



Elan
Drug
Technologies

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-

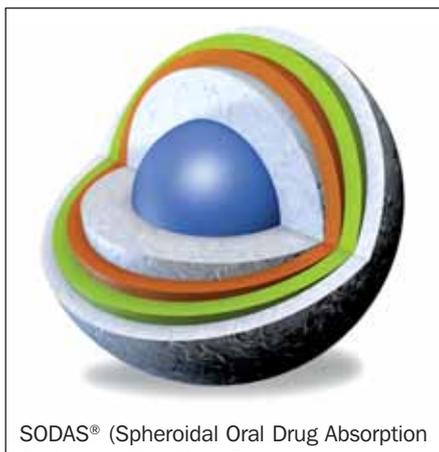


Gurvinder Singh Rekhi, PhD
Senior Director, Oral Controlled Release Product Development
T: +1 770 538 6321
F: +1 770 538 6421
E: gsingh.rekhi@elan.com

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

www.elandrugtechnologies.com



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

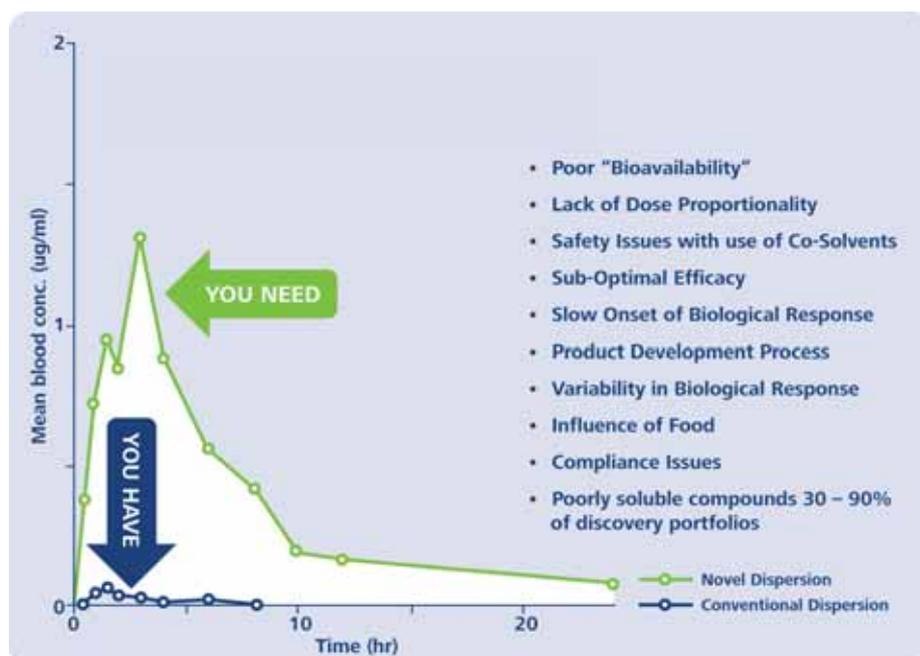
Rapamune®. In-market sales for these three products in 2008 were over US\$1.8 billion. Other technologies designed to overcome problems associated with poor water solubility include Skyepharma's IDD® solubilisation technology which has been used to launch Triglide® (Shionogi Pharma Inc), and LifeCycle 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

**“SINCE 2001, 11 ORAL DRUG DELIVERY PRODUCTS
HAVE BEEN LAUNCHED THROUGH LICENSEES/PARTNERS
IN THE US ALONE, MAKING ELAN DRUG TECHNOLOGIES
THE MOST SUCCESSFUL DRUG DELIVERY SERVICE PROVIDER
WORLDWIDE OVER THAT PERIOD”**

**SUCCESSFUL BUSINESS MODEL
BUILT ON DEMAND**

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.

