ORAL DRUG DELIVERY:

FORMULATION SELECTION METHODS & NOVEL DELIVERY TECHNOLOGIES

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"Oral Drug Delivery: Formulation Selection Approaches & Novel Delivery Technologies"

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NO LONGER A HIT-OR-MISS PROPOSITION:

ONCE-DAILY FORMULATION FOR DRUGS WITH PH-DEPENDENT SOLUBILITY

In this article, Dr Gopi Venkatesh, Director of R&D, and Dr Anthony Recupero, Senior Director, Business Development, both of Aptalis Pharmaceutical Technologies (formerly Eurand), describe a specific application of Diffucaps® technology, which allows the creation of once-daily oral formulations of weakly basic active pharmaceutical ingredients, previously extremely difficult to achieve, but with significant benefits to patient adherence.

MEDICATION ADHERENCE

It is estimated that 33-69% of all medication-related hospital admissions in the US are due to poor medication adherence, with a resultant cost of approximately US$100 billion a year.[1-6] Taking medications exactly as prescribed and following appropriate lifestyle recommendations is highly beneficial and may reduce the impact of side effects.

Practitioners should always assess adherence to therapy and may improve adherence by emphasising the value of a patient's regimen, making the regimen as simple as possible, and customising the regimen to the patient's lifestyle.[7] Simple dosing (one pill, once daily) can help maximise adherence, particularly when combined with reinforcing visits / messages from healthcare practitioners, despite the fact that 10-40% of patients on simple regimens continue to have imperfect dosing adherence.[8,9]

WHY AREN'T ONCE-DAILY ORAL DOSAGE FORMS AVAILABLE FOR ALL DRUGS?

As the orally administered pharmaceutical dosage form passes through the human gastrointestinal (GI) tract, drug should be released from the dosage form and be available in solution at or near the optimal site for drug absorption to occur.[10-12] The rate at which the drug is released from a dosage form and goes into solution is important for the kinetics of drug absorption. The dosage form and hence the pharmaceutical ingredient (API) is subjected to varying pH levels during GI transit.[13-16] Specifically, pH varies from a minimum of about 1.2 to a maximum of around 7.4 (stomach pH: 1.2-2.5, which increases to 3.5-6.1 upon consumption of food; bile pH: 7.0-7.4; pH 5.0-6.0 in small intestine; and pH: 6 to 7 in the large intestine).

GI fluid volume and agitation can vary significantly, which has substantial impact on drug dissolution and absorption.[17] Moreover, transit time may vary significantly in individual parts of the GI tract, depending on individual size and prevailing local conditions.[18]

Truly once-daily dosage forms of many weakly basic drugs are not commercially available. Several attempts have been made in the past at developing once-daily delivery systems of weakly basic drugs, such as carvedilol, ondansetron, and dipyridamole, with limited success.[19-22] This is largely because the absorption of a weakly basic drug is critically affected by its solubility and the required total daily dose. The ability to maintain these drugs in a soluble form as the drug passes through the GI tract throughout the day has been a substantial challenge for oral formulators.

SOLUBILITY ENHANCEMENT BY ORGANIC ACIDS

The solubility-enhancing property of organic acids[23] is exploited during the manu-

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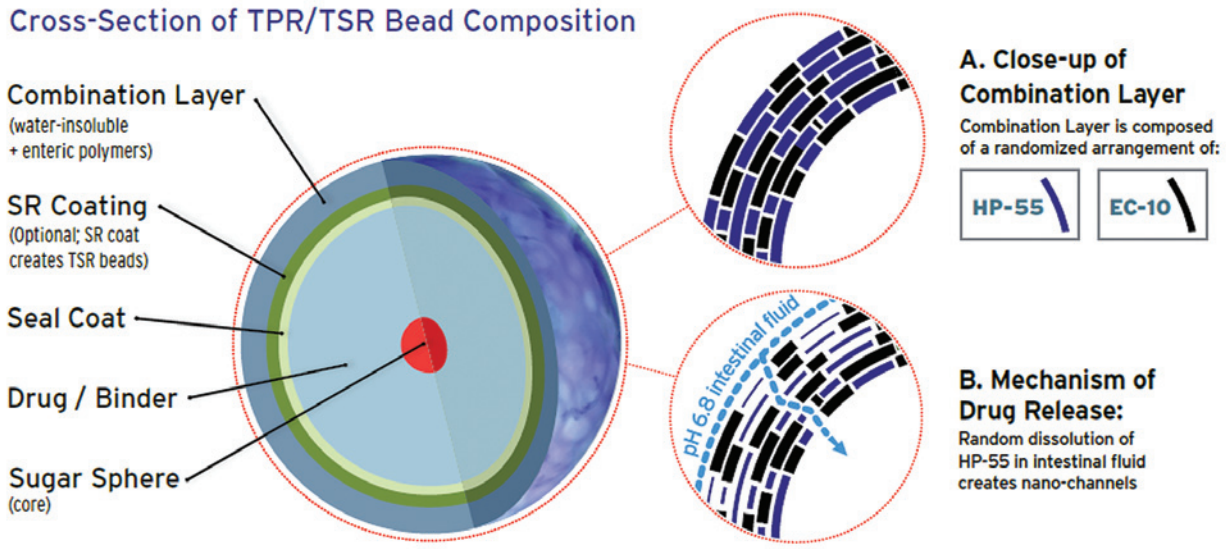

Figure 1: Diffucaps®– Customised Drug Release Bead (A) soaked in pH 1.2 or resident in the stomach and (B) soaked in pH 6.8 or in transit in the intestinal tract.

facture of customised-release (CR) dosage forms using *Diffucaps®* technology. The potential for in situ formation of acid addition compounds[24] is averted by using a sustained-release (SR) coating membrane between the inner organic acid layer and the weakly basic drug layer. The SR-coating membrane thus applied, precisely controls the release of the organic acid ensuring drug is not retained in the dosage form for lack of solubilising acid in the *Diffucaps®* formulation.

DIFFUCAPS® TECHNOLOGY

Diffucaps® technology in its simplistic form (see Schematic of the Time Pulsatile Release / Time Sustained Release (TPR/TSR) bead shown in Figure 1) involves the preparation of:

(1) drug-containing cores by drug-layering on inert particles
(2) customised release (CR) beads by coating immediate release (IR) particles with one or more functional dissolution rate controlling polymers or waxes
(3) combining one or more functional polymer coated *Diffucaps®* bead populations into hard gelatin or hydroxypropyl methylcellulose (HPMC) capsules.[24]

MECHANISM OF DRUG RELEASE FROM TPR/TSR BEADS

The water-insoluble and enteric polymers are dissolved in a common solvent mixture and the solution is sprayed onto drug particles. These two polymers may exist as molecularly dispersed or as molecular clusters in the lag-time coating membrane applied on the drug cores (Figure 1).

During dissolution testing in two-stage dissolution media (first two-hour dissolution testing in 700 mL of 0.1N HCl and thereafter testing in 900 mL of pH 6.8 buffer obtained by adding 200 mL pH modifier) or upon oral administration, water or body fluid is blocked from imbibing into the core as the polymeric system is impermeable in the acidic medium or gastric fluid. When the pH of the medium is changed to 6.8 or following exit from the stomach, the penetrating dissolution medium or intestinal fluid selectively dissolves the enteric polymer molecules or molecular clusters starting from the outermost membrane layer, thereby creating tortuous nanopore channels for dissolved drug to pass through.[23]

The tortuosity increases with increasing coating thickness and/or decreasing enteric polymer content, and consequently, the drug release from the TPR beads having no barrier coat becomes sustained with increasing thickness of the TPR coating.

DEVELOPMENT OF ONCE-DAILY DOSAGE FORMS OF WEAKLY BASIC DRUGS

Below is shown the method for the preparation[25] of CR drug delivery systems comprising one or more IR, SR, TPR/TSR, Delayed-Release (DR) bead populations, themselves containing a weakly basic, nitrogen moiety-containing API such as ondansetron, carvedilol, dypiramidole, lamotrigine or iloperidone, which is moderately soluble at pH <4, but it is practically insoluble at a pH >6, and at least one pharmaceutically acceptable organic acid as a solubiliser (see the schematics of SR organic acid bead & TPR/TSR bead containing a weakly basic drug shown in Figure 2). The method comprises the following steps:

a) layering an organic acid on 25-30 mesh sugar spheres;
b) applying an SR coating on acid-layered beads with a water-insoluble polymer to control the rate of release of the acid;

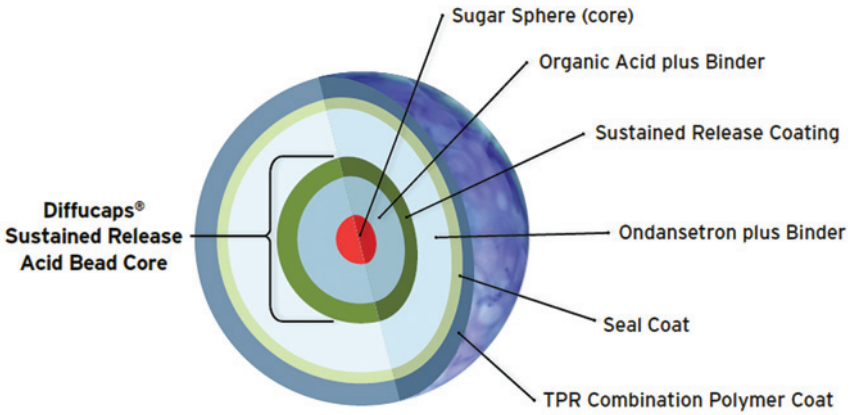

Figure 2: Diffucaps®: Customised Drug Release Bead for pH-sensitive Drugs (e.g. Ondansetron HCl).

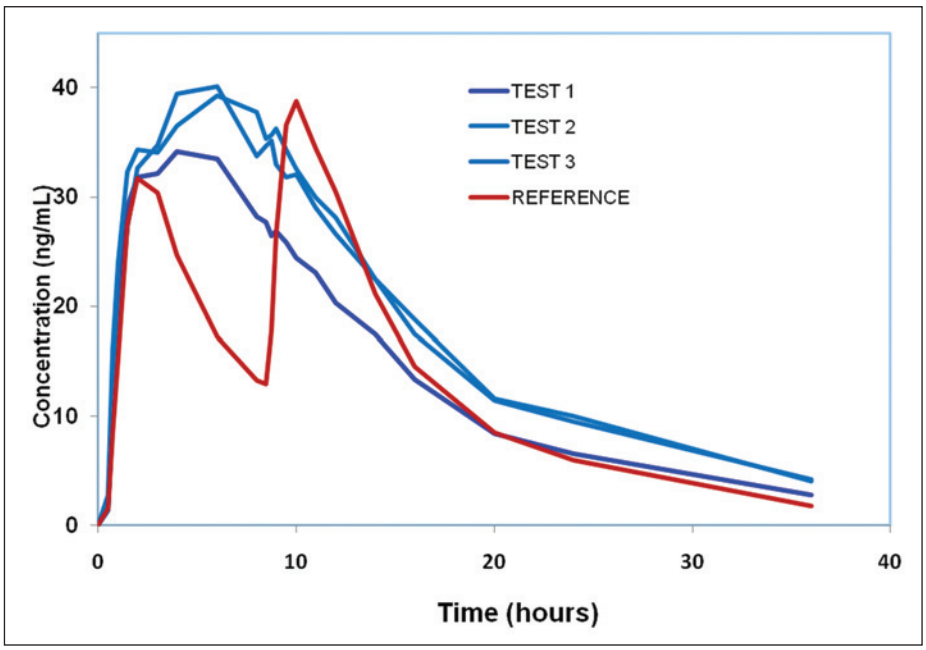

Figure 3: Pilot PK Study - Ondansetron QD versus Ondansetron IR (Zofran®).

c) preparing IR beads by layering the weakly basic nitrogen moiety-containing API and applying a protective seal-coat with a water-soluble polymer;
d) preparing SR beads by applying a barrier (SR) coating of a water-insoluble polymer on the IR beads to sustain the drug release over several hours (if needed);
e) preparing TPR beads by applying a lag-time coating on IR beads or SR beads (called TSR beads) comprising water-insoluble and enterosoluble polymers for a weight gain sufficient to achieve a lag time (a time period of less than 10% drug release) of 2-6 hours followed by a sustained-release profile; and
f) filling into a capsule a mixture of IR beads and one or more TPR bead populations at appropriate amounts to achieve a target pharmacokinetics profile suitable for a once-daily dosing regimen.

The following examples demonstrate how Aptalis Pharmaceutical Technologies utilised the above process to formulate once-daily dosage forms of ondansetron and iloperidone.

NAUSEA AND VOMITING FOLLOWING CHEMOTHERAPY, RADIATION THERAPY, OR SURGERY

Radiotherapy-induced nausea and vomiting (RINV), chemotherapy-induced nausea and vomiting (CINV), and postoperative nausea and vomiting (PONV) remain the most common and distressing challenges facing patients receiving these cancer therapies or following surgical procedures under general anaesthesia (occurring in up to 80% of cases).[25-33]

Nausea and vomiting very often occur together but can also occur independently. RINV and CINV during cancer therapy can have a direct and significant impact on adherence to primary therapy. Some of the most highly prescribed anti-emetics suffer from a short-half life requiring multiple daily doses for control of emesis. Between doses, the plasma levels of the anti-emetic can drop well below efficacious levels increasing the risk for breakthrough nausea and vomiting, particularly when subsequent doses are not taken exactly as scheduled. Proper control of acute and breakthrough nausea and vomiting therefore can be achieved with a higher probability and a higher level of confidence with a customised-release (CR) dosage form for oral administration, preferably administered prior to the procedure.

Weakly basic ondansetron HCl dihydrate

Ondansetron HCl dihydrate, the API in the branded product, *Zofran*® Tablets (4 and 8 mg base equivalent) and *Zofran*® Oral Solution, marketed by GlaxoSmithKline, is a selective serotonin 5-HT_3 blocking agent (an antiemetic). The API in *Zofran*® ODTs (orally disintegrating tablets, 4 and 8 mg) is ondansetron base. All products are immediate release (IR) formulations. Ondansetron is indicated for the prevention of nausea and vomiting associated with radiotherapy (adults: 8 mg tid) and/or chemotherapy (adults: 8 mg bid to tid) and prevention of postoperative nausea and/or vomiting (adults: 8 mg bid).

Ondansetron is a weakly basic drug having a pKa of 7.4 and an elimination half-life averaging approximately 3.8±1 hours. It is practically insoluble in the pH environment of the intestinal tract. However, there is a dramatic increase in solubility in aqueous organic acid solution, making it a good candidate for developing once-daily dosage forms based on the organic acid approach of *Diffucaps*® technology.

Modified release (MR), once-daily dosage forms of ondansetron HCl dihydrate using *Diffucaps*® technology

Pharmacokinetic/biopharmaceutical modeling and simulation of possible plasma profiles based on available pharmacokinetic data as a guide in the design of customised-release (CR) dosage forms in order to be suitable for a once-daily dosing regimen is typically performed using *WinNonlin*® and/or *GastroPlus*™ computer simulation and modeling techniques. The CR capsule product was designed to comprise appropriate amounts of both IR and TPR components wherein the TPR component used SR-coated organic acid beads as inert cores to design multiple TPR bead populations with different lag times.[33] The use of such methods resulted in reduced feasibility development time and enhanced the probability of success of the program.

For the IR component of the formulation, rapid release (RR) granules comprising ondansetron, mannitol, and organic acid were developed, which are designed to release the drug faster than, or similar to, *Zofran*® IR tablets even under alkaline pH conditions.[33]

Ondansetron HCl CR capsules were designed to comprise appropriate amounts of both RR granules and TPR beads. Three CR formulations were prepared for pharmacokinetic (PK) testing in healthy volunteers.[33]

A randomised, four-way crossover pilot PK study was conducted that included 12 healthy male volunteers, aged 18-55 years, with a wash-out period of seven days. Each volunteer was dosed with one of three test formulations of Ondansetron MR at 0800h, or two *Zofran*® (8 mg) at 0800h and 1630h after an overnight fast. Figure 3 shows the mean plasma concentration-time profiles achieved. The relative bioavailability compared with 8 mg IR bid reference was approximately 0.85 for all test formulations (Test Formula 1, 2, and 3) at the end of 24 hours.

