decision to choose one drug candidate over another has become more complicated because increasing numbers of these drugs fall into BCS Classes II to IV.

The decision to choose a poorly soluble drug over a more soluble counterpart may be required for improved efficacy and safety, if the formulation can address the solubility issues. In drug discovery, time is of essence, and a fast *in vitro* method is required to screen the drug in the formulation alongside the drug itself.

No longer is it the drug alone, but the drug in combination with its formulation additives, that determine the probability of success for that molecule. SRI International has successfully used the above strategy for many client companies, helping these companies screen out many potential drug candidates at a faster rate. We anticipate that the next few years will see many such time- and resource-saving revolutions in the way we attempt to develop these formulations.

ACKNOWLEDGEMENTS

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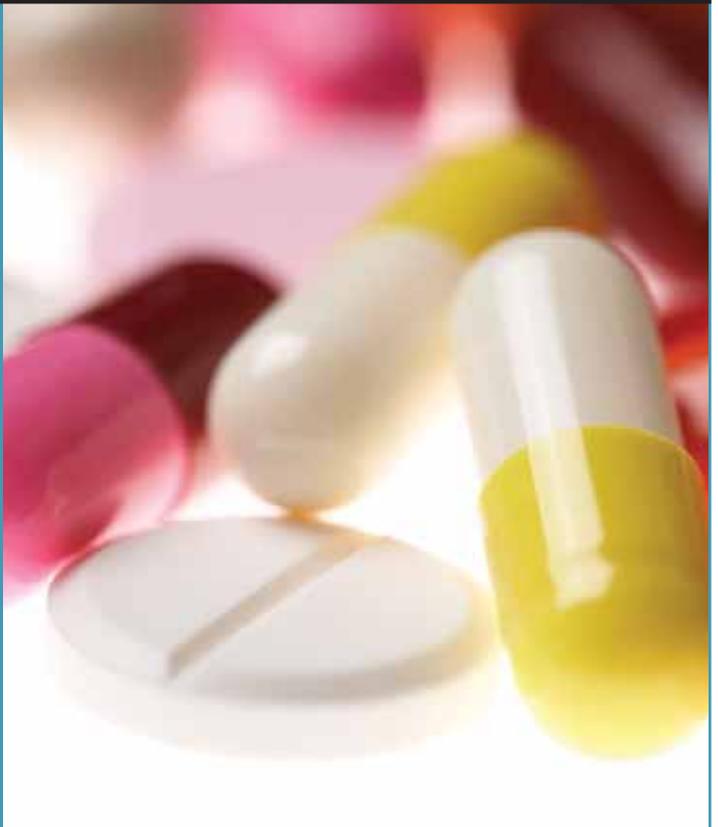
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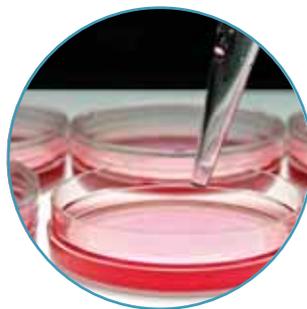
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SOLUBEST'S SOLUMER™ SOLUBILISING PLATFORM: AN "ALL IN ONE" TECHNOLOGY

Recently SoluBest has implemented a significant strategy shift: from developing proprietary pipeline products that would compete in the nano-generic space, to a licensing-based model where its unique solubilisation platform, Solumer™, is used by clients to formulate their pipeline molecules, both for discovery and marketed products. The platform is currently being tested by multiple companies, from CMOs/CROs to drug delivery/specialty pharma companies and large pharmas. In this article, Amir Zalcenstein PhD, MBA, Senior Director, Business Development and Planning at Solubest, describes Solumer, its applications and reports proof-of-concept study data.

Solubility, or the lack of it, is one of the most prevalent problems in drug development. A number of non-proprietary solubilisation methods exist – for example, salt creation and solubilisation by co-solvents, amongst others – but these are often suboptimal. Furthermore, recent years have seen high-throughput discovery technologies uncover vast numbers of insoluble compounds demanding both more versatile and friendly solubilisation solutions.

The advent of nanotechnology, most significantly Elan's NanoCrystal technology, pioneered the first generation of solubilisation technologies which affected solubility through particle size reduction to a nano-scale, employing sophisticated milling methodologies.

Solid dispersions have been repeatedly noted as a most promising approach for formulation development as they have inherent advantages over other approaches: namely straightforward processing of an API into a molecular or nanoparticle dispersion which shows enhanced bioavailability.

However, only a very small number of products on the market incorporate solid dispersions as they present a number of significant problems, including: laborious methodologies; difficulties in particle characterisation; limited *in vivo* proofs of concept; complications in conversion into suitable dosage forms; batch reproducibility issues; problems in process scale-up and manufacturing; and, perhaps most significantly, inherent instability. It is recognised that a technology able to overcome these challenges would be highly desirable.

SoluBest has taken on this challenge and in the last four years has developed a proprietary platform for the creation of solid dispersions which effectively and reproducibly improves the bioavailability of insoluble drugs. The platform, referred to as Solumer™, is robust, versatile, and is readily and cost effectively implementable towards a wide range of molecules.