REFERENCES:

1. 2010 report from New England Healthcare Institute
2. The Freedomia Group. Drug Delivery Systems to 2012—Demand and Sales Forecasts, Market Share, Market Size, Market Leaders. Study # 2294. Cleveland, Ohio: The Freedomia Group, March 2008
3. Colombo P, Sonvico F, Colombo G, et al. Novel platforms for oral drug delivery. *Pharm Res.* 2009;26(3):601-611.
4. Merisko-Liversidge EM, Liversidge GG. Drug nanoparticles: formulating poorly water-soluble compounds. *Toxicol Pathol.* 2008;36(1)43-48.
5. Technology Innovation Award at 14th Annual Drug Delivery Partnership Meeting, Orlando, Florida January 26th, 2010
6. Bottomley K, NanoTechnology for Drug Delivery: a Validated Technology? *Drug Delivery Report.* 2006:20-21

7. US Patent 6,110,494, Article Butler et al. *Pharm. Tech.* 1998, 22(3), 122-138
8. Associated Press. Scientists explore abuse-resistant painkillers, Associated Press, March 12, 2007. Available at <http://www.msnbc.msn.com/id/17581544/>
9. Pain Therapeutics Receives Complete Response Letter From FDA for REMOXY® - Press release, 11 December 2008. Available at <http://investor.paintrials.com/releasedetail.cfm?ReleaseID=354003>
10. R&D Focus, IMS Portal, accessed April 2009. Available at http://www1.imshealth.com/web/product/0,3155,64576068_63872702_71263548_71480111,00.html
11. Wheeler H. Short acting and anti-abuse technologies set to fragment and grow the market , *Datamonitor Report Reference Code: DMHC2377, March 2008*
12. Dubin C, *Discussing Gastro-retentive drug delivery systems, Drug Delivery Technology, June 2007 Vol 7 no 6, pp26-29*
13. Touitou E, Barry BW, *Enhancement in Drug Delivery, Enhancement in Drug Delivery, CRC Press, 2006, pp 77-80*
14. United States Food and Drug Administration website. Available at <http://www.fda.gov/>
15. Business Insights. Lifecycle management strategies: maximizing ROI through indication expansion, reformulation and Rx-to-OTC switching. *Business Insights report.* February 2006.
16. Grudzinskas C, Balster R L, Gorodetzky C W, Griffiths R, Henningfield J , Johanson C-E, Mansbach R S, McCormick C G, Schnoll S G, Strain E, Wright C. Impact of formulation on the abuse liability, safety and regulation of medications: The expert panel report. *Drug and alcohol dependence, June 2006 vol 83, (Supp 1):S77-S82.*
17. Collier R, *Drug development cost estimates hard to swallow, CMAJ.* 2009 February 3; 180(3): 279–280.
18. PriceWaterhouseCooper Report, *Pharma 2020, The Vision.* PWC Publication , 2007 June 2007. Available at: www.pwc.com/extweb/pwcpublishings.nsf/docid/91BF330647FFA402852572F2005ECC22.



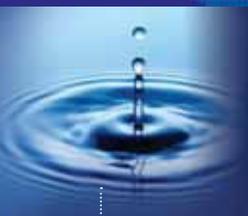
**IN WHICH EDITION SHOULD
YOUR COMPANY APPEAR?**

WWW.ONDRUGDELIVERY.COM



Elan
Drug
Technologies

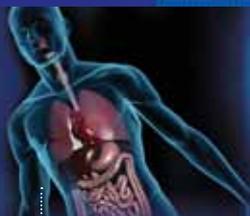
World Leading Drug Delivery Technologies



NanoCrystal®
Technology



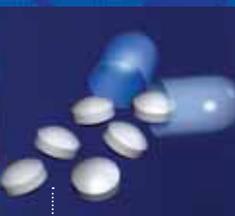
SODAS®
Technology



IPDAS®
Technology



CODAS®
Technology



PRODAS®
Technology



MXDAS™
Technology



DUREDAS™
Technology

NanoCrystal® Technology

Proven innovation for poorly water soluble compounds

Oral Controlled Release Platform

Customized, robust, commercialized technologies

Elan Drug Technologies develops and manufactures innovative pharmaceutical products that deliver clinically meaningful benefits to patients, using its extensive experience and proprietary drug technologies in partnership with pharmaceutical companies.

- 3 million+ patients
- 40 years in business
- 1,900+ patent/patent applications
- 36 products 100+ markets
- 14 products in clinical development
- 500,000 sq ft dedicated manufacturing facilities
- \$20B+ in-market sales

www.elandrugtechnologies.com