Based on these results, Test Formula 3, given the product code EUR1025, was advanced into pivotal PK studies which have been completed.[34] In these trials, single and repeated oral administrations of 24 mg EUR1025 resulted in similar rate and extent of exposure as 8 mg *Zofran*® tid. Steady-state concentrations of Treatment 2 (8 mg *Zofran*® bid) and Treatment 3 (8 mg *Zofran*® tid) are equivalent to that of single administrations of two and three 8 mg *Zofran*®, respectively.[34] The total exposure of ondansetron (AUC_{0-24}) from EUR1025 on day six was approximately 13% higher than that observed on day one, suggesting minor accumulation following repeated dosing.

The total exposure of Treatment 1 (24 mg EUR 1025) appears to be nearly equivalent to that of Treatment 3 (8 mg *Zofran*® tid) at steady state. The product is now ready to enter Phase III clinical development.[34]

ILOPERIDONE TPR BEADS AND RELEASE PROFILES

The *Diffucaps*® organic acid approach used with ondansetron is applicable to any weakly basic drug, which is at least slightly soluble at a pH≤3, but is poorly soluble or practically insoluble above pH 6. Iloperidone, the API in *Fanapt*®, is a weakly basic, dopamine and serotonin receptor antagonist exhibiting antipsychotic activities. Iloperidone (12 mg) is dosed twice daily.

The incidence of adverse effects in patients treated with *Fanapt*® 20-24 mg/day were twice that occurring in patients treated with *Fanapt*® 10-16 mg/day indicating an MR, once-daily formulation may improve the side effect profiles of iloperidone. Initial studies indicate that by combining IR and TPR bead populations at appropriate quantities (as determined by simulation and modeling) to provide desired *in vitro* release profiles, it would be possible to achieve target plasma profiles suitable for a once-daily dosing regimen.

ADVANTAGES OF CR DIFFUCAPS® DRUG DELIVERY SYSTEMS

Controlled-release drug delivery systems consisting of coated multiparticulates, particularly based on *Diffucaps*® technology, which typically have a particle size in the range of 200-600 μm, exhibit characteristic target *in vitro* profiles, as well as target plasma concentration-time profiles to be suitable for a once-daily dosing regimen.

Multiparticulate drug delivery systems, such as *Diffucaps*®, offer the following advantages over conventional controlled-release monolithic dosage forms such as matrix or coated tablets including osmotic delivery systems:

- Dispersed along the GI Tract for more effective delivery
- Predictable and consistent GI transit time thereby minimising food effect
- Low probability of dose dumping
- Reduced inter- and intra-subjectvariability
- Easy adjustment of multiple dose strengths

In addition, the *Diffucaps*® technology offers incremental advantages:

- Easy adjustment of target plasma profiles including combining bead populations exhibiting differing release profiles
- Ability to create combination products of incompatible actives or actives requiring differing target plasma profiles
- Capability to create micro-environments:
  - Create a sustainable acidic pH micro-environment within coated bead to solubilise the weakly basic drug (which is practically insoluble at pH 6.0 or above) in order to extend its release into the GI tract
  - Create a sustainable alkaline pH micro-environment within coated bead to moderate the solubility of a weakly basic drug (which is extremely soluble in the entire physiologically relevant pH range of 1.0 to 8.0) to avoid dose dumping
- Improve patient adherence due to reduced frequency of dosing, ease of oral administration, reduction in incidence of adverse events, and/or improved safety profile
- Additional product patent protection

CONCLUSIONS

Adherence to oral medication regimens, and therefore effective therapy, is a common issue for patients across multiple indications. Although simple dosing regimens (one pill, once daily) as provided by extended release (ER) formulations for a number of products are available, there are still many drugs for which an ER, once-daily form has proven to be exceptionally challenging to develop. These challenging molecules frequently have water solubility issues which may also be complicated by limited molecule half-life.

The *Diffucaps*® technology is one approach that effectively overcomes such challenges, allowing for straightforward development of ER, once-daily formulations that help to improve adherence, which can result in improved efficacy and patient quality of life.

REFERENCES

1. *McDonnell PJ, Jacobs MR. Hospital admissions resulting from preventable adverse reactions. Ann Pharmacother 2002; 36:1331-6.*
2. *Senst BL, Achusim LE, Genest RP, et al. Practical approach to determining costs and frequency of adverse drug events in a healthcare network. Am J Health Syst Pharm 2001; 58:1126-32.*
3. *Levy G, Zamacona MK, Jusko WJ. Developing compliance instructions for drug labeling. Clin Pharmacol Ther 2000;68:586-91.*
4. *Berg JS, Dischler J, Wagner DJ, Raia JJ, Palmer-Shevlin N. Medication compliance: a healthcare problem. Ann Pharmacother 1993;27:Suppl 9:S1-S24.*
5. *LaRosa JC. Poor compliance: the hidden risk factor. Curr Atheroscler Rep 2000;2: 1-4.*
6. *Horwitz RI, Horwitz SM. Adherence to treatment and health outcomes. Arch Intern Med 1993;153:1863-8.*
7. *Osterberg, L, and Blaschke, T. Adherence to Medication. N Engl J Med 2005; 353:487-97.*
8. *Greenberg RN. Overview of patient compliance with medication dosing: a literature review. Clin Ther 1984;6:592-9.*
9. *Eisen SA, Miller DK, Woodward RS, Spitznagel E, Przybeck TR. The effect of prescribed daily dose frequency on patient medication compliance. Arch Intern Med 1990;150:1881-4.*
10. *P.K. Gupta, J.R. Robinson, "Oral controlled release delivery", in: "Treatise on controlled drug delivery", Kydonieus, A. (ed.), Marcel Dekker, New Jersey (1992) 255-310.*
11. *R.E. Notari, "Biopharmaceutics and clinical pharmacokinetics", Marcel Dekker, Inc., New York, 1987.*
12. *D.J. Greenblatt, L.L. van Moltke, J.J. Harmatz, and R.I. Shader, Pharmacokinetics, pharmacodynamics, and drug disposition", In: "Neuropsychopharmacology", K.L Davis, D. Charney, J.T. Coyle, and C. Nemerof (eds), Lippincott, Williams & Wilkins, Philadelphia, (2002) 507-524.*
13. *G. Chawla, P. Gupta, V. Koradia, and A.K. Bansal, "A means to address regional variability in intestinal drug absorption", Pharm. Technol., July 2003, 50-68.*
14. *Davis, S.S., 1987. Evaluation of the gastrointestinal transit and release characteristics of drugs. in. Johnson, P., Lloyd-Jones, J.G. (Eds), Drug Delivery systems [Fundamentals and techniques]. Ellis Harwood, Chichester, pp. 164-179.*
15. *J.B. Dressman, R.R. Berardi, L.C. Dermentzoglou, T.L. Russell, S.P. Schmaltz, J.L. Barnett, K.M. Jarvenpaa, Upper gastrointestinal (GI) pH in young healthy men and women, Pharm. Res. 7 (1990) 756–761.*
16. *C. Schiller, C.P. Prohlicht, T. Giessmann, W.,Siegmund, H. Monnikess, and N. Hosten, "Intestinal fluid volume and transit of dosage forms as assessed by magnetic resonance imaging", Aliment. Pharmacol. Ther., 22 (2005) 871-879.*
17. *Davis, S.S., Hardy, J.G., Taylor, M.J., Whalley, D.R., Wilson, C.G., 1984. A comparative study of the gastrointestinal transit of a pellet and tablet formulation. Int. J. Pharm. 21, 167-177.*
18. *W. Eisert and P. Gruber, "US 6,015,577 B1: Pharmaceutical compositions containing dipyridamole or mopidamol and acetylsalicylic acid or the physiologically acceptable salts thereof; processes for*

preparing them and their use in treating clot formation", assigned to Dr. Karl Thomae GmbH.
19. G.K. Jain, O. Anand, and A. Rampal, "WO 2004/096182 A1: Extended release matrix tablets of carvedilol", assigned to Ranbaxy Laboratories Limited.
20. V. Andronis, K. A. Lamey, and C.K. Oh, "US 20040019096 A1: Novel formulations of carvedilol", assigned to SmithKline Beecham Corporation.
21. February 6, 2007 at 3:00 PM: (Business Wire) Scolr Pharma announces positive results from its Second 24 Hour CDT Ondansetron Trial at http://www.scolr.com.
22. G. Venkatesh, "US 20070196491 A1: Drug delivery systems comprising weakly basic drugs and organic acids", assigned to Eurand, Inc.
23. G. Venkatesh, "Diffucaps® technology for controlled release drug delivery", In. Chronotherapeutics", B.-B.C.Youan (Ed.), John Wiley & Sons, New York (2009) 121-144.
24. R. Sun, K.W. Klein, and P.F. White, "The effect of timing of ondansetron administration in outpatients undergoing Otolaryngologic surgery". Anesth. Analg. 84 (1997) 331-6.
25. J.L. Parlow, A.T. Meikle, J. v. Vlymen, "Post discharge nausea and vomiting after ambulatory laparoscopy is not reduced by promethazine prophylaxis", Can. J. Anesth. 46 (1999) 719-724.
26. T.J. Gan, R. Franiak, J. Reeves, "Ondansetron orally disintegrating tablet versus placebo for the prevention of post-discharge nausea and vomiting after ambulatory surgery", Anesth. Analg. 94 (2002) 1199-1200.
27. F. Roila, P.J. Hesketh, J. Herrstedt, "Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer. Prevention of chemotherapy and radiotherapy induced emesis: results of the 2004 Perugia International Antiemetic Consensus Conference, Ann. Oncol. 17 (2006) 20-28.
28. T.J. Gan. "Risk factors for postoperative nausea and vomiting" Anesth. Analg. 102 (2006) 1884-98.
29. D.S. Wagner, V. Gauger, D. Chiravuri, and K. Faust, "Ondansetron oral disintegrating tablet for the prevention of post-operative vomiting in children undergoing strabismus surgery", Ther. Clin. Risk Manag. 3 (2007) 691-694.
30. T.J. Gan, C.C. Apfel, A. Kovac, B.K. Philip, N. Singla, H. Minkowitz, A.S. Habib, J. Knighton, A.D. Carides, H. Zhang, K.J. Horgan, J.K. Evans, F.C. Lawson, and The Aprepitant-PONV Study Group, "A randomzed, double-blind comparison of the NK1 antagonist, Aprepitant, versus ondansetron for the prevention of postoperative nausea and vomiting", Anesth. Analg. 104 (2007) 1082-1089.
31. P.C. Feyer, E. Maranzano, A.M. Molassiotis, F. Roila, R.A. Clark-Snow, and K. Jordan, Radiotherapy induced nausea and vomiting (RINV): MASCC/ESMO guideline for antiemetics in radiotherapy: Update 2009", Support Care Cancer Published online: 10 August 2010, DOI 10.1007/s00520-010-0950-6.
32. B. Nevidjon and R. Chaudhary, Controlling emesis: Evolving challenges, novel strategies", The J. Support. Oncol. 8 (2010) 1-10.
33. G. Venkatesh, J.-W. Lai, N.H. Vyas, and V. Purohit, "US 20090232885 A1: Drug delivery systems comprising weakly basic drugs and organic acids", assigned to Eurand, Inc.
34. G. Venkatesh, S. Perrett, and R. Thieroff-Ekerdt, "US 20090232885 A1: Methods of treating PDNV and PONV with ER Ondansetron compositions", assigned to Eurand, Inc.

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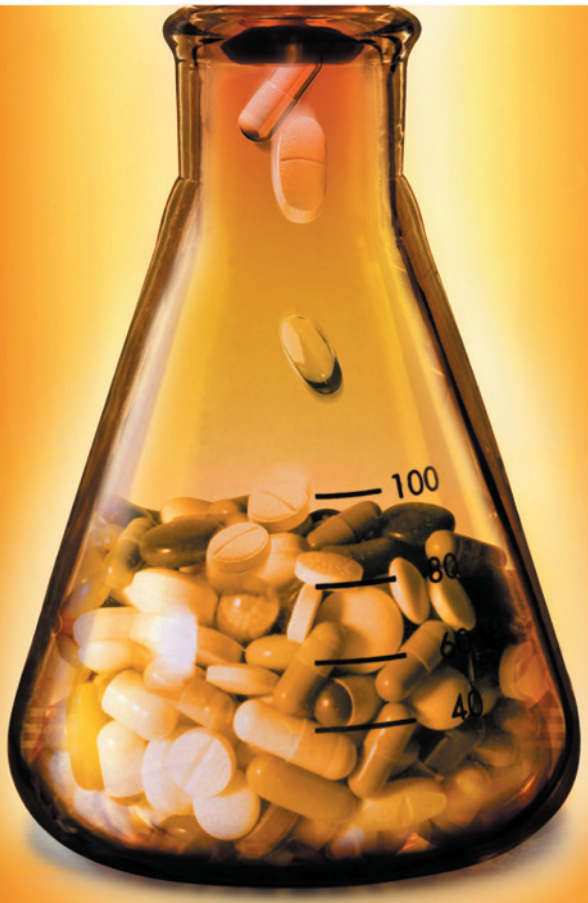

We are now transitioning from a technology transfer-based operation to a specialty pharmaceutical company capable of developing and delivering new product lines by ourselves.

We are making enormous efforts and ever striving forward as an R&D oriented specialty company to provide a range of value-added products and unmet-need products.

	Project	Indication
GL2701	Tamsulosin 0.2mg + Finasteride 5mg FDC	BPH
GL2702	Tamsulosin 0.4mg GLARS	BPH
GL2903	Tianeptin GLARS	Depression
GL2904	Bosentan SR	PAH
GL2907	Oxycodone SR	Pain
GLA2DLT	Tamsulosin 0.2mg + Dutasteride 0.5mg FDC	BPH
GLA3FT	Tamsulosin 0.4mg GLARS + Finasteride 5mg FDC	BPH
GLA5PR	Pregabalin SR	Pain

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A POSSIBLE APPROACH FOR THE DESIRE TO INNOVATE

Here, Hunsik (Brian) Wang, Chief Executive Officer, and Junsang Park, PhD, Chief Scientific Officer, both of GL PharmTech, introduce GLARS, a novel concept extended-release triple-layered tablet delivery technology for delivery to the intestine and colon.

How did you feel when you heard your brand product was easily copied by a generic company after the expiration of its new chemical entity patent? And what about the case when someone from sales & marketing came and complained of setbacks in developing a pre-defined reformulation product?...

For various reasons, with which readers will already be familiar, individuals working in pharmaceutical product development and formulation have been under significant pressure for some time. This pressure may have made possible various kinds of open-innovation by prompting the adoption of technologies or products from outside.

The drug delivery industry has been working as an innovator and excellent partner over the past 30 years, providing technologies that have enabled brand pharmaceutical companies to take new steps. This is surely one reason why the number of reformulated products reached about triple that of new chemical entities (NCEs) in 2009 (75 *versus* 26).[1] As a player in the oral drug delivery field, we at GL PharmTech were pleased to note that oral drug delivery products captured about 10% of the top 200 product sales, which reportedly reached US$14.5 billion.

> "HOW DID YOU FEEL WHEN YOU HEARD YOUR BRAND PRODUCT WAS EASILY COPIED BY A GENERIC COMPANY AFTER THE EXPIRATION OF ITS NEW CHEMICAL ENTITY PATENT?"

UNDER PRESSURE FOR REFORMULATION

As product developers using oral drug delivery technology, GL PharmTech is constantly considering what gaps innovators want to fill in their currently marketed products. What should be the factor to drive reformulation?

There are many reasons why currently marketed products could be reformulated. These can originate from aspects of marketing, manufacturing, regulation, generic competition, and even sometimes a purely scientific basis. These various reasons can come alone, together, or complicatedly combined.