THE TECHNOLOGY

Solumerisation is based on the self assembly of select components, enabling the design and production of new polymer-drug constructs with well defined physico-chemical properties. Leveraging the thermodynamic behavior of amphiphilic and hydrophilic polymers in mixed solvents, SoluBest's platform creates drug-polymer solid dispersions in which the lipophilic drug is interwoven within a multi-polymer entity. The drug in this solid dispersion is homogeneously dispersed in the polymer matrix. In addition, due to the interaction with the amphiphilic polymer, *Solumerised* drugs exhibit modified physico-chemical properties (for example, decreased enthalpy and temperature of melting) compared with the crystalline lipophilic APIs.

Candidate molecules' solubility parameters are used as a semi-empirical tool to predict component interactions, facilitating their selection and accelerating the development process. Once selected, the optimal ratios of specific amphiphilic and hydrophilic polymers yield solid dispersions with a unique built-in hydrophobic-hydrophilic gradient. This gradient ena-

Amir Zalcenstein, PhD, MBA
Senior Director, Business
Development & Planning
T: +972 8 940 3023 x102
F: +972 8 930 2878
E: amir@solubest.com

SoluBest Ltd
Weizmann Science Park
POB 4053
18 Einstein Street
Ness Ziona 74140
Israel

www.solubest.com

bles the rapid disintegration of the powder in aqueous media generating easily measurable colloidal nanodispersions.

For our purposes, amphiphilic polymers are those soluble both in organic solvents and in water (PEG and Poloxamer, for example), while hydrophilic polymers are those soluble in water or in a mixture of organic solvent and water, but not in organic solvent alone (sodium carboxymethylcellulose and chitosan, for example).

Significantly, SoluBest formulations utilise only US FDA-approved polymers in the amounts appropriately noted in the Inactive Ingredients List.

The Solumer process is an easily scalable two-step methodology (see figure 1). In step one, a liquid feed is prepared which is a homogeneous solution of the lipophilic drug and at least two polymers in a mixed solvent (organic solvent–water). In step two, the solution is spray-dried to obtain a well characterised powder. There are no additional intermediate steps, nor post-drying steps required. The simplicity of the methodology eliminates the drawbacks associated with other nanoparticle platforms (such as agglomeration of nanoparticles or degradation under shear force) as it does not necessitate isolation of nanoparticles during processing.

It is in fact exactly the simplicity of the process that makes it readily amenable in an industrial setting. Spray drying is an inherently flexible, continuous and automatic process. Moreover, spray dryers are common in pharmaceutical plants; as the process requires no equipment modification it can be easily implemented without increasing the manufacturing footprint.

The resultant spray-dried powder is well-defined and exhibits the collective unique “fingerprints” of a Solumer solid dispersion:

- Solubilised drug homogeneously interwoven into a polymer matrix
- Modified thermal behaviour: depressed melting temperature and enthalpy of melting
- Spontaneous formation of nano-colloidal dispersions upon contact with aqueous media
- Enhanced dissolution rate/solubility of the drug as well as the ability to achieve prolonged supersaturation in dissolution media and model biological fluids

Validated with multiple proofs of concept, the Solumer platform has been shown to avoid pitfalls common with other solid dispersion techniques. Namely, Solumer has been shown to generate formulations which are: a) clinically proven to enhance bioavailability (or show bioequivalence to marketed nano-