Therefore, a single outside technology or reformulated product could not fill all the gaps or cover possible voids the innovator did not feel compelled to address at one time. This might be the driving force for why innovative pharma companies have their departments of development review outside technology as often as possible and compile it in their databases.

Whenever we imagine someone at an innovator company trying to align all the variables to find a fit for their molecules or products with outside drug delivery technologies, the picture gives a strong feeling that a new drug delivery player might be what is required to make every thing click together.

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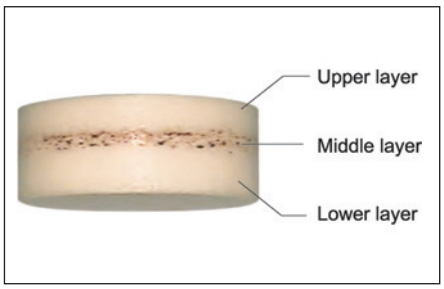


Figure 1: Triple-layered structure of GLARS

NEEDS FOR MEETING A NEW CONCEPT IN ORAL EXTENDED RELEASE

This situation could be particularly true in the field of oral extended-release dosage forms. The first big successes – OROS® from Alza (now Johnson & Johnson, New Brunswick, NJ, US) and Geomatrix® from Skyepharma (London, UK) – had a large impact in the field of oral extended-release drug delivery technology. However, there has not since been a other strong player showing a comparable, remarkable success, and the platform patents of both technologies have expired. In addition, the relatively short gastro-intestinal transit time cannot expectedly or unexpectedly give a new start to blockbuster products, even by applying the already-existing technologies. In other words, the molecule candidates on the market or under development must have a suitable half-life for those technologies to be applied.

Recently, a novel oral extended release technology was presented. Astellas Pharma (Tokyo, Japan; formerly Yamanouchi Pharma) suggested a possible cause for limited absorption in the colon and developed a new dosage form capable of dragging and retaining gastro-intestinal fluid into the dosage form itself, which could, in turn, act as drug-releasing media in the colon.[3, 4]

They found another main reason for malabsorption in the colon to be that there was no additional surrounding fluid present for active substance in dosage form to be released from, and described how this limitation could be overcome to some degree by incorporating highly water-retaining polymers into the dosage form. They named this technology OCAS (Oral Controlled Absorption System).

Up until now, Astellas has applied this technology to at least two products, according to the literature, including tamsulosin, a global leading drug for anti-benign prostatic hyperplasia (BPH), and mirabegron, an anti-incontinence drug. The reformulated tamsulosin product has been on sale in European regions under various local brand names such as Alna OCAS®, Omnic OCAS®, Flomaxtra XL®, Urolosin OCAS® and Praf T®. Mirabegron has been in Phase III clinical trials in various countries.

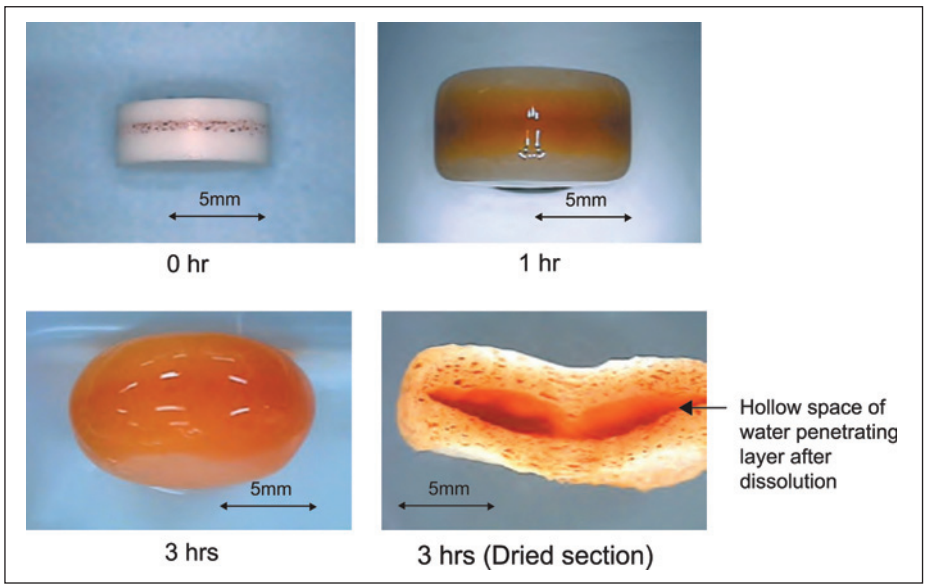


Figure 2: Morphological changes in GLARS upon water contact

The reformulated OCAS tamsulosin product was reported to show not only higher night-time maintenance of plasma concentrations during but also no food effects upon its pharmacokinetic profiles.[5, 6]

GLARS: A NOVEL INTESTINAL AND COLONIC EXTENDEND-RELEASE TECHNOLOGY

The focus of GL PharmTech over the past ten years has been on developing a technology named GLARS (Geometrically Long Absorption Regulated System). The system entraps more gastro-intestinal fluid into the dosage form at early dissolution time to give further extended absorption in the colon.

We have now reached a remarkable milestone. During the course of our work, we fabricated a triple-layered tablet, where the drug and very hydrophilic excipients are incorporated into the middle layer while highly water-retaining and swellable materials are embedded in the upper and lower layers (see Figure 1).

After oral administration, the surrounding GI fluid can penetrate very quickly into the middle layer, thus the upper and lower layers concurrently swell rapidly. These rapidly swollen upper and lower layers enclose the lateral side of the middle layer in quick-time (as shown in Figure 2).

The amount of water drawn into the tablet reaches about 3-5 times the weight of the tablet itself and it can function, in turn, as additional media which enables further later drug release out of the dosage form when it passes into the colon.[7]

The key feature of GLARS is the middle layer, where it horizontally divides the tablet structure. As long as the surrounding water penetrates into the tablet core, it can perform its role to diffuse outward from the core. During the diffusion process the water can also move upwards and downwards, and this additional diffusion, together with the diffusion of GI fluid present outside the tablet, allows the upper and lower layers to be quickly swollen and gelled, at the same time.

As is already recognised in the field, a conventional matrix sustained-release tablet has its own erosion, diffusion, swelling front, and un-swollen intact core. Achieving complete swelling of a tablet without an intact core before considerable erosion during normal gastro-intestinal transit time has appeared to be challenging. From this standpoint the insertion of a highly water-penetrating middle layer into GLARS was a radical approach.

Another feature of this system is rapid enclosing of the tablet's lateral side with the upper and lower layers in a relatively short time. As shown in Figure 3, after closing, drug release is mainly demonstrated through the enclosed lateral side, where the orange colour (from the incorporated colourant) in the middle layer is much thicker than on the other sides.

PROOF OF CONCEPT

Tamsulosin

The first target for determining whether this system could actually operate was the blockbuster molecule, tamsulosin.[8] Marketed under the name Harnal®, as well as Flomax®, this product was originally formulated into enteric-matrix granules in a hard gelatin capsule. In Asia, including Japan and Korea, a normal dose is 0.2 mg, compared with 0.4 mg in the Americas and Europe.

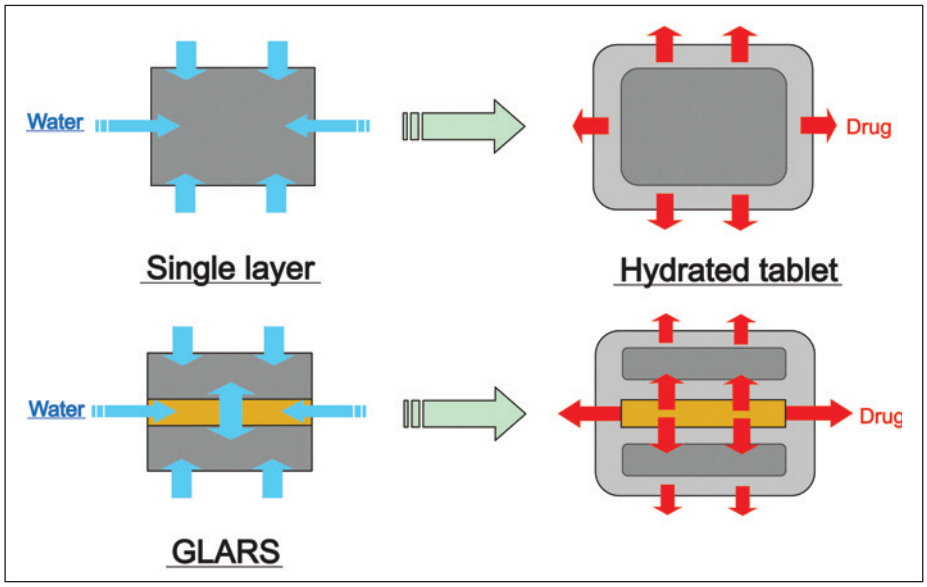


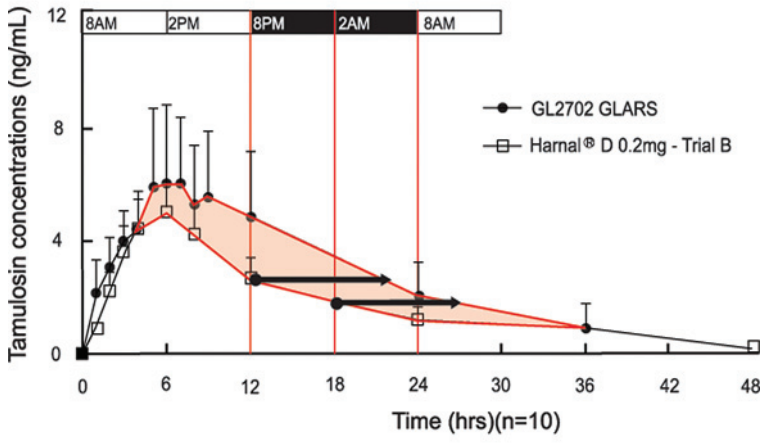
Figure 3: Schematic representation of rapid water penetration through middle layer as well as swelling and enclosing of upper and lower layers

As presented in Figure 4, Tamsulosin GLARS, including a double amount of the API (0.4mg), showed a nearly similar peak concentration to Harnal® containing only 0.2 mg of the API. Nonetheless, the extent of absorption, AUC, was not reduced but, instead, nearly doubled.

When considering normal cases of most types of drug product with dose proportionality – the greater the dose administered, the proportionally higher the pharmacokinetic parameters C_{max} and AUC. However, the GLARS system demonstrated a proportionally higher extent of absorption without a remarkable increase in the rate of absorption. This result suggests that the system can be applied to types of drugs with the very close relationship of peak concentration versus adverse effects, for which extended release dosage forms are desired.

Another finding in the application was that the therapeutic concentration was persistent even during the night. Considering reports that nocturia is a key worry frequently raised by BPH patients, longer duration of action at night could be a very meaningful step for meeting patients' ongoing needs.[9]

The relatively rigid swollen matrix structure of GLARS formulations allows drug release to be unaffected by surrounding mechanical flux, which can provide relatively consistent *in vivo* drug release irrespective of the degree of gastrointestinal motility.



Product	Cmax (ng/mL)	AUCt (hr ng/mL
Harnal® (0.2mg; qd)	5.16±0.97	69.6±22.3
GLPT's GLARS (0.4mg; qd	6.60±2.70	114.34±39.9

Figure 4: Pharmacokinetic profiles of Tamsulosin GLARS, which shows doubled extent of absorption without a dose-proportional increase of peak concentration

Tianeptine

Another proof on concept study was carried out with tianeptine, an anti-depressant, developed and marketed under the name Stablon® by Servier (Neuilly-sur-Seine, France). The purpose of the application was to determine whether the system could reduce the number of daily administrations for better patient compliance.

Figure 5 represents the results of the pharmacokinetic study, where the total amount of the API was the same, 37.5 mg. In terms of the pharmacokinetic parameters, no large difference was shown between Tianeptine GLARS (GX-2903) once daily, and three-times-daily administration of the immediate-release dosage form.

Of course, this should be further evaluated to determine whether this kind of plasma profile is clinically effective and comparable with the performance of existing immediate-release dosage forms.

CREATING EARLY PARTNERSHIPS

Several oral drug delivery technologies have come and gone, and new systems still emerge even today. However, their fates appear to be very similar to those of NCEs. Approximately five years is needed to demonstrate any pharmaceutical or clinical evidence of one technology. In addition, reformulated products must be exclusively marketed for at least ten years.

Then, we, as drug delivery industry workers, have only five years between showing evidence and launching a product into market.

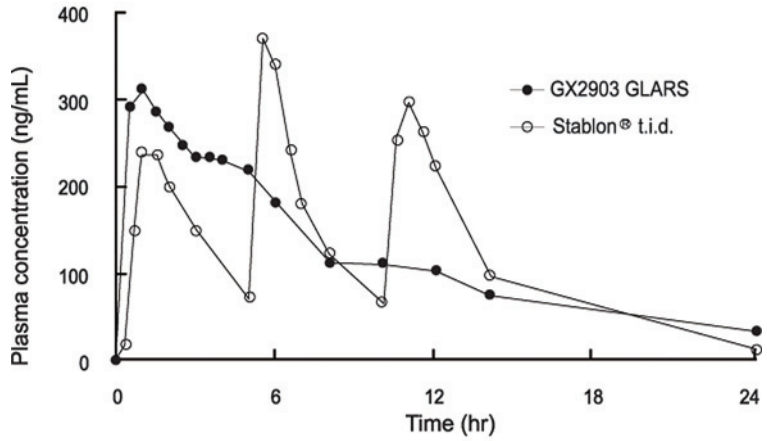
Another aspect to be considered is that there comes a time when additional innovative pharmaceutical applications are needed over the previously much-used simple matrix-type sustained release form. When exclusivity expires, there is the likely tendency of copying by generic companies in a very short time.

Considering both aspects in combination, the marriage of the NCE with the drug delivery system, through a partnership between pharma company and drug delivery company, should be created as early as possible.

Early partnering would represent a great step towards securing more valuable next-generation reformulated products.

REFERENCES:

1. *Rekhi GS. "Advances in solid dose oral drug delivery." ONdrugDelivery: Oral drug Delivery & Advanced Excipients, 2010, 14-18.*
2. *Bossart J ."Oral drug delivery: the numbers behind the business." ONdrugDelivery: Oral drug Delivery & Advanced Excipients, 2010, 4-6.*



Product	Cmax (ng/mL)	AUCt (hr ng/mL
Stablon® (12.5mg x tid)	335±107.6	2705.3±601.8
GLPT's GLARS (37.5mg qd	359.2±74.2	2849.7±622.9

Figure 5: Pharmacokinetic profiles of Tianeptine GLARS, which shows the possibility of once daily administration

3. *Sako K et al. "Influence of physical factors in gastrointestinal tract on acetaminophen release from controlled-release tablets in fasted dogs." Proceedings of the 6th Conference of the Academy of Pharmaceutical Science and Technology, Japan. 1990, 30-31.*
4. *Sako K et al. "Relationship between gelation rate of control-release acetaminophen tablets containing polyethylene oxide and colonic drug release in dogs." Pharm Res, 1996, 13(4), 594-598.*
5. *Michel MC et al. "The pharmacokinetic profile of Tamsulosin oral controlled absorption system(OCAS®)." Eur. Urol. Suppl. 2005, 4, 15-24*
6. *Djavan B et al. "The impact of Tamsulosin oral controlled absorption system(OCAS) on nocturia and the quality of sleep: preliminary results of a pilot study." Eur Urol Suppl, 2005, 4, 61-68.*
7. *Park JS et al. "A novel three-layered tablet for extended release with various layer formulations and in vitro release profiles." Drug Devel Ind Pharm, 2011, 37 (in press).*
8. *Park JS et al. "Formulation variation and in vitro-in vivo correlation for a rapidly swellable three-layered tablet of Tamsulosin HCl." Chem Pharm Bull, 2011, 59 (in press).*
9. *Schulman CC et al. "The impact of nocturia on health status and quality of life in patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia(LUTS/BPH)." Eur Urol Suppl, 2005, 4, 1-8.*

COMPANY PROFILE - MAYNE PHARMA INTERNATIONAL

A leading pharmaceutical organisation built on a heritage of 160 years of industry excellence, Mayne Pharma International is a market-driven company offering a range of drug delivery technologies. Mayne Pharma International offers contract development and commercial manufacture 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
- intellectual property and 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.

Mayne Pharma's drug delivery systems include:

Technology to control drug release
To enable pulsed release, extended release, and delayed release profiles (pellet/bead formulations produced using extrusion and marumerisation, or spheronisation processes, see below). Pellets may be tabletted or encapsulated. This technology is very flexible and it can be adapted to the specific formulation needs of a particular drug substance.

Technology to improve oral bioavailability
Particularly for insoluble drugs (SUBA™ technology, see below).

Technology to taste mask liquids and tablets
To improve palatability and aid swallowing (Cleantaste™ technology, see below).

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. Pellets can be presented in capsule or tablet dosage forms.

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

- The first of these processes, which allows drug 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 these particles with an appropriate polymer. Mayne Pharma International has particular expertise in polymer selection and processing. The company can also work with a wide range of solvent systems.

SUBA™

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

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

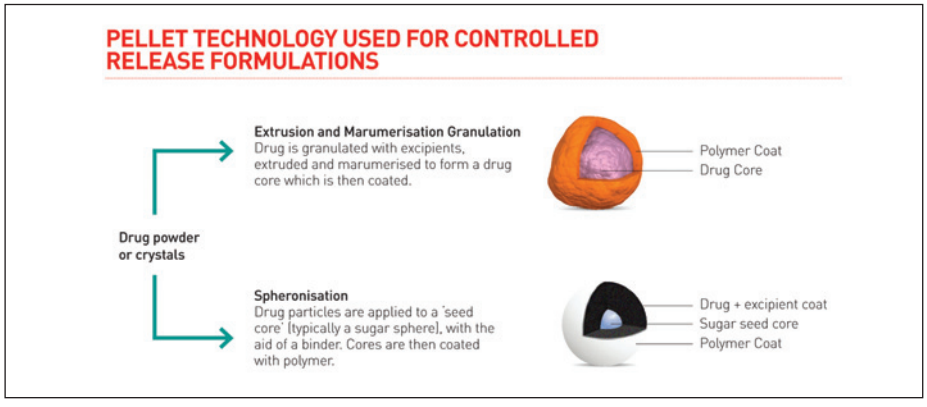
CLEANTASTE™

Cleantaste™ technology allows a polymer coat to be applied to very small 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 and ambroxol have been commercialised and launched in Australia, the US and Japan.

SERVICES SUMMARY

Mayne Pharma International can develop and manufacture oral and topical formulations for clinical trials and commercial supply. Mayne Pharma International can provide:

- **Tablets** (immediate, extended, delayed or pulsed release and taste masked)
- **Capsules** (powder, pellets (beads)
- **Liquids and Creams**



Pellet technology used for controlled release formulations.

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

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.

ABOUT MAYNE PHARMA

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

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:

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

The site is approved by all major regulatory authorities:

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

Mayne Pharma International has generated numerous patents in the drug delivery field.

• 9 patent families
• 48 registered patents
• 14 pending applications

Mayne Pharma International is located at Salisbury (Adelaide), South Australia. There is 12,000 m^2 of manufacturing space on a 19-hectare site. Mayne Pharma International is a wholly owned subsidiary of Mayne Pharma Group Ltd, an Australian public company listed on the ASX.

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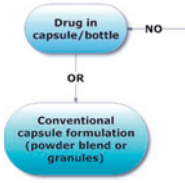
molecular profiles™

PHARMACEUTICAL DEVELOPMENT SERVICES



FROM POWDER TO PILL:

A RATIONAL APPROACH TO FORMULATING FOR FIRST-INTO-MAN STUDIES

Making the right choice of formulation for the first-into-human studies of a product candidate is extremely important and has significant time and cost implications for the development programme. Here, Robert Harris, PhD, Director, Early Development at Molecular Profiles, describes various formulation options available and suggests methods that can be used to select the best formulation option for a new orally delivered drug substance.

A new experimental drug substance shows great promise from pre-clinical studies for the treatment of a disease which afflicts millions of patients worldwide. What is the best strategy for testing the drug in man for the first time? This is a question that all companies developing new drugs face on a regular basis.

Entering Phase I clinical trials is a key milestone in any drug development project and to reach this stage as quickly as possible is of paramount importance – especially for those with limited budgets. Of equal importance is to ensure that the new drug substance is administered in a form that will give it the best chance of success in early clinical assessment. A poor choice of formulation strategy can lead to poor clinical data – which can lead to re-formulation and a prolonged Phase I clinical programme, or even termination of the project.

So how do you decide what is the best formulation for a new drug, assuming at this stage that it is intended for oral administration?

KNOW YOUR DRUG SUBSTANCE

From preclinical studies, there should be sufficient information to be able to define the drug according to its water-solubility and permeability characteristics in accordance with the biopharmaceutics classification system (BCS).[1] Also, Lipinski's "Rule of Five" [2] is a useful tool in predicting the oral bioavailability of drug molecules based on certain molecular attributes.

The BCS has proved a useful tool to formulators for classifying drug substances, but its primary purpose is for establishing criteria for biowaivers, and alternative 'developability' classification systems have recently been proposed.[3,4]

How well a drug is absorbed into the bloodstream from the gastro-intestinal tract (GIT) is governed predominantly by (i) drug solubility in the gastric and intestinal fluids and (ii) permeability through cell lipid bilayers. BCS Class I drugs are freely soluble in GIT fluids and permeate easily through lipid bilayers. These drugs are well absorbed when given orally and present the easiest task when choosing a formulation strategy. BCS Class IV drugs on the other hand are defined as poorly soluble (in GIT fluids) and permeate poorly across lipid bilayers. Consequently, these drugs exhibit poor oral bioavailability and pose the formulator the greatest challenge.

Additional physicochemical and biological factors which can challenge formulators are:

- Drug instability:
  - during processing or in the formulation (e.g. apomorphine)
  - in the GIT (e.g. when drug is acid labile, as with omeprazole).
- Narrow absorption window in the intestine (e.g. acyclovir, captopril).
- Drug metabolism and/or efflux within the intestinal wall (e.g. cyclosporin A).

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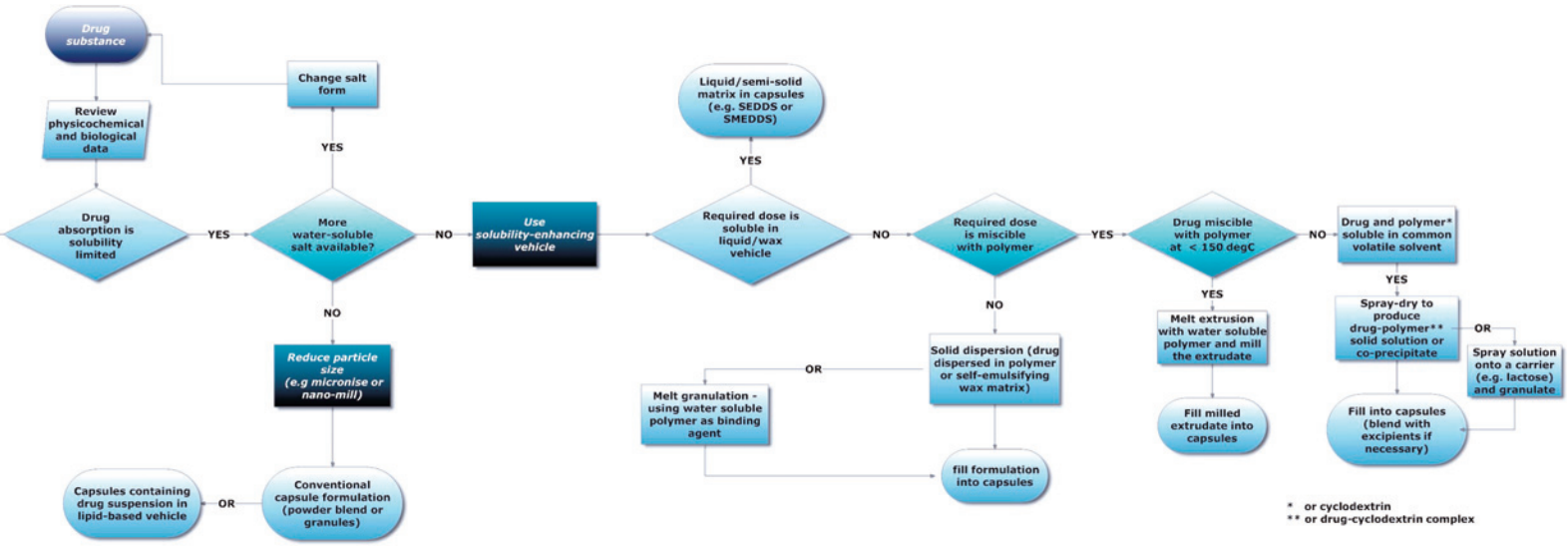


Figure 1: Formulation strategy decision tree for 'first-into-human' studies.

Drug absorption and metabolism can vary between animal species and therefore it is not always possible to predict the influence of biological factors (e.g. pre-systemic metabolism) on drug uptake in humans from preclinical animal studies.

DECIDE ON A FORMULATION STRATEGY

For first-into-human studies it is usual to administer the drug either as powder-in-bottle (for reconstitution prior to administration) or in capsules, which offer the greatest flexibility for dose adjustment. Choosing a formulation will depend on the properties of the drug substance and the target dose. Decision trees can be very effective tools in helping select the most appropriate formulation strategy.[5,6] Figure 1 is an example of a decision tree which can be used to select a suitable formulation strategy for first-into-human clinical trials.

The simplest formulation strategy is not to formulate – just administer the drug substance with no additional excipients. In this case the required quantity of drug active is added directly to a container (for reconstitution with a suitable liquid prior to ingestion) or to a capsule. This approach is widely used within the industry as it significantly reduces the time and cost for progressing to first-into-man studies. For small quantities of units the active is weighed into each capsule or bottle by hand. For large quantities of capsules or where the required dose is < 10 mg, capsule filling can be achieved accurately by use of specialised precision powder dosing equipment (for example, Xcelodose® (Capsugel, Peapack, NJ, US), as shown in Figure 2).

The 'drug-in-capsule/bottle' approach is particularly suited for BCS Class I compounds, which are absorbed easily from the GIT.

Although there are obvious benefits in adopting a drug-in-capsule/bottle approach, it should be considered with caution if the compound is not BCS Class I. If a drug substance does not wet easily or if its solubility in water is poor the drug may be poorly absorbed from the GIT and hence exhibit poor bioavailability. If there is a known history of poor or variable absorption in animal models then a formulation strategy to enhance water-solubility of the drug substance should be considered.

Two basic principles for enhancing water-solubility of the drug substance are (i) reduction of the particle size of the drug substance and (ii) use of solubility-enhancing vehicles.

Brief descriptions of typical solubility-enhancing formulation strategies are given below. Regardless of the formulation strategy chosen, it is vital to assess drug solubility following dilution of the test formulations in aqueous media. The dissolution test procedures used should simulate both gastric and intestinal conditions (in terms of pH, fluid volume, etc).

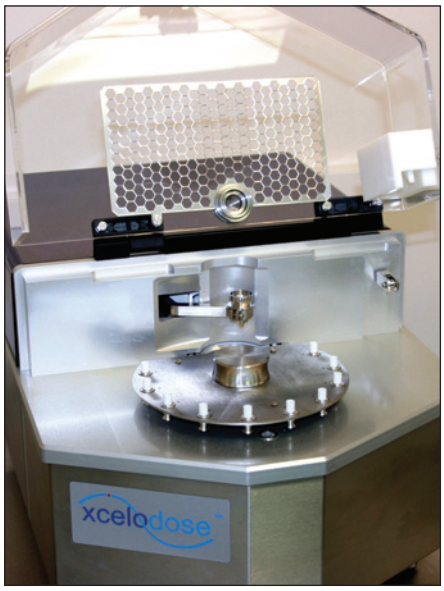


Figure 2: Xcelodose® precision powder dispenser.

Particle size reduction

Increasing the overall surface area of a solid can lead to more rapid dissolution of the drug substance. Micronising equipment (e.g. fluid energy mills) can reduce particle size down to 2-10 μm. Taking the principle of size reduction even further, there are now technologies available to produce submicron 'nanocrystals' through precipitation (bottom up) or wet milling (top down) techniques.[7,8] Following particle size reduction the drug substance can be dispensed into capsules, either as drug alone or as a powder blend (with excipients), depending on the required dose and flow properties of the milled drug substance.

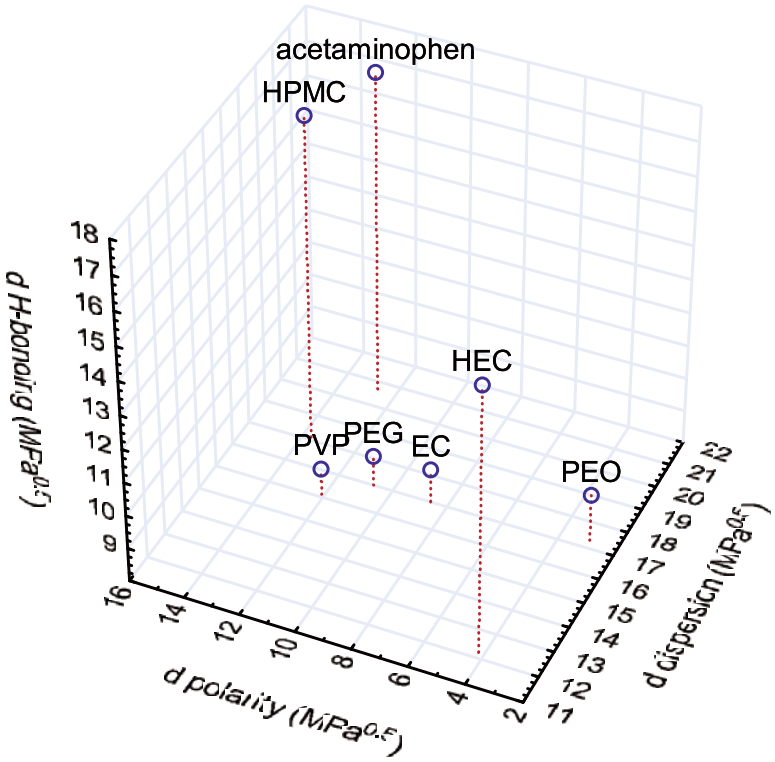
Solubility-enhancing vehicles

For each of the strategies described below the resulting formulation can be filled into capsule shells for administration. Capsule filling machines which are suitable for this purpose include the IN-CAP® (Dott. Bonapace, Limbiate, Italy), suitable for powders or liquids/semi-solids, and the CFS 1200 (Capsugel) which is suitable for liquids/semi-solids.

Solution/semi-solid capsule formulations:

If the drug can be dissolved in a suitable pharmaceutically acceptable vehicle then it may be appropriate to consider preparation of a solution of the drug which can be filled into capsules. The main benefit of this approach is that pre-dissolving the compound overcomes the initial rate limiting step of particulate dissolution in the aqueous environment within the GIT.

However, a potential problem is that the drug may precipitate out of solution when the formulation disperses in the GIT, particularly if the solvent is miscible with water (e.g. polyethylene glycol). If the drug is sufficiently lipophilic to dissolve in a lipid vehicle there is less potential for precipitation on dilution in the GIT, as partitioning kinetics will favour the drug remaining in the lipid drop-



PVP= polyvinyl pyrrolidone **PEG=** polyethylene glycol **EC=** ethyl cellulose
HEC= hydroxyethyl cellulose **PEO=** polyethylene oxide **HPMC=** hydroxypropylmethyl cellulose

Figure 3: Comparison of acetaminophen and polymer excipients according to their Hansen partial solubility parameters.

lets. Also, lipidic vehicles are generally well absorbed from the GIT and in many cases this approach alone can significantly improve the oral bioavailability [9,10] compared with administration of the solid drug substance, but there may be significant inter and intra-subject variation in drug uptake, depending on the capacity of individuals to digest these lipid-based formulations.