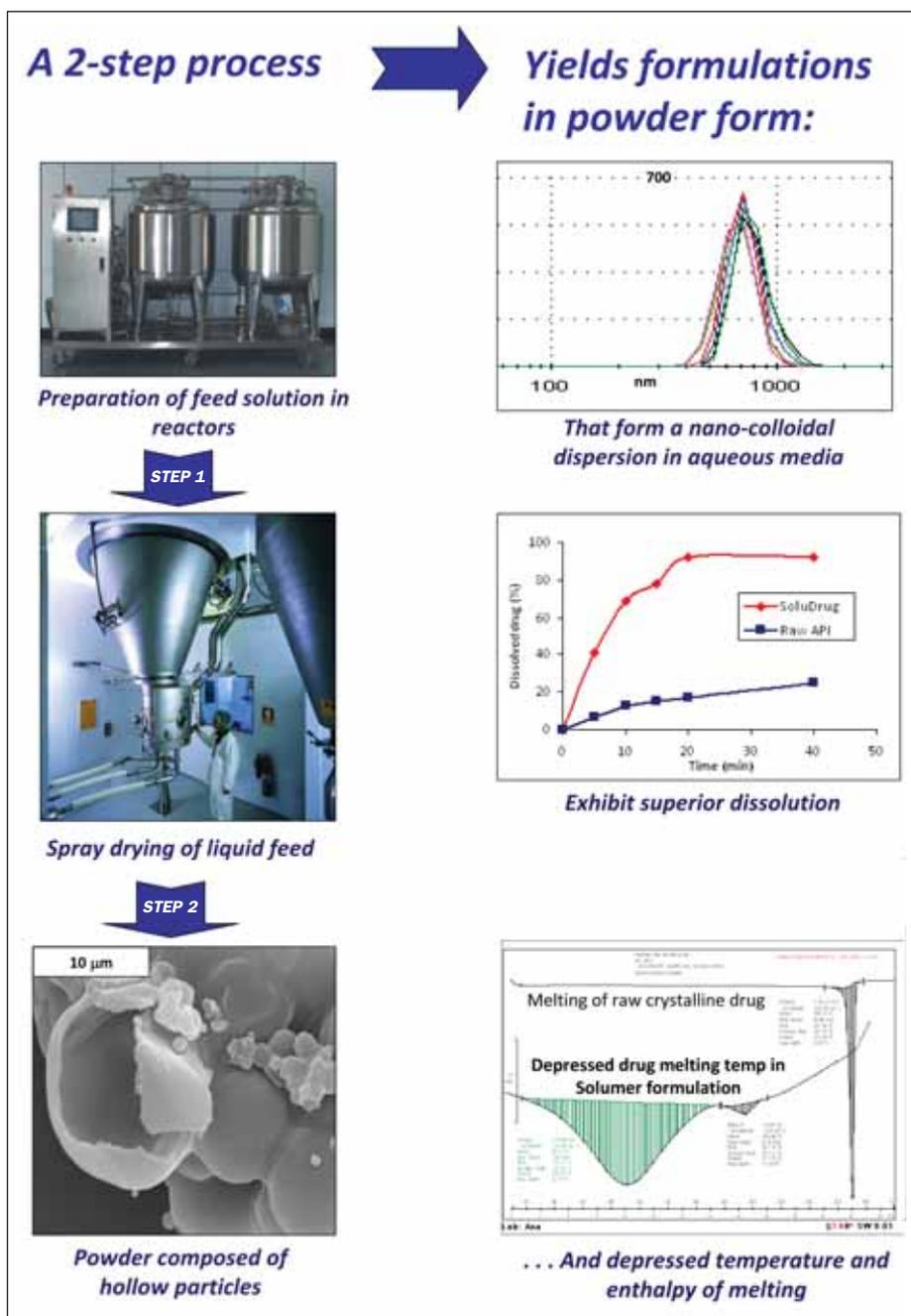


Figure 1: A brief overview of the Solumer process and the resulting formulations unique characteristics

products); b) reproducible on a batch-to-batch basis; c) stable (measured up to two years in accelerated conditions); and d) amenable to industrial scale-up. The results of SoluBest’s preclinical and exploratory clinical trials are discussed below.

Finally, and perhaps most significantly from a commercial point of view, the Solumer platform has a clear advantage in terms of project “turnaround time”. The elegantly simple methodology allows SoluBest to generate initial formulations in as little as 2-3 weeks, while progressing from feasibility studies to pilot clinical formulations and industrial scale-up can be achieved in as little as six months.

PROOF OF CONCEPT 1: ALBENDAZOLE

Albendazole is an insoluble anti-helminthic medication. The Solumer formulation of this drug yielded a composition with decreased temperature and enthalpy of melting (161°C from 215°C and 31 J/g from 210 J/g respectively, DSC). X-ray analysis indicated that the active compound in the SoluBest formulation has a crystalline structure with effective crystallite size of 33 nm. Laser diffraction and dynamic light scattering analysis showed that upon disintegration in water the formulated powder forms a colloidal dispersion with a mean particle size of 419 nm.

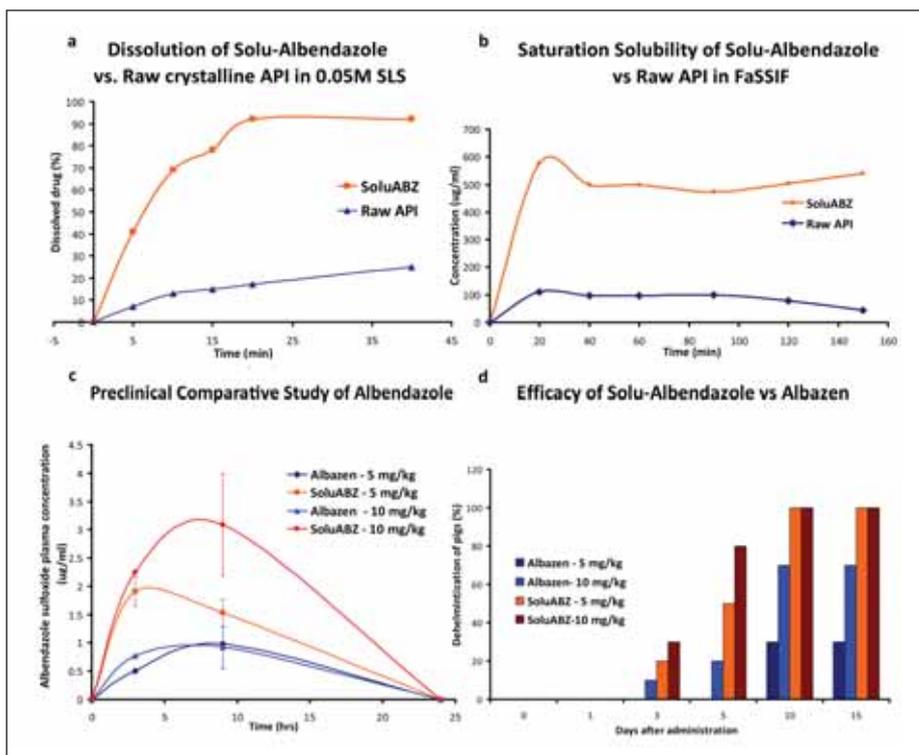


Figure 2: a) Dissolution of SoluAlbendazole vs raw bulk material in SLS; b) supersaturation in physiological media, fasted state simulating intestinal fluid (FaSSIF); c) a comparative evaluation of bioavailability of Solu-Albendazole and a commercial formulation (Albazen). A total of 40 spontaneously infected pigs were treated with oral suspensions at doses of 5 and 10 mg/kg; d) therapeutic efficacy was estimated through coproscopy on days 0, 1, 3, 5, 10 and 15.

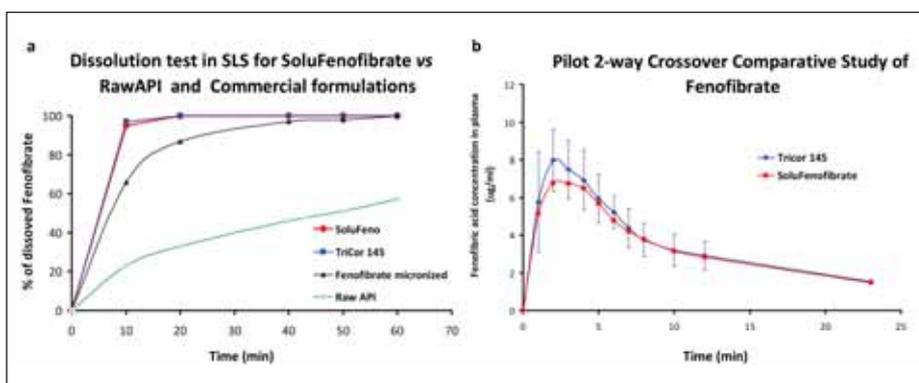


Figure 3: a) Dissolution rate of Solumerised fenofibrate compared with raw API, commercial micronised Fenofibrate, and TriCor 145; b) results of a randomised crossover study on 12 healthy volunteers comparing a single 145mg dose of Solumerised fenofibrate with TriCor 145 under fasted conditions.

Formulation	Mean pharmacokinetic parameters		
	C_{max} (µg/ml)	AUC_t (µg·hr/ml)	T_{max} (hr)
TriCor 145	8.10 ± 1.63	113.9 ± 38.70	2.0 ± 0.8
SoluFeno	7.06 ± 1.16	109.20 ± 37.45	3.0 ± 0.8
SoluFeno / TriCor 145	0.87	0.98	-
90 % Confidence intervals	0.76 – 1.01	0.91 – 1.01	-

Figure 4: Summary table of Tricor 145 pharmacokinetics compared with Solu-Fenofibrate

Together, these properties result in a high dissolution rate of *Solumerised* albendazole in sodium lauryl sulfate (SLS) (see figure 2a) and its ability to reach supersaturation solubility in physiological media, exemplified by fasted state simulating intestinal fluid (FaSSIF) (see figure 2b).

Subsequent *in vivo* studies in pigs validated the correlation between the formulation's physico-chemical properties and its bioavailability. A comparative study between SoluBest's formulation and commercially available albendazole (Albazen) showed that oral absorption of albendazole administered as Solu-Albendazole is significantly higher than its absorption from Albazen suspension. Solu-Albendazole exhibits a clear dose dependence, while Albazen does not.

A comparison of both formulations' anti-helminthic activity (figure 2d) clearly favours Solu-Albendazole, achieving complete dehelminthiation within 10 days at the lowest dose, a result not obtained with even the highest dose of Albazene. Thus, this study demonstrated good correlation between the *in vitro* and *in vivo* behavior of *Solumerised* albendazole, as well as a correlation between improved bioavailability and efficacy.

PROOF OF CONCEPT STUDY 2: FENOFIBRATE

Fenofibrate, a cardiovascular drug used to lower triglyceride and cholesterol levels, is practically insoluble in water. When *Solumerised*, the composition yields a formulation with decreased temperature and enthalpy of fenofibrate melting (64.4°C down from 82°C and 9.3 J/g down from 74.3 J/g, DSC). X-ray analysis indicated the effective crystalline size of formulated fenofibrate at about 40 nm. Disintegration of formulated powder in water results in a colloidal dispersion with a mean particle size of 774 nm as measured by dynamic light scattering. These collective properties result in a higher dissolution rate of solubilised fenofibrate when compared with the raw API and commercially available micronised fenofibrate. Indeed, the formulation's dissolution was shown to be virtually identical to the market leading nano-formulation of this drug, Abbot's TriCor 145 (figure 3a).