In recent years there have been significant advances in the use of lipidic excipients and surfactants to produce self-emulsifying drug delivery systems (SEDDS) and self-micro-emulsifying drug delivery systems (SMEDDS) for oral drug delivery.[11] These formulations form emulsions or micro-emulsions spontaneously on contact with aqueous media. Both SEDDS and SMEDDS use pharmaceutically acceptable surfactant excipients to achieve self-emulsification, therefore eliminating the reliance on the gastro-intestinal secretions (such as bile salts) to emulsify the lipids in the formulation.

Solid solutions

Solid solutions [12] (also sometimes described as solid dispersions) are molecular dispersions of the drug molecules in a polymer matrix. This approach combines two principles to enhance water solubility of a drug:

1. *Conversion of the drug material into its amorphous state* – generally, a drug substance is easier to dissolve when in the amorphous state compared with the crystalline state, due to absence of ordered intermolecular bonds
2. *Incorporation of the amorphous drug substance in a hydrophilic polymeric matrix* – a number of hydrophilic, polymeric materials have been used as solubility-enhancing matrices for drug substances. For example, polyvinyl pyrrolidone (PVP) and polyethylene glycol (PEG 6000) have been used for preparing solid solutions containing poorly soluble drugs.

Solid solutions can be prepared by dissolving both the drug compound and the polymer in a suitable volatile solvent. On removing the solvent (e.g. by spray drying) an amorphous drug-polymer complex is produced. On cooling, the drug is then trapped in an amorphous state within the water-soluble polymer matrix, thus enhancing the water-solubility of the drug.

One potential problem with this type of formulation is that the drug may favour a more thermodynamically stable crystalline state, which can result in the drug compound crystallising in the polymer matrix. Therefore the physical stability of such formulations needs to be assessed using techniques such as differential scanning calorimetry (DSC) and X-ray crystallography.

For formulations in which the drug is to be dissolved (in liquid or solid vehicles) miscibility of the drug substance with the vehicle is a key requirement – to maximise water-solubility of the drug and to maintain the physical stability of the formulation (i.e. prevent drug precipitation). A comparison of the solubility parameters for drug and excipients can be used to predict miscibility of the drug the excipients.[13,14,15] The closer together the solubility parameters are between drug and excipient the higher the probability of the drug and excipient being miscible. An example of how this information can be used to gauge miscibility of drug with excipients is illustrated in Figure 3. The graph shows that the polymer with the closest spatial proximity to acetaminophen is HPMC and we would therefore expect there to be a high probability that the drug will be miscible in this polymer.

SOLID DISPERSIONS

Solid dispersions are similar to solid solution formulations, except that the drug exists in the form of discrete particles dispersed within a polymer or wax matrix.

MELT EXTRUSION

This technique [16,17] is an extension of the 'solid solution' approach described previously. It consists of extruding a co-melt of the drug substance and a polymer through a heated screw to produce a solid extrudate which can then be milled to produce granules (for encapsulation or compression into tablets). As with the solid solution approach, the production of a melt extruded drug/polymer matrix is an effective method of increasing the water solubility of a poorly water-soluble drug substance. The effectiveness of this approach depends on miscibility of drug and polymer substances and on the drug substance and the polymer exhibiting similar melting points.

MELT GRANULATION

With this approach a water soluble polymer is used as a binding agent in a powder mixture to produce a granule blend. The blend is heated to a temperature at which the polymer binding agent softens (without completely melting) which results in formation of aggregates comprised of the drug and excipients. The granule mass is then cooled, sieved and is then suitable

for either encapsulation or compression into tablets. This technique has proved to be effective in enhancing water-solubility of several drugs.[18,19]

INCLUSION COMPLEXES SUCH AS CYCLODEXTRINS

Cyclodextrins [20] are doughnut-shaped molecules with a lipophilic surface on the inside ring and a hydrophilic surface on the outer surface of the ring. The principle behind this strategy is that the poorly soluble drug molecule fits into the inner ring and the outer hydrophilic surface of the cyclodextrin holds the complex in solution. The inclusion complex can be prepared by dissolving the drug and cyclodextrin in a common solvent or by solid-state mixing of the materials using a high-attrition technique, such as ball milling.

CONCLUSION

In conclusion, a number of factors need to be taken into consideration in deciding how best to take a new drug entity into first-into-man studies. The drug-in-capsule approach is often seen as a cost effective and time saving option for testing a drug in Phase I studies. Indeed, it significantly reduces the complexity of early stage development and progression from drug substance to a Phase I clinical trial can be achieved within weeks. However, if the drug substance has known solubility/bioavailability limitations (as is the case for more than 40% of NCEs) then due consideration should be given to formulation strategies which can enhance drug solubility in the GIT.

Developing a suitable drug formulation for first-into-human studies can be problematic and time consuming, especially for poorly water-soluble drugs. By predicting drug-excipient miscibility (through comparison of solubility parameters) and subsequently using a decision tree approach for choosing an appropriate formulation strategy, it is possible to eliminate a significant proportion of trial and error from a drug formulation development project. This rational approach to formulation development offers obvious advantages in reducing time for project completion and maximising the effectiveness of formulations for Phase I studies.

REFERENCES

1. *FDA Guidance for Industry. "Waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system." (August, 2000).*
2. *Lipinski, CA et al. "Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings." Adv. Drug Deliv. Rev. (1997), 23: 3-25.*
3. *Wu, CY & Benet, LZ. "Predicting drug disposition via application of BCS: transport/absorption/elimination interplay and development of a biopharmaceutics drug disposition classification system." Pharm. Res. (2005), 22: 11-23.*
4. *Butler, JM and Dressman, JB. "The developability classification system: application of biopharmaceutics concepts to formulation development." J. Pharm. Sci. (2010), 99: 4940-4954.*
5. *Brachu. S, et al. "A decision-support tool for the formulation of orally active, poorly soluble compounds." Eur. J. Pharm. Sci. (2007), 32: 128-139.*
6. *Hariharan, M, et al. "Reducing the time to develop and manufacture formulations for first oral dose in humans." Pharm. Tech., October 2003, 68-84.*
7. *Kesisoglou, F, et al. "Nanosizing — Oral formulation development and biopharmaceutical evaluation." Adv. Drug Deliv. Rev. (2007), 59: 631–644.*
8. *Eerdenbrugh, BV, et al. "Top-down production of drug nanocrystals: Nanosuspension stabilisation, miniturization and transformation into solid products." Int. J. Pharm. (2008), 364: 64-75.*
9. *Hauss, DJ. "Oral lipid-based formulations." Adv. Drug Deliv. Rev. (2007), 59: 667–676.*
10. *O'Driscoll, CM & Griffin, BT. "Biopharmaceutical challenges associated with drugs with low aqueous solubility – the potential impact of lipid-based formulations." Adv. Drug Deliv. Rev. (2008), 60: 617–624.*
11. *Pouton, CW & Porter, CJH. "Formulation of lipid-based delivery systems for oral administration: Materials, methods and strategies." Adv. Drug Deliv. Rev. (2008), 60: 625–637.*
12. *Vasconcelos, T, et al. "Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs." Drug Discovery Today (2007), 12: 1068-1075.*
13. *Greenhalgh, DJ, et al. "Solubility parameters as predictors of miscibility in solid dispersions." J. Pharm. Sci. (1999), 88: 1182-1190.*
14. *Adamska, K, et al. "Selection of solubility parameters for characterization of pharmaceutical excipients." J. Chromatogr. A (2007), 1171: 90-97.*
15. *Albers, J, et al. "Evaluation of predictive models for stable solid solution formation." J. Pharm. Sci. (2011): 100: 667-680.*
16. *Crowley, MM, et al. "Pharmaceutical applications of hot-melt extrusion: Part 1." Drug. Dev. Ind. Pharm. (2007), 33: 909-926*
17. *Repka, MA, et al. "Pharmaceutical applications of hot-melt extrusion: Part 2." Drug. Dev. Ind. Pharm. (2007), 33: 1043-1057*
18. *Yang, D, et al. "Effect of the melt granulation technique on the dissolution characteristics of griseofulvin." Int. J. Pharm. (2007), 329: 72-80.*
19. *Passerini, N, et al. "Preparation and characterisation of ibuprofen–poloxamer 188 granules obtained by melt granulation." Eur. J. Pharm. Sci., (2002), 15: 71–78.*
20. *Brewster, ME & Loftsson, T. "Cyclodextrins as pharmaceutical solubilizers." Adv. Drug Deliv. Rev., (2007), 59: 645–666.*

Flamel Technologies

LIQUITIME* ORAL LIQUID CONTROLLED RELEASE DRUG DELIVERY PLATFORM

In this article, Camille Rivail, Business Development Analyst, and Jean Chatellier, PhD, Vice-President, Alliance Management, both of Flamel Technologies, describe the company's LiquiTime technology, which enables liquid formulations that are palatable, can incorporate various modified-release profiles, and are stable with long shelf-lives. The technology meets the need for liquid oral formulations in the large and growing number of patients who have difficulty swallowing conventional tablets and capsules, including the young and the elderly.

Paediatric and geriatric drug delivery are major challenges in drug development: it is estimated that 50% of the population have difficulties in swallowing solid oral dosage forms. This is especially true among children under 12 years and the elderly; there is a real need for age-adapted formulations to promote better treatment compliance.

Indeed, patients have been found to break tablets into fragments in order to facilitate administration or to adapt the dose, generating major risks such as inaccurate dosing, or stability issues of the residual fragments.

Liquid formulations are thus one of the most appropriate dosage forms for these subpopulations, as they allow better compliance compared with classic tablets or capsules as well as better dose adaptability (age- and weight-dependent).

However, a number of challenges are related to the use of liquid formulations:

- The palatability or taste of the solution, which must be sufficiently agreeable in flavour to be consumed. With respect to bitter-tasting drugs, adding sweeteners and flavors to mask the taste is often not sufficient.
- A lack of enteric or modified drug delivery technologies as compared with tablets and capsules.
- Stability issues of drugs in liquid form.

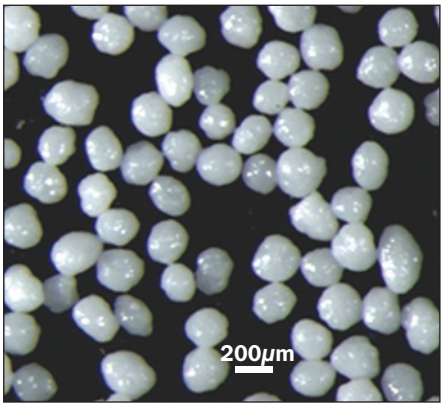


Figure 1 : Flamel Technologies' LiquiTime-based coated microparticles have an average diameter <200 µm.

LiquiTime, Flamel Technologies' innovative delivery platform, meets these different challenges.

Based on a multi-microparticles approach, LiquiTime allows stable, controlled-release, ready-to-use liquid oral suspensions, with good "mouth feel", of one or several combined drugs over time.

The microparticles (shown in Figure 1) are composed of a drug core coated with a proprietary multifunctional diffusion film. The expertise developed by Flamel in coating in fluidised beds allows accurate and reproducible coating on very small drug cores to manufacture microparticles with narrow size distribution and final particle diameters below 200 µm.

The microparticles size and the narrow distribution optimise mouth-feel, generating a smooth, liquid formulation with the possibility to adjust the flavour using aroma agents. The encapsulation of the active within the microparticles allows taste-masking, even for the most unpleasant-tasting drugs.

LiquiTime enables tailoring and accurate fitting of any release profile, especially zero-order kinetics, to optimise pharmacokinetics (Figure 2) for a wide range of therapeutic applications and drugs (unlike ion exchange resin-complex technology, which is limited solely to ionic drugs).

Other benefits may also be obtained, such as the possibility to mix immediate-release and extended-release kinetics for fast onset and extended release, or the possibility of mixing different drugs with different release kinetics. The multiparticulate nature of the dosage form minimises inter- and intra-individual variation as compared with conventional tablets or capsules.

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Regarding stability, one of the main technical hurdles related to liquid forms is to maintain the performance of the drug over time to provide an acceptable shelf-life. Due to its unique approach, LiquiTime has demonstrated long-term physical and performance stability of over 24 months of storage.

The physical properties of LiquiTime, such as viscosity, density, have been optimised to ensure precise and reproducible sampling to be delivered with existing marketed dosing devices (for example, plastic syringes), allowing flexible and accurate dose titration adapted to individual patients.

Development time of LiquiTime formulations has been optimised through the use of cutting-edge equipment and the skill and experience of the Flamel development team. Beyond the lab, cGMP manufacturing of clinical trial material and scale-up to commercial size can be rapidly executed at Flamel's US FDA-approved industrial plant.

LiquiTime is protected by a strong IP portfolio, including several granted patents in territories including the US, EU and Japan.

KEY BENEFITS OF LIQUITIME

- Easy to swallow, good mouth feeling, taste masked
- Liquid formulations stable over 24 months
- Applicable to a wide range of drugs, not limited to ionic drugs as with resin-complex based technology
- Zero-order kinetics
- Combination of immediate-release and extended-release kinetics possible
- Combination in the same formulation of different drugs with different release kinetics possible
- Use GRAS materials to warrant safety
- Rapid development time under cGMP conditions
- Ease to scale-up to industrial scale
- Clinical Proof of Concept achieved in humans for a liquid suspension of an undisclosed drug for treatment of children
- Broad and strong IP protection

ABOUT FLAMEL TECHNOLOGIES

Flamel Technologies SA (NASDAQ: FLML) is a leading drug delivery company focused on the goal of developing safer, more efficacious formulations of drugs that address unmet medical needs.

Flamel Technologies has collaborations with a number of leading pharmaceutical and biotechnology companies, including Baxter, GlaxoSmithKline (Coreg CR®, carvedilol phosphate), Merck Serono and Pfizer.

Its product development pipeline includes biological and chemical drugs formulated with the Micropump®, Medusa® and other proprietary platforms.

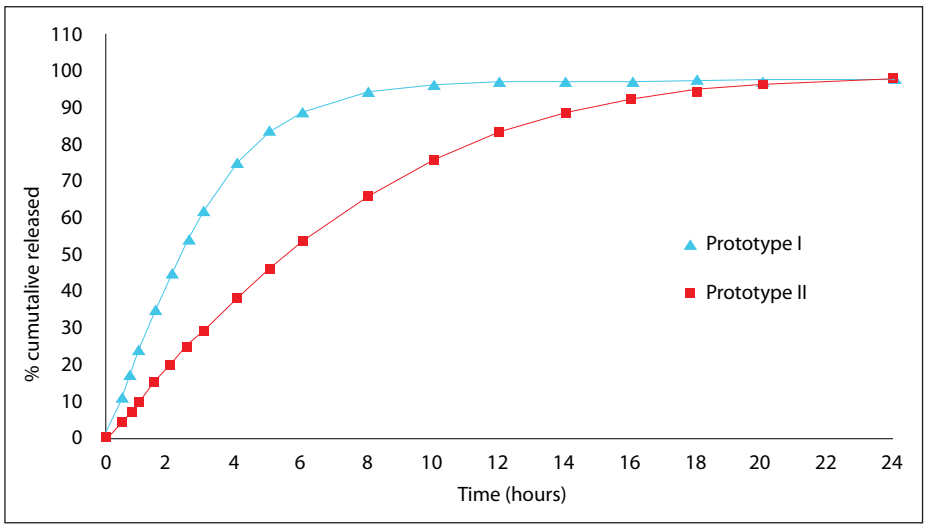

Figure 2: This graph illustrates the different zero-order release profiles achieved for LiquiTime-based formulations (easily tailored to obtain the appropriated targeted product profile).

MICROPUMP

The Micropump micro-encapsulation oral drug delivery platform, for the formulation and the controlled release of chemical drugs, is designed to increase absorption time, particularly for drugs only absorbed in the small intestine, and to deliver the drug to specific sites in the gastro-intestinal tract. Micropump allows tailoring the exact kinetics required to optimise the final product and offers the advantage of easily and accurately mixing microparticles with different release kinetics, in different ratios, with every individual particle performing independently. A single Micropump formulation can be presented in various dosage forms such as capsule, tablet, sachet or oral suspensions without affecting the release rate.

Flamel has developed US FDA- and EMA-approved products and manufactures Micropump-based microparticles.

TRIGGER LOCK™

In addition to Micropump and LiquiTime, Flamel has developed another oral drug delivery technology, Trigger Lock™, which provides controlled release of narcotic and opioid analgesics while deterring tampering (particles cannot be crushed to extract the active).

MEDUSA

Medusa is a proprietary injectable nanogel platform for the formulation and/or the extended release of a broad range of biologics (including proteins, antibodies, peptides and vaccines) and of small molecules. The nanogel has been proven to be safe and biodegradable (DMF filed with the FDA in February 2011).

Medusa enables the controlled delivery from one day up to 14 days of non-modified drugs that remain fully active (as opposed to protein engineering or chemical modification approaches). It may be used to develop Biobetters with potentially improved efficacy, reduced toxicity and enhanced patient compliance. Several Medusa-based products are at various clinical stages of development. Flamel's lead internal Medusa-based product candidate IFN-a XL (long-acting interferon alpha-2b) is currently the subject of a Phase II trial in HCV patients.

DeliVax*, Medusa's vaccine application, permits the efficient formulation of vaccines.

These versatile drug delivery platforms may be used to address threshold formulation problems such as poor solubility, aggregation and instability for both chemical and biological drugs. Flamel's innovative delivery platforms are used for the lifecycle management of marketed products, including Biobetters, and the development of new compounds with many unique competitive advantages:

- Improvement of drug characteristics such as efficacy, bioavailability and pharmacokinetics
- Improvement of the drug safety profile with a noticeable diminution of peak dose concentrations, which in turn allows administration of higher effective doses and potentially greater efficacy
- Potential improvement of patient compliance due to reduced side-effects and greater convenience
- Protection of market position through patent extension and/or product differentiation
- Extension of market to new indications and new patient populations.

* *pending trademarks*

FORMULATION FLEXIBILITY BROADENS THE SCOPE FOR ORAL THIN FILM TECHNOLOGY

Oral thin films were first launched in 2004 for systemic drug delivery and are now widely accepted. In this article, Scott Barnhart, MS, Technical Director, and Martha Sloboda, MBA, Business Manager, both of ARx, LLC, detail the latest formulation and manufacturing techniques for oral thin films and describe how novel forms with, for example, controlled-release capabilities are emerging.

Rapidly dissolving oral thin films (OTFs; see Figure 1) are widely accepted by patients and caregivers for their ease-of-delivery, portability and accurate dosing. Since the first commercial launch of OTFs for systemic drug delivery in 2004, [1] the platform has evolved as more pharmaceutical researchers evaluate ways to apply the benefits of this technology across more markets and therapeutic classes for localised and systemic drug delivery.

As a result of these efforts, new applications are emerging. Advances in chemistries and the manufacturing processes used in the formulation and scale-up of this technology play a significant role in advancing the potential of OTFs beyond immediate-release oral applications.

OTF FORMULATION

The chemistry and art behind formulating OTFs draws on polymer expertise derived from traditional solid, buccal and transdermal dosage forms. By understanding these formats and leveraging their similarities, formulators can effectively deliver unique and compliant products within a shortened product development timeframe.

The formulation flexibility of the OTF platform enables formulators to evaluate a broad range of excipients and active pharmaceutical ingredient (API) forms when embarking on new product development initiatives. This formulation flexibility may also increase a programme's chance for success by presenting chemists with a wider range of available material sets to produce both an acceptable and stable product.

When selecting an OTF to replace an existing product, the film's dissolution rate, material selection and absorption rate are all considered so that an equivalent or an improved product profile may be produced over existing liquids, capsules and tablets. The robustness of thin-film dosage forms has been demonstrated through 24-month ICH stability studies.

Ongoing research is extending the dissolvable film technology to more complicated systems for modified or controlled release. This also includes applications for topical delivery. In some cases, there is convergence with transdermal technology that enables films to have more tangible adhesive properties such as increased dwell time in the mouth or other alternative delivery sites. This work relies on a strong understanding of the suitability, compatibility, and availability of material sets.

EXCIPIENTS

Robust OTFs are developed using current commercially available generally regarded as safe (GRAS) excipients. Most major excipient suppliers of solid oral dosage forms materials now offer excipients that are appropriate for use in OTFs and potentially enhance disintegration properties.

The majority of film formulations are first compounded as a liquid prior to being cast into films. A host of water, solvents, and combinations of both exist as process aides. Based on the solubility and compatibility of the API, a formulator can choose to develop a 100% water-based system; or in the event that the API degrades in water, other pharmaceutically-acceptable organic solvents can be selected. Solvent selection can also be used to enhance manufacturing efficiency based on the relative

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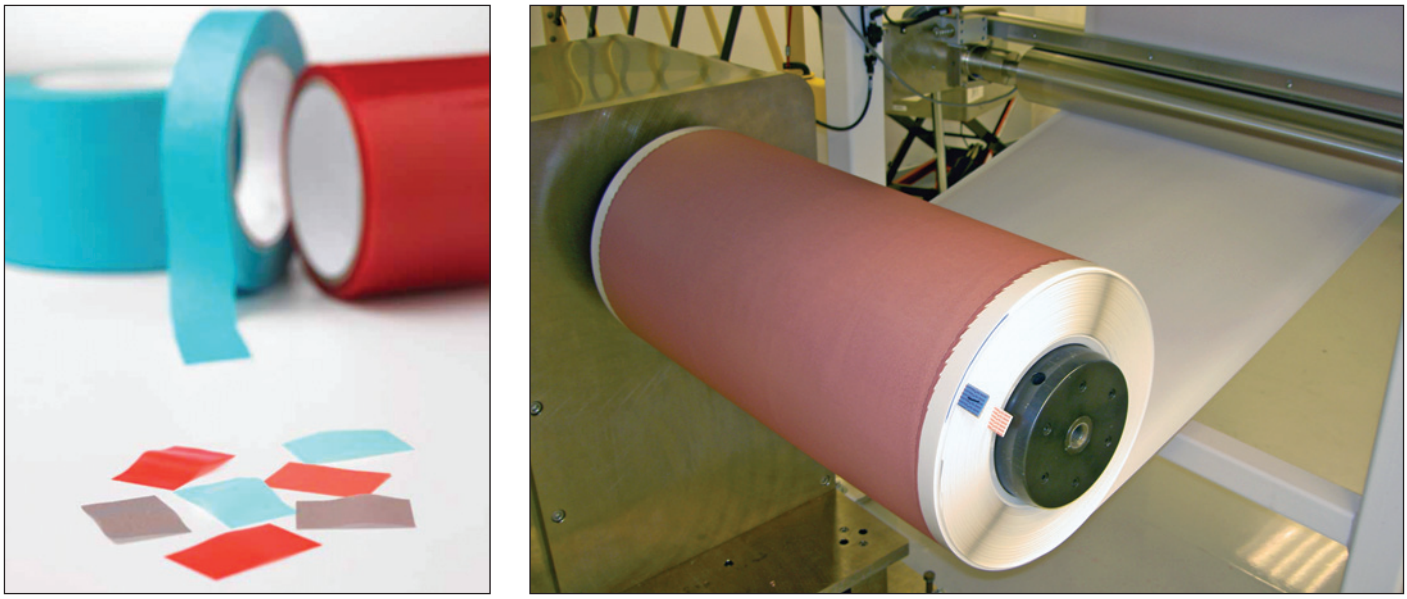

Figure 1: Rolls of dissolvable films (left) and film being wound on a roll (right).

energy required to remove the volatile liquid during the film casting process.

RELEASE LINERS

Significant research and expertise derived from the transdermal arena has resulted in a wide range of release liner technologies that may be used as processing aids in the manufacture of OTFs. These materials are comprised of a plastic film or paper substrate coated with silicone or non-silicone chemistries for a clean release of the film when appropriate in the conversion process. By coating a compounded liquid formulation to a continuous web of release liner material, film manufacturers are able to maintain the integrity of the OTF film product throughout the manufacturing process because this component provides added strength, support and environmental protection to wound rolls of OTF film prior to finishing. Release liners can be incorporated strictly as a processing aide that is removed in the film finishing stage, or as seen in new product launches, this component can remain affixed to the OTF to aid in dispensing and administering the drug product.

ACTIVE INGREDIENTS

OTFs can integrate most available forms of APIs, including micronised, granulated, salt, and free-base forms. Both soluble and insoluble drugs have been successfully compounded into solutions, emulsions, or dispersions that have subsequently resulted in the launches of the OTF products currently available in the market today. Larger particle size compounds do present some constraints in regards to the final OTF's thickness, but in general, most APIs and nutritional compound particle size distributions fall within typical OTF production requirements.

A number of taste-masking options exist and have been used in the development of OTFs. This includes sophisticated masking technology specifically designed for highly bitter materials with an affinity for the oral cavity. Key considerations in selecting any taste-masking approach beyond palatability include cost, impact to API particle size or mass and solvent compatibility.

Researchers have some latitude in both how much API can be incorporated and how other product attributes can be tailored for each thin film drug product. API concentrations are typically limited to 50% of the final unit mass. However, the size of the final unit strip is adjustable to deliver the proper dose. Thicker OTFs can be produced to yield higher strengths. In this case, it is up to the formulator to determine at what point the thickness of the product detracts from the desired disintegration profile. Furthermore, a formulator can elect to produce multiple formulas to obtain multiple strengths for a specific API, or produce a single formula that is cut into multiple strengths based on the size of the unit area. For

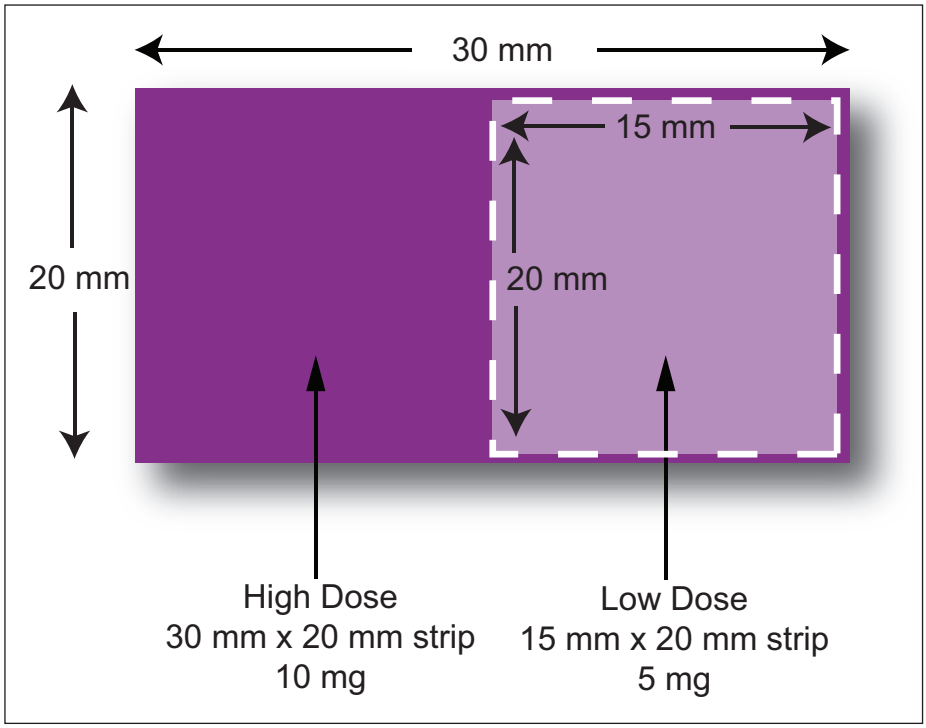

Figure 2: Formulators can choose to produce a single OTF formula that is cut into multiple strengths based on the size of the unit area.

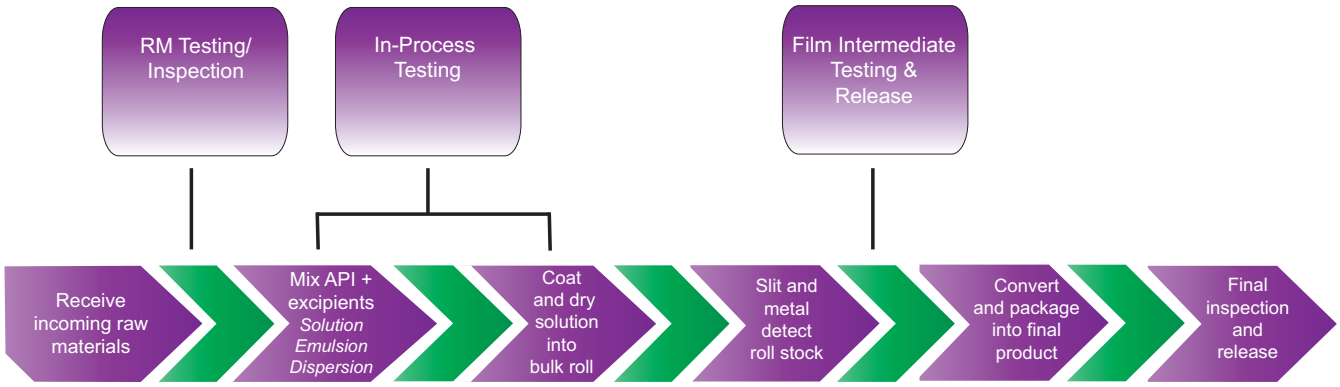

Figure 3: The manufacturing techniques for oral thin films are well understood and lend themselves to holding exceptionally tight tolerances throughout the process.

example, 10 mg strength of a given formula could become a 5 mg strength dose by halving the unit size with no additional formulary work required (see Figure 2).

Looking forward, the use of micronised and nano particle APIs in OTFs opens the door for potentially more effective drug delivery methods. With the increased surface area of the API and the larger direct-contact surface area of the film, there is the possibility to improve bioavailability and to increase uptake from the mucosal surface. By modifying the residence time of the OTF on the mucosal tissue in conjunction with the micronised or nano-API, early stage work suggests that this type of system has the potential to effectively deliver drugs in a shorter timeframe.

OTF MANUFACTURE

Based on precision adhesive coating technologies used for decades in the transdermal industry, the manufacturing techniques for OTFs are well-understood and lend themselves to holding exceptionally tight tolerances throughout the process. The precision-coating techniques derived from transdermal production are now used for producing OTF base chemistries into final individual doses with unit tolerances as tight as ± 2.5% around the potency target.[2] Specialised coat-weight monitoring systems and liquid deposition techniques enable any OTF product to hold and maintain consistent cross and downstream uniformity during manufacture. This continuous process monitoring also lends itself to process analytical technology (PAT) initiatives and identifying any processing variability in real time (Figure 3).

Coating technology from other markets continues to advance OTF production and cost-effectiveness. Multi-functional mixers drawn from the food industry enable multiple products to be manufactured out of the same process footprint. New approaches in coating techniques are leading to more sophisticated OTF constructions. An example of this can be seen in the adhesive coating techniques utilised in the electronics market for enabling multi-lane simultaneous coating. [3] By applying this technique to OTF manufacturing, the potential exists to coat incompatible materials, or synergistic chemistries, side-by-side without triggering any pre-dose reaction.

Packaging has commonly been a single-unit dosage format that accommodates one or two strips per pouch and enables portability of the product. It also allows for multiple-count options to accommodate dispensing needs and regional requirements. However, a number of new, stable formats are emerging that maintain dose integrity while also offering a more cost-effective dispensing option that complies with stability and regulatory requirements.