To determine Solu-Fenofibrate's bioavailability in comparison with a reference product (TriCor 145) a randomised crossover study was conducted in 12 healthy volunteers. The results of this pharmacokinetic study are presented in figures 3b and 4. The geometric mean of test/reference ratios for AUC and C_{max} values fall well within the accepted limits for bioequivalence, while some subject values for C_{max} fell outside the accepted confidence interval. It is expected that a larger study

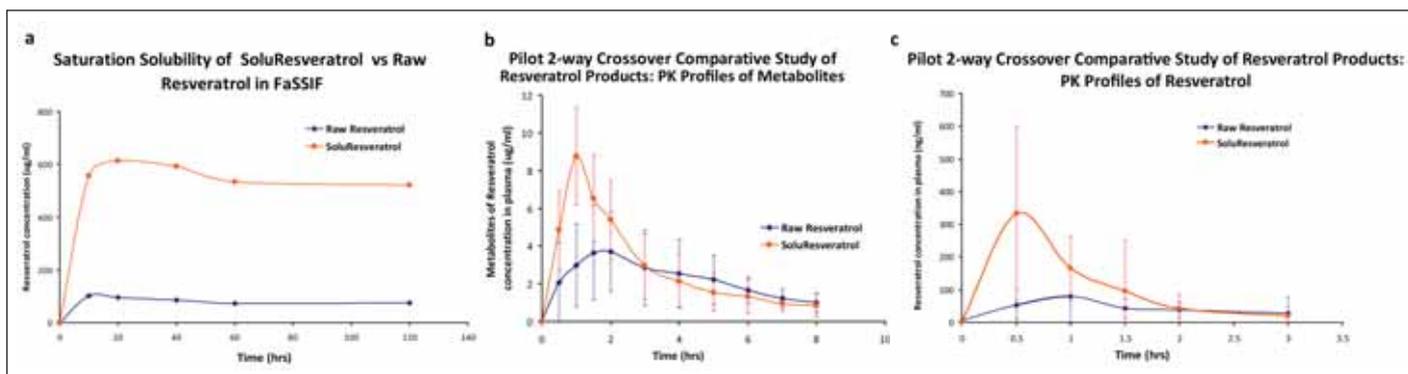


Figure 5: a) Saturation solubility for Solumerised Resveratrol vs raw API in a fast state simulating intestinal fluid; b,c) an exploratory clinical study comparing Solumerised Resveratrol with the raw API.

would ameliorate this problem. There is some potential for increasing the C_{max} in the course of tablet development with the appropriate excipients. Notably, the administration of the Solu-Fenofibrate formulation did not result in any adverse effects or abnormal changes of the blood and urine parameters.

PROOF OF CONCEPT 3: RESVERATROL

Resveratrol is a small-molecule activator of sirtuins, enzymes which may control age-related disorders in various organisms and in humans. Resveratrol is practically insoluble in aqueous media, demonstrates very low bioavailability and rapid, extensive metabolism resulting in only trace amounts of unchanged resveratrol in the systemic circulation.

The physico-chemical characteristics of resveratrol are similar to other lipophilic small molecules, which are appropriate candidates for *Solumerisation*. The Solumer formulation of resveratrol yields a composition including only the active form of the compound – trans-resveratrol. As demonstrated with other formulations, *Solumerised* resveratrol possesses

decreased temperature and enthalpy of melting (199°C from 267°C and 14 J/g from 254 J/g, respectively, as measured by DSC). X-ray analysis indicated that the effective crystallite size of formulated resveratrol is 45 nm. Disintegration of the formulated powder in water results in a colloidal dispersion with a mean particle size of 1244 nm as shown by laser diffraction analysis. These collective properties impact a significantly increased saturation solubility for *Solumerised* resveratrol versus raw API in a FaSSiF (figure 5a).

The above *in vitro* data correlates well with the enhanced bioavailability of Solu-Resveratrol demonstrated in an exploratory clinical study. The two-way crossover randomised trial in 12 healthy volunteers was carried out with a single oral administration resveratrol 500mg under fasting conditions. *Solumerised* resveratrol (test) and raw API (control) were administered as a powder dispersed in water. Plasma concentrations of resveratrol and its metabolites were analysed by HPLC-UV with complementary LC-MS analysis.

The results of these pharmacokinetic studies are depicted in figures 5b, 5c and 6. As can be clearly seen from the data presented, a

significantly higher bioavailability was demonstrated using *Solumerised* resveratrol, not only for the total resveratrol metabolites but also for intact resveratrol.

SOLUBEST'S COMMERCIAL DIRECTION & VALUE PROPOSITION

SoluBest intends to become a major player in the field of oral nano-formulations for solubility-compromised drugs. As such, SoluBest's general strategy calls for the inclusion of the technology in as many drug products as possible. Thus, our first milestone is to gain industry validation, and to this end SoluBest has engaged multiple parties in its "Formulate-it-Free" initiative which took place during the first quarter of 2010. Interested parties were welcomed to formulate their selected drugs using the Solumer platform with no commitment.

SoluBest is confident that this approach, designed to demonstrate the platform's capabilities, will encourage participants to progress towards development and licensing while convincing other clients to come aboard with their solubility-compromised drug candidates.

This thus reflects SoluBest's priorities: first to gain recognition of our solubilisation solution, and then leverage this recognition in order to secure multiple partnership deals with drug developers.

We both welcome and encourage interested parties to approach SoluBest and inquire about the suitability of their molecules to our platform. Our strength lies in our ability to turn around projects quickly and cost effectively, allowing clients to evaluate the technology rapidly, with minimum risk and commitment – both in the feasibility stage, and throughout the development process.

Formulation	Resveratrol			Resveratrol Total Metabolites			
	Mean AUC_t (ng·hr/ml)	Mean C_{max} (ng/ml)	Median T_{max} (hr)	Mean AUC_{inf} (ng·hr/ml)	Mean AUC_t (ng·hr/ml)	Mean C_{max} (ng/ml)	Median T_{max} (hr)
SoluResveratrol	504	330	0.50	28410	27600	8820	1.00
Raw Resveratrol	331	111	2.00	23960	22430	4160	1.50
Test / Reference	1.52	2.97	-	1.19	1.23	2.12	-
90% Confidence Intervals	0.90-2.58	1.95-4.54	-	0.95-1.48	0.97-1.56	1.58-2.83	-
Statistical Significant	NS*	<0.00009	<0.0013	NS*	NS*	<0.0009	<0.003

* NS = No statistically significant difference

Figure 6: Summary table of resveratrol and metabolite pharmacokinetics – test compound (Solu-Resveratrol) compared with reference compound (raw resveratrol API)



**How far could you go with a
Nanotechnology platform that's simple,
reliable, and cost effective?**

SoluBest's Solumer technology:

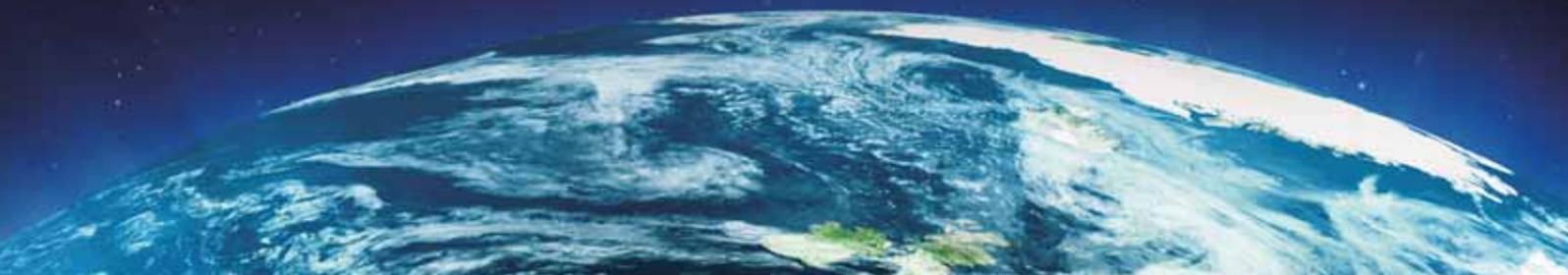
A Robust, 2-step process for solubilization of insoluble
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ONdrugDelivery EDITORIAL CALENDAR

Publication Month	Issue Topic	Materials Deadline
May 2010	Delivering Injectables: formulation focus	n/a
June 2010	Delivering Injectables: device focus	June 4th
July 2010	Targeted Drug Delivery	July 2nd
September 2010	Needle-Free Injection Devices	August 7th
October 2010	Prefilled Syringes	September 3rd
November 2010	OINDP (Pulmonary & Nasal Delivery)	October 1st
December 2010	Delivering Biologics: proteins, peptides & nucleotides	November 5th
January 2011	Prefilled Syringes	December 6th
February 2011	Oral Drug Delivery & Advanced Excipients	January 3rd
March 2011	Transdermal Delivery	February 7th



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ORALLY DISINTEGRATING EXTENDED RELEASE (ODT-ER) DOSAGE FORMS

In this article, Woubalem Birmachu, PhD, Senior Manager of New Technology at CIMA Labs, summarises CIMA's ability to combine orally disintegrating tablet technology with extended release delivery systems, providing all of the benefits of these two drug delivery technologies in a single pharmaceutical product.

The goal of controlled-release drug delivery systems is to provide the optimum dosage of a drug so as to increase efficacy, reduce side effects and increase patient compliance. Extended release (ER) formulations enable less frequent dosing of drugs with short half lives and avoid the 'peaks and troughs' of drug plas-

(GERD) and inflammation of the oesophagus, oesophagitis as well as oesophageal cancer. In these cases, rapidly disintegrating dosage forms which melt in the mouth add great clinical value.

CIMA builds on its expertise in taste-masking and orally disintegrating tablet technology to develop orally disintegrating extended release (ODT-

**"CIMA BUILDS ON ITS EXPERTISE
IN TASTE-MASKING AND
ORALLY DISINTEGRATING TABLET
TECHNOLOGY TO DEVELOP ORALLY
DISINTEGRATING EXTENDED RELEASE
(ODT-ER) DOSAGE FORMS"**

ER) dosage forms. A variety of different solvents and polymer systems are utilised to encapsulate the drug, resulting in polymer-coated fine particles. These particles are then incorporated into an ODT matrix. The resulting ODTs are capable of providing a variety of custom release profiles ranging from immediate-release to enteric-coated, delayed release to

ma concentrations associated with rapid release drugs and the resulting time variant efficacy.