The manufacturing flexibility of OTFs reduces capital requirements and capacity consumption. It also enables formulators to consider new options for delivery. Because these manufacturing approaches are also well understood and controlled, robust, efficient development can occur from bench to commercial scale.

THE FUTURE OF OTFS

The application of OTFs now extends beyond traditional immediate release oral dosage forms. Development of topical films, probiotic strips,[4] and controlled-release OTF products are new forms made possible through this delivery format's flexibility, proven robustness and stability.

The future of OTF formulation and processing is a direct reflection of evolving healthcare needs. Demographically, most established markets have aging populations that benefit from simple, easy-to-dispense and dose products. As emerging markets require flexibility in the number of units dispensed at any given time and providers continue to look for options that can increase compliance, minimise dosage levels and frequency, and reduce costs. OTFs have increasingly become the solution to satisfy all of these needs. In addition development teams are able to capitalise on the flexibility of OTFs by adapting the technology for their program.

ABOUT ARX, LLC

ARx, LLC, a wholly owned subsidiary of Adhesives Research, Inc (AR), was created in 2005 to address the growing global need for innovative delivery of active drug-containing systems. This was a natural extension of AR's 20+ years of experience manufacturing pressure-sensitive adhesives and components for transdermal and other pharmaceutical applications.

ARx is dedicated to developing and manufacturing innovative pharmaceutical products, including adhesive laminates and dissolvable films, for customised drug delivery platform technologies. As part of this commitment, in 2007, ARx opened a new, state-of-the-art 25,000 square-foot (2,323 m^2) pharmaceutical manufacturing facility designed to manufacture dissolvable film, transdermal, and buccal drug delivery systems for over-the-counter, prescription and biopharmaceutical products. The globally-compliant facility triples ARx's manufacturing capacity and laboratory space to support the rapid growth in the industry.

REFERENCES

1. *"Novartis launches first systemic OTC in film strip format." Available at: http://www.in-pharmatechnologist.com/Materials-Formulation/Novartis-launches-first-systemic-OTC-in-film-strip-format. Accessed October 1, 2009.*
2. *Van Arnum, P. "Pediatric Formulations: Technical and Regulatory Considerations: A Roundtable." Pharm. Tech 2009. 33 (8) Outsourcing Resources suppl. s58-s67.*
3. *Greb, E. "Are Orally Dissolving Strips Easy for Manufacturers to Swallow?" Available at: http://pharmtech.findpharma.com/pharmtech/article/articleDetail.jsp?id=615617&sk=&date=&pageID=3. Accessed October 5, 2009.*
4. *"Ganeden Biotech Introduces the First Probiotic Thin Strip." Available at: http://news.prnewswire.com/ViewContent.aspx?ACCT=109&STORY=/www/story/09-15-2009/0005094056&EDATE=. Accessed September 28, 2009.*

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Track 1: Outlook for Global Market Trend of Drug Delivery Systems

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Track 4: Medical Devices for Effective Drug Delivery

Track 5: Nanotech for Drug Delivery

Track 6: Regulatory Issues, Quality Control, and Business Development

Workshop 1: Key Regulatory and Legal Issues in Improving Bioequivalence or Bioavailability by New DDS

Workshop 2: Strategic Planning for Patient Centered Drug Delivery Product

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PARTICLE SCIENCES
DRUG DEVELOPMENT SERVICES

SoluBest

SOLUMER™ TECHNOLOGY:

A VIABLE ORAL DOSAGE FORM OPTION FOR BCS CLASS II MOLECULES

In this article, Mark Mitchnick, MD, Chief Executive Officer, and Robert Lee, PhD, Vice-President, Pharmaceutical Development, both of Particle Sciences, and Amir Zalcenstein, PhD, Chief Executive Officer, SoluBest, introduce Particle Sciences' formulaic DOSE™ system for dosage form development and drug delivery technology selection, and discuss one such technology, Solubest's Solumer™, a scalable solid dispersion approach based on spray drying that is suitable for BCS Class II APIs and NCEs.

In the lifecycle management of pharmaceutical products, novel drug delivery technologies that offer positive differentiation over first-generation products provide an important means for staying competitive in today's business environment.

Many existing active pharaceutical ingredients (APIs) and new chemical entities (NCEs) are poorly water soluble and subsequently have low oral bioavailability if formulated in their unmodified forms. Traditional approaches to overcoming this include:

- Improvement of water miscibility by employing self-emulsification,[1] lipid-based techniques,[2] solubilisation into micellar cores,[3] or alternatively complexation with cyclodextrins.[4]
- Reduction of particle size to nano-scale via mechanical milling or high-shear processing accompanied by particle stabilisation.[5]
- Impacting crystal lattice energy using polymorphs or co-crystals,[6] or through the creation of solid dispersions of drug in inert carriers or matrices.[7]

Increasingly, solid dispersions are being looked at as a viable solution to this pervasive issue. Although only a few solid dispersions are currently marketed, the approach has some inherent advantages over other approaches. Presence of an active compound as a molecular or nanoparticle dispersion combines the benefits of decreasing crystal lattice energy and maximising surface area, thus facilitating better contact with dissolution media. Fortuitously, many of the carriers that can be employed for the production of solid dispersions are generally recognised as safe (GRAS) and are already extensively used as excipients in marketed products, easing the regulatory burden.

Particle Sciences has developed DOSE™, a formulaic approach to dosage form development that rapidly narrows in on the drug delivery technology of choice. When solid dispersions are called for, Particle Sciences has a number of approaches. One of them, thorough its partnership with SoluBest, is to use the Solumer™ technology,[8] a unique solid dispersion technology that significantly improves the dissolution and bioavailability of poorly soluble drugs. The technology has been proven in human trials and has been scaled to commercial levels.

> "THIS METHODICAL ITERATIVE APPROACH ALLOWS ONE TO RAPIDLY NARROW IN ON THE FORMULATION APPROACHES MOST LIKELY TO YIELD THE DESIRED RESULTS."

Under Particle Sciences' DOSE™ system, APIs are first extensively characterised as to their physicochemical properties, including a proprietary solubility screen. Then, after excipient compatibility studies, formulation prototypes

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are screened for their impact on solubility and permeability. This methodical iterative approach allows one to rapidly narrow in on the formulation approaches most likely to yield the desired results.

THE CHALLENGE

An increasing number of compounds coming out of discovery are poorly soluble. By some estimates 40-70% of new lead compounds in development fall into this category.[9,10] Additionally many new compounds also exhibit poor permeability. In 1993, the Biopharmaceutical Classification System (BCS) [11,12,13,14] was proposed as a way to facilitate the marketing of generic drugs. The system classifies a given compound by its aqueous solubility and gut permeability.

Beyond its regulatory use, the BCS provides a very useful framework in which to evaluate APIs and chart a logical course to achieve the desired pharmacokinetics (PK), including greater bioavailability. For BCS II and IV molecules, where solubility is the main or largely contributing limiting property, there are a number of approaches including increasing surface area through particle size reduction, surface morphology modification and solid solutions.

ONE POSSIBLE SOLUTION: SOLUMER™ TECHNOLOGY

Generating human data as quickly as possible is a goal of every drug developer and there are several philosophies as to how best to achieve first in human (FIH) dosing. It has been estimated that 3-6 formulation changes occur from FIH to commercialisation.[15] At Particle Sciences, we believe that FIH experience should be in a formulation that will provide useful developmental data. For a BCS Class I molecule, the prototypical formulation could be a simple powder-filled capsule. For a poorly water-soluble molecule, BCS Class II or IV, such a simple system is unlikely to provide any commercially helpful data, speed development or bring to light clinically relevant findings. Therefore, a FIH formulation designed to deliver the drug in a commercially viable way is, in our view, important. For drugs with limited aqueous solubility, one such approach is Solumer™, a patented dual polymer system utilising GRAS excipients and traditional processing techniques.

In this approach, the API is solubilised in an organic solvent, usually ethanol. An amphiphilic and a hydrophilic polymer are separately mixed in water. The drug and polymer solutions are then mixed and spray dried. The exact compositions of the feed stocks are determined in an extensive, yet efficient, preformulation phase utilising Design of Experiment (DoE) methodology, when appropriate. Key drivers include the APIs solubility in various organic solvents, the APIs molecular weight, the solubilities of the polymeric excipients, and the compatibility of the API and polymeric excipients in the spray drying solution.

In the context of the Solumer technology, amphiphilic polymers are defined as soluble both in organic solvents and in water.

Examples of amphiphilic polymers suitable for use with Solumer include but are not lim-

SOLUMER FINGERPRINTS

Formulating lipophilic crystalline drugs results in a self-assembled drug-polymer complex. This provides two features that are required for improved bioavailability:

- Depression of melting temperature and energy
- Formation of colloidal dispersions upon contact with aqueous media

	API		Formulation		
	T_{melt} (°C)	ΔH_{melt} (J/g)	T_{melt} (°C)	ΔH_{melt} (J/g_{drug})	Particle size nm
Reservatrol	267.4	253.6	199.1	14.0	1224
Hesperetin	231.0	166.2	No peak of melting		1310
Nifedipine	172.4	113.4	140.9	8.4	749
Fenofibrate	81.5	74.3	64.4	9.3	669
Tacrolimus	135.0	60.5	118.0	52.0	836
Clarithromycin	227.6	70.2	207.9	40.1	1190
Albendazole	215.2	209.7	161.4	31.2	555
Fenbendazole	239.2	166.3	203.7	8.9	892
Itraconazole	169.7	84.4	155.6	21.9	910

Particle Sciences

Figure 1: Comparative Thermodynamic Characteristics (Melting Temperatures and Melting Energies) of Various Unformulated APIs and their Corresponding Solumer™ Formulations.

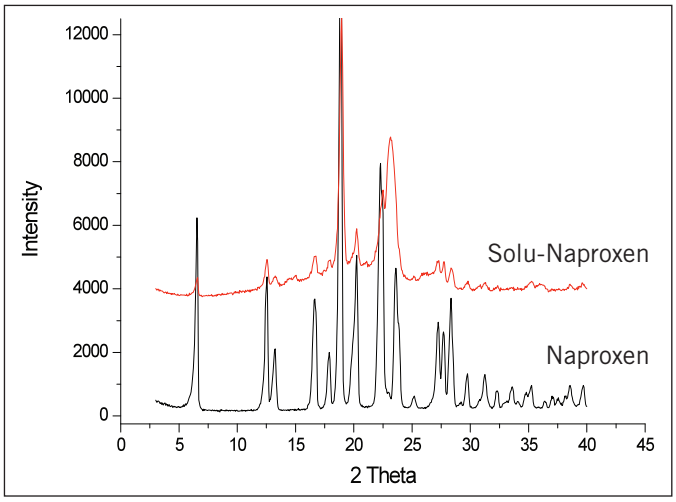

Figure 2: Comparason of X-ray Diffraction Patterns of Naproxen API (Naproxen) and Naproxen processed using the Solumer™ Technology (Solu-Naproxen).

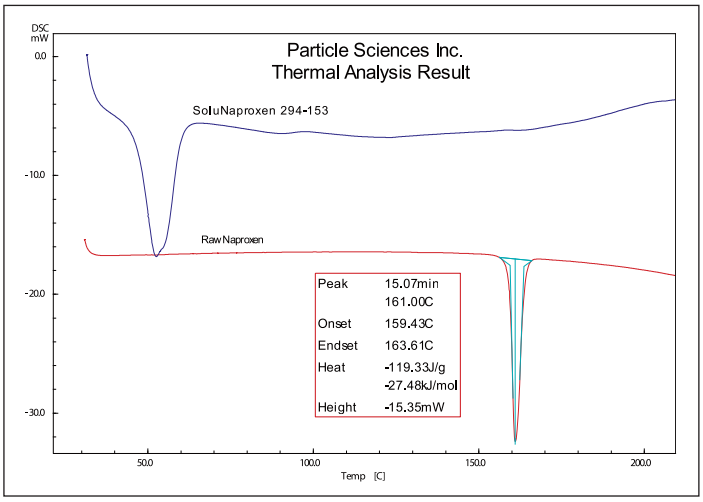

Figure 3: Differential Scanning Calorimetry of Naproxen API (Raw Naproxen) and Naproxen processed using the Solumer™ Technology (SoluNaproxen 294-153).

ited to polyethylene oxides (PEO, also commonly referred to as polyethylene glycol or PEG), PEO derivatives, PEO copolymers such as PEO/polypropylene glycol (PPG) copolymers, PEG-modified starches, poloxamers, poloxamines, polyvinylpyrrolidones, hydroxypropyl cellulose, hypromellose and esters thereof, vinyl acetate/vinylpyrrolidone random copolymers, polyacrylic acid, and polyacrylates. Hydrophilic polymers are defined as those soluble in water or in a mixture of organic solvent and water, but not soluble in organic solvent alone. Examples of hydrophilic polymers include but are not limited to starch, sodium carboxymethylcellulose, hydroxyethylcellulose, polyvinyl alcohol, sodium alginate, chitosan, and carrageenan. Notably, Solumer formulations utilise only FDA-approved polymers.

The use of hydrophilic polymers that ionise at different pH allows for the design of formulations targeted either to the stomach or the intestine. For example, chitosan, which is ionised at low pH, promotes drug release in the stomach, while sodium carboxymethyl cellulose and sodium alginate, ionised at neutral conditions, facilitate release in the small intestine.

The resulting powder is free flowing and will contain 25% or more API. Characteristics of the drug product include:

- Solubilised drug homogeneously interwoven into a polymer matrix
- Formation of crystalline drug within the polymer matrix
- Modified thermal behavior demonstrating depressed melting temperature and enthalpy of melting of the drug (see Figure 1)
- Spontaneous formation of nanocolloidal dispersions upon contact with aqueous media
- Enhanced dissolution rate/solubility of the drug in aqueous media as well as prolonged supersaturation in relevant biological fluids, and GI site-targeted release of the drug.

CHARACTERISATION

Comparing X-Ray diffraction patterns of a model API, naproxen, with its corresponding Solumer™ formulation, shows that in the Solumer™ formulation, the drug (naproxen) is present in its crystalline form (see Figure 2). In contrast to some systems dependent on amorphous forms, this technology results in very stable constructs since the drug is present in its most thermodynamically favoured state.

Several commercial compounds have been thoroughly evaluated using this technology. In Figure 3, the impact of the technology on melting temperature and enthalpy of melting is clearly demonstrated. It is believed that these thermal property alterations are responsible for the drastic increase in solubility provided by the technology.

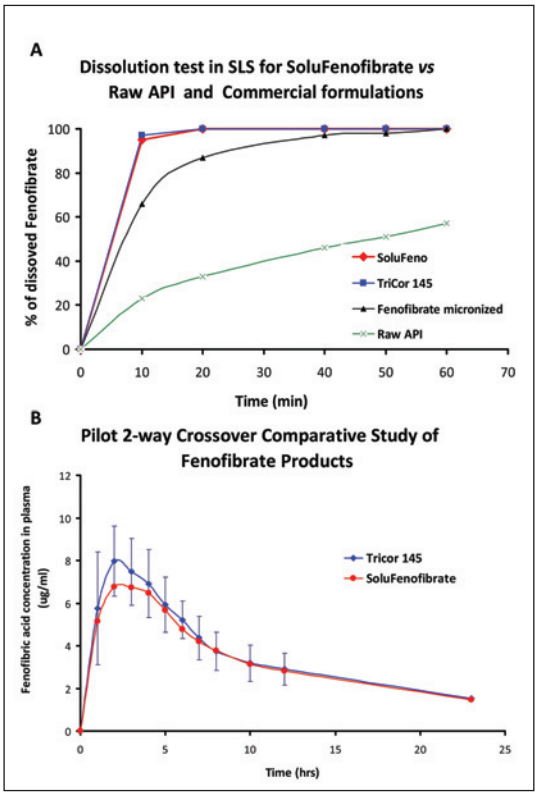

Figure 4: Dissolution Profiles and Porcine Pharmacokinetic Data for Fenofibrate

Figure 4 shows the dissolution profiles and porcine pharmacokinetic data for fenofibrate. (A: dissolution profiles of raw API, commercial product, and Solumer™ fenofibrate (Solu-Fenofibrate); and B: porcine PK data for commercial product versus Solu-Fenofibrate).

Figure 5 shows the dissolution profiles and porcine pharmacokinetic data for albendazole (A: dissolution profiles of raw API and Solu-Albendazole in 0.05 M SLS; B: dissolution profiles of raw API and Solu-Albendazole in fasted simulated intestinal fluid; C: porcine PK data for commercial product versus Solu-Albendazole; and D: efficacy in porcine model of commercial product versus Solu-Albendazole).

CONCLUSION

Drug product formulation development will become increasingly sophisticated over time. Whether reformulating an existing compound or working with an NCE, the ability to understand and manipulate those factors within our control that dictate PK behavior is key. For compounds with low solubility, we have presented one approach to oral dosage form development. Using GRAS ingredients and a readily scaled, patented process, Solumer™ technology results in stable crystalline constructs that increase bioavailability by increasing the solubility of the API. To date the technology has been demonstrated in more than a dozen compounds and is currently being scaled for Phase III commercialisation.

REFERENCES

1 *Kohli K, Chopra S, Dhar D, Arora S, Khar RK. "Self-emulsifying drug delivery systems: an approach to enhance oral bioavailability." Drug Discov Today. 2010 Nov;15(21-22):958-65.*

2 *Rahman MA, Harwansh R, Mirza MA, Hussain MS, Hussain A. "Oral Lipid Based Drug Delivery System (LBDDS): Formulation, Characterization and Application: A Review." Curr Drug Deliv. 2011 Apr 1.*

3 *Kadam Y, Yerramilli U, Bahadur A, Bahadur P. "Micelles from PEO-PPO-PEO block copolymers as nanocontainers for solubilization of a poorly water soluble drug hydrochlorothiazide." Colloids Surf B Biointerfaces. 2011 Mar 1;83(1):49-57.*

4 *Kanwar JR, Long BM, Kanwar RK. "The Use of Cyclodextrins Nanoparticles for Oral Delivery." Curr Med Chem. 2011 Apr 26.*

5 *Peltonen L, Hirvonen J. "Pharmaceutical nanocrystals by nanomilling: critical process parameters, particle fracturing and stabilization methods." J Pharm Pharmacol. 2010 Nov;62(11):1569-79.*

6 *Miroshnyk I, Mirza S, Sandler N. "Pharmaceutical co-crystals-an opportunity for drug product enhancement." Expert Opin Drug Deliv. 2009 Apr;6(4):333-41.*

7 *Janssens S, Van den Mooter G. "Review: physical chemistry of solid dispersions." J Pharm Pharmacol. 2009 Dec;61(12):1571-86.*

8 *Zalcenstein, A. "SoluBest's Solumer Solubilising Platform: An All-in-One Technology." ONdrugDelivery, Oral Drug Delivery & Advanced Excipients, April 2010, 27-30.*

9 *Hauss DJ. "Oral lipid-based formulations." Adv Drug Deliv Rev. 2007 Jul 30;59(7):667-76.*

10 *Dubin CH. "Formulation strategy for poorly soluble drugs." Drug Del Technol 2006;6(6):34–38.*

11 *Yu LX, Amidon GL, Polli JE, Zhao H, Mehta MU, Conner DP, Shah VP, Lesko LJ, Chen ML, Lee VH, Hussain AS. "Biopharmaceutics classification system: the scientific basis for biowaiver extensions." Pharm Res. 2002 Jul;19(7):921-5.*

12 Chen ML, Amidon GL, Benet LZ, Lennernas H, Yu LX. "The BCS, BDDCS, and Regulatory Guidances." Pharm Res. 2011 Apr 14.

13 Tsume Y, Amidon GL. "The biowaiver extension for BCS class III drugs: the effect of dissolution rate on the bioequivalence of BCS class III immediate-release drugs predicted by computer simulation." Mol Pharm. 2010 Aug 2;7(4):1235-43.

14 Takagi T, Ramachandran C, Bermejo M, Yamashita S, Yu LX, Amidon GL. "A provisional biopharmaceutical classification of the top 200 oral drug products in the United States, Great Britain, Spain, and Japan." Mol Pharm. 2006 Nov-Dec;3(6):631-43.

15 Hussain AS. "Quality by Design: Integration of prior knowledge and pharmaceutical development into CMC submission and review: FDA Perspective." AAPS Workshop, Oct. 2005.

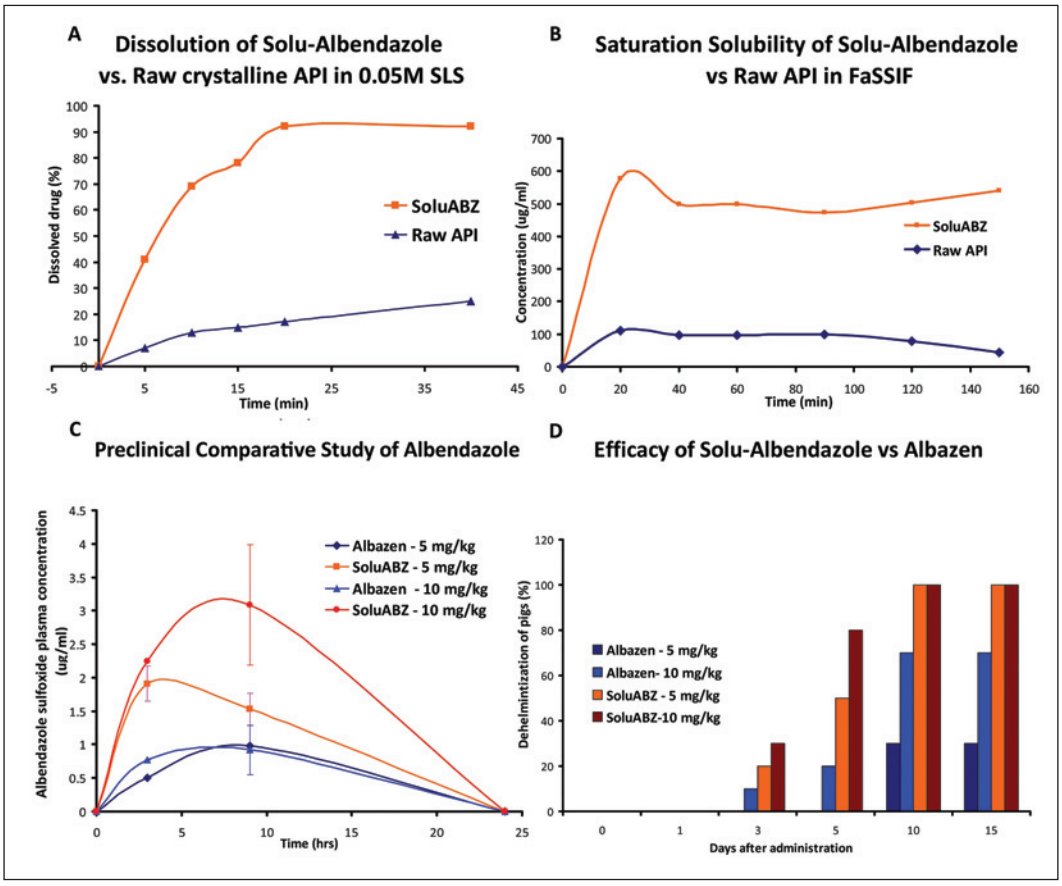

Figure 5: Dissolution Profiles and Porcine Pharmacokinetic Data for Albendazole.

CONTROLLED DRUG RELEASE:

NOVEL TIME-DELAYED FORMULATIONS AND THEIR CLINICAL EVALUATION

Drug Delivery International Ltd has developed oral drug delivery preparations that provide a range of drug-release profiles that can be developed for single- or multiple-drug delivery. The profiles can combine separate pulse releases, or an initial release combined with delayed, sustained release. Here, Carol Thomson, PhD, Chief Operating Officer, Drug Delivery International, explains how the preparations' behaviour in man has been demonstrated using the nuclear imaging technique, gamma scintigraphy. Dr Thomson outlines how potential applications in sleep maintenance, pain management and cardiovascular disease have been demonstrated in this way, although the formulations are not limited to these therapeutic areas; indeed, they could be applied to a broad range of drugs and disease groups.

There are many benefits offered by controlled drug delivery systems. For example, sustained-release technologies allow prolonged delivery of a therapeutic dose, thus reducing the number of times that a patient needs to take their medication while maintaining a steady state of drug in the bloodstream, and time-delayed release introduces a lag time before dose release, providing pulsatile delivery of drug to specific sites, such as the colon, or at a specific time.

Temporal control of drug release has particular advantages in the treatment of disorders that demonstrate a circadian pattern, such as cardiovascular disorders, asthma, anxiety and hypercholesterolemia. In such cases, the development of controlled-release formulations that deliver the payload at an optimal time can greatly enhance the therapeutic effects of the drug and reduce the dose required. This is particularly beneficial for drugs with a narrow therapeutic window.

Further, there is an expanding body of evidence concerning the relationship between circadian rhythms and the responsiveness of the body to drugs. As a consequence of this relationship, the absorption, distribution, metabolism and elimination of a drug and its subsequent therapeutic efficacy and/or toxicity can vary considerably with the circadian cycle.

Drug Delivery International (DDi) is a start-up formulation development company that specialises in providing solutions for "difficult" formulations, such as those for drugs with poor solubility, poor bioavailability or other properties that prevent APIs from reaching the market or achieving their full therapeutic potential. DDi has an expanding intellectual property portfolio, providing licensing or collaborative research opportunities in controlled release and chronopharmaceutics.

> "THE ABSORPTION, DISTRIBUTION, METABOLISM AND ELIMINATION OF A DRUG AND ITS SUBSEQUENT THERAPEUTIC EFFICACY AND/OR TOXICITY CAN VARY CONSIDERABLY WITH THE CIRCADIAN CYCLE."

DDi has developed a series of novel delivery systems, based on compressed tablet technology, that can be readily configured to provide immediate, biphasic (two pulses of drug(s) separated by a defined delay) or time-delayed sustained release patterns of one or more drugs for a wide range of medical applications. The

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technology is unique and distinct from other delivery technologies in the marketplace and offers the following advantages:

- Widespread applicability to different drugs and dosages
- High degree of flexibility in manipulating drug release profiles
- Simple assembly and production processes
- Formulations are not pH-sensitive.

These formulations have been developed for three therapeutic areas: sleep maintenance; cardiovascular disease; and pain management. Formulations have been clinically evaluated using the non-invasive imaging technique of gamma scintigraphy to visualise the release of the drug.

The gamma scintigraphy work was carried out by Bio-Images Research Ltd (Glasgow, UK), a complete clinical research services company which, with a high level of expertise in drug delivery systems, provides clients with early-stage guidance in the drug development process.

SLEEP MAINTENANCE

Sleep maintenance insomnia is characterised by frequent and prolonged nocturnal awakenings, typically in the second half of the night. It is a common problem which has increased incidence with age and detrimentally impacts on the quality of life of individuals. Difficulty in resuming sleep has been associated with reduced sleep quality, leading to anxiety, mood disorders and consequently daytime impairment.[1] DDi has developed a time-delayed hypnotic formulation that provides a two-hour-delayed release of zolpidem for the treatment of sleep maintenance insomnia. Gamma scintigraphy and pharmacokinetic analysis was used to monitor the *in vivo* performance of the formulation.

In vitro validation was carried out by standard dissolution studies. The mean time to onset of radiolabel release was 95 min (n=3) post-dose and the mean time to completion of radiolabel release was 171.7 ±15.3 min (n=3) post-dose (see Figure 1).

Clinical evaluation was carried out using gamma scintigraphy in six healthy male volunteers. The mean time to onset of radiolabel release was 98 ±10 min post-dose and the mean time to completion of radiolabel release was 153 ±8 min post-dose. This gave a mean time of 55 ±16 min for complete dispersion, from onset to completion.

These data correlate with the *in vitro* results and show the tablet's barrier layer to prevent drug release successfully until close to the target time of two hours post dose. Onset of radiolabel release occurred in the stomach in five subjects and in the small intestine in the remaining subject. Complete release was noted in the stomach for four subjects and in the small intestine for two. Figure 2 shows scintigraphic images of key events in the GI transit of a tablet in Subject 001.

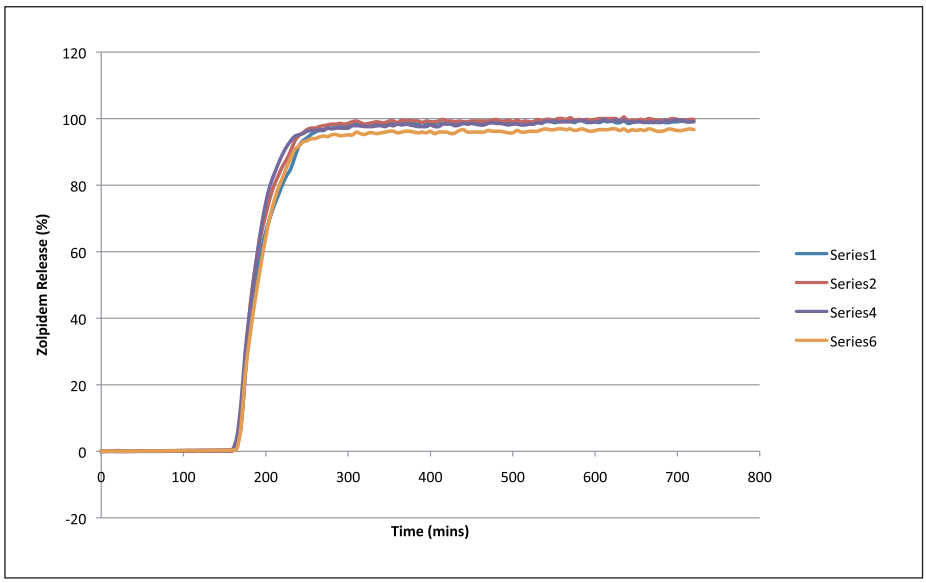

Figure 1: Time delayed in vitro release of zolpidem

Almost immediately after radiolabel release was confirmed by scintigraphy, the subjects reported feeling drowsy and fell asleep. No clinically significant deviations from normal blood pressure and pulse ranges were noted.

The formulated tablet proved successful in delivering the drug after a predicted time delay. The release parameters were comparable among the six subjects, indicating robustness of the formulation in providing accurate time-delayed release. The physiological effects of the sleep tablet coincided with the scintigraphic confirmation of release.

CARDIOVASCULAR

Hypertension has been shown to follow a circadian pattern. Specifically, both heart rate and blood pressure blood pressure peak early in the morning and in many people with hypertension there is a marked rise in blood pressure

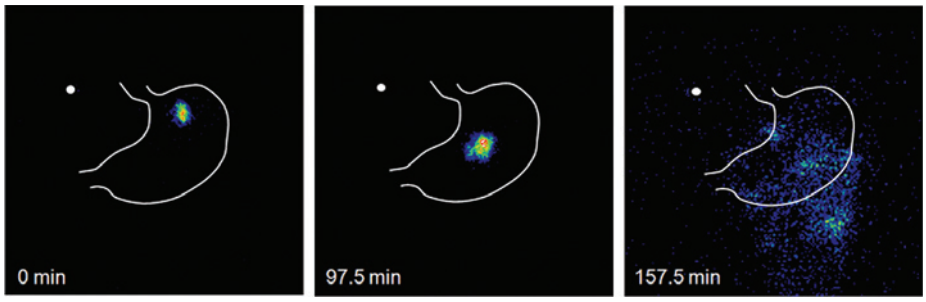

Figure 2: Scintigraphic images of Subject 001 at various times post-dose: 0 min (immediately post-dose); 97.5 min (onset of ^{99m}Tc release); and