The drug plasma concentrations remain inside the therapeutic range for a longer period of time compared with conventional rapid-release formulations. Once-a-day extended-release formulations provide an additional advantage for the paediatric population and adult patient populations where compliance is an issue.

Orally disintegrating tablets (ODT) which melt fast in the mouth are easy to swallow and easy to administer to paediatric populations and increase patient compliance in this population.

These dosage forms also provide additional advantages for patients who experience dysphagia (difficulty swallowing). Dysphagia may result as a consequence of neurological disorders such as stroke, brain or spinal cord injury, multiple sclerosis, muscular dystrophy, or Parkinson's disease. Dysphagia may also result from gastro-intestinal disorders such as gastro-oesophageal reflux disease

extended-release, once-daily formulations.

EXTENDED RELEASE ORALLY DISINTEGRATING TABLET TECHNOLOGY

Using its OraSolv[®], DuraSolv[®] and Lyoc[™] technologies CIMA has been successful in the formulation of orally disintegrating tablets (ODT) with extended-release profiles.

These ODT technologies meet the CDER definition of an ODT: "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue".

ODTs are popular because they offer many advantages to patients and physicians, such as:

- Convenience – can be taken with or without water.
- Great taste – bitter drugs can be taste-masked and many flavour options are available.

Woubalem Birmachu, PhD
Senior Manager of New Technology
T: +1 763 488 4700
F: +1 763 488 4800
E: woubalem.birmachu@cimalabs.com

CIMA Labs, Inc
7325 Aspen Lane
Brooklyn Park
MN 55428
United States

www.cimalabs.com

“DRUG PLASMA CONCENTRATIONS REMAIN INSIDE THE THERAPEUTIC RANGE FOR A LONGER PERIOD OF TIME COMPARED WITH CONVENTIONAL RAPID-RELEASE FORMULATIONS”

- Ease of administration – disintegration of the dosage form in the mouth makes swallowing the dosage form an easy task.
- Discreet – taken whenever and wherever patients want. Quick disintegration of tablet, convenient unit dose blister packaging.
- Safety – blisters can be made to meet many child-resistant packaging requirements.

The combination of ODT technology with ER technology results in ODT-ER dosage forms, which provide additional clinical value to patients, including:

- Extended release – reduction in dosing frequency, better compliance.
- Better maintenance of therapeutic levels.
- For patients who experience dysphagia due to stroke, brain or spinal cord injury, multiple sclerosis, muscular dystrophy, Parkinson's disease, GERD, oesophagitis and oesophageal cancer.

ABOUT CIMA

CIMA Labs, a world leader in the drug delivery partnering business, specialises in the formulation, taste-masking and manufacturing of pharmaceuticals utilising its orally disintegrating tablet (ODT), oral transmucosal (OTM), tamper deterrent, solubilization and oral powder drug delivery technologies.

Orally Disintegrating Tablets disintegrate in the mouth and can be taken without water. CIMA offers compressed (OraSolv® and DuraSolv®) and lyophilized (Lyoc™) tablets with customised release profile, enteric coating, flavouring and colouring options.

The Oravescent®, oral transmucosal buccal tablet technology delivers drugs directly through the oral mucosa rather than in the gastro-intestinal tract. Transmucosal drug delivery can result in a greater rate and extent of drug uptake into the systemic circulation, which may also reduce the dose of drug required to produce a therapeutic effect.

OraGuard™ extended release / tamper deterrent technology. This technology provides robust extended-release PK profile, even during co-administration with alcohol. It is also resistant against various tampering methods including crushing and ingestion, injection or snorting, chewing, aqueous extraction for IV dosing and alcohol extraction.

For insoluble drug candidates, CIMA has developed a solubilisation technology known as MicroSolv™. It is a solid self emulsifying drug delivery system (S-SEDDS). The drug is emulsified and adsorbed onto a powder that can be manufactured as a tablet, capsule or ODT.

Finally, CIMA offers a granules / oral powder formulation system, comprised of drug granules, packaged in a sachet. It can accommodate high doses (>1 g) of drug product. Customised granule size, release profile, enteric coating, flavouring and colouring options are available.

CIMA Labs has proven commercialisation success with more than 20 products marketed in more than 70 countries around the world. Our expertise includes R&D, formulation, manufacturing and packaging. We put these capabilities to work for our partners to commercialise their products and bring them to doctors and patients around the world.

Changing World of APIs

Join the growing market of biotech-based proteins

Protein Pharmaceuticals

Hanns-Christian Mahler, Gerrit Borchard, Henrik L. Luessen

ISBN 978-3-87193-382-0

- € 126.00
- 1st edition 2010
- 15,3 x 23 cm, 464 pages, paperback

The book covers principal topics on the basics in protein chemistry in order to understand the particular behavior of such molecules and their analytical characterization. Particular issues related to stability aspects and aggregation have been addressed as well.

As a second area the book then discusses the formulation of biopharmaceuticals and drying techniques to stabilize proteins, as well as further specific areas such as highly concentrated protein formulations, primary packaging materials, and manufacturing challenges.

In addition, the in vivo fate of biopharmaceuticals considering their pharmacokinetic/pharmacodynamic behavior is addressed in this section.

Since a second generation of biopharmaceutical products are facing market authorization or are already launched, some chapters were also dedicated to the polyethylene

glycolation of proteins, targeting aspects and still evolving technologies to modify delivery of such protein therapeutics by depot formulations or lipid complexation. Considering its importance of safety and efficacy, also immunogenicity and considerations for product development have been addressed.

Last but not least, two chapters address regulatory aspects that pharmaceutical and biopharmaceutical scientists should keep in mind when being involved in the development of biopharmaceuticals.

Tel. +49 (0)7525-940 135, Fax: +49 (0)7525-940 147, eMail: vertrieb@ecv.de
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- Scientists in Drug Metabolism and Pharmacokinetics
- Engineers in Production
- Manager in Quality Control / Quality Assurance
- Formulation Scientists
- Packaging Development Experts
- Qualified Persons

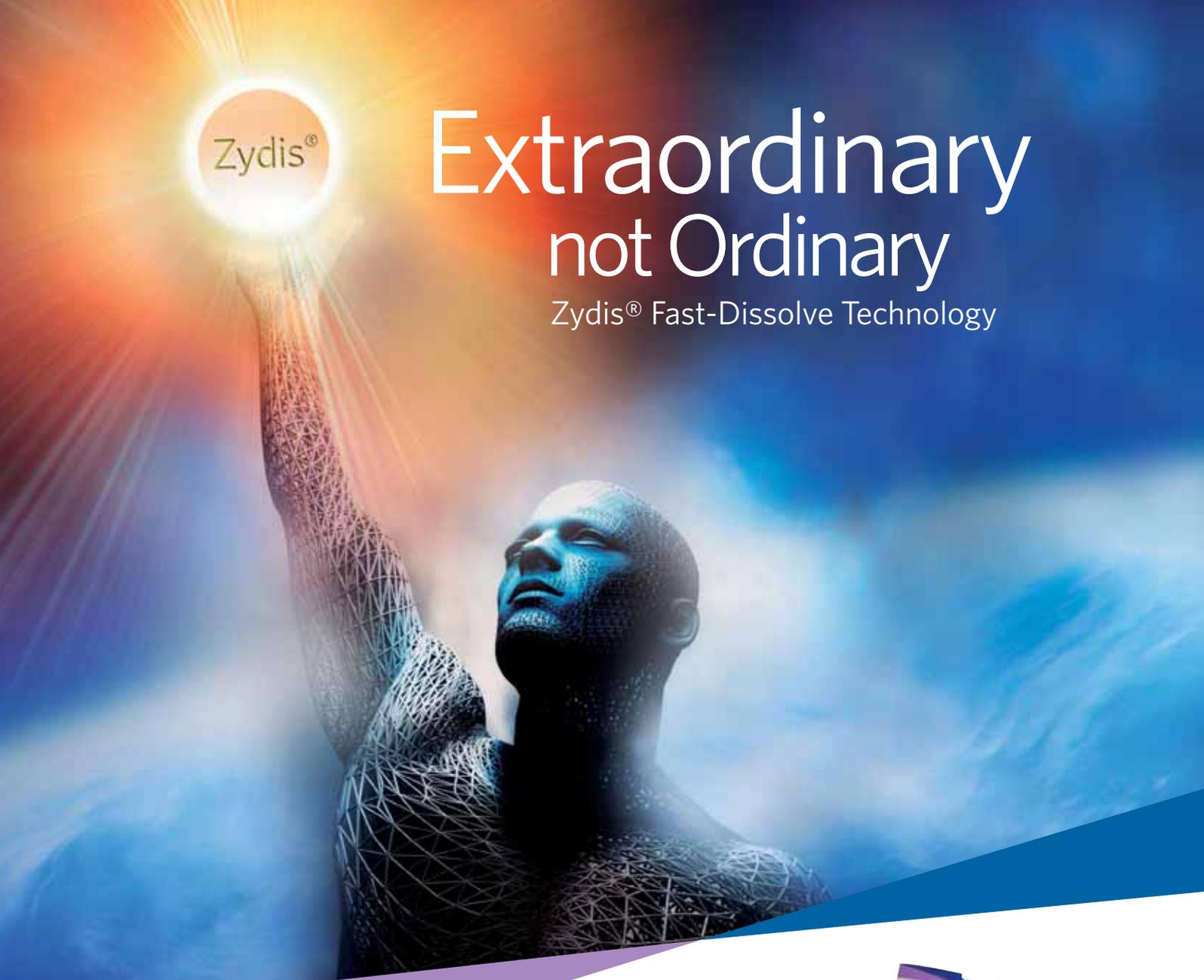
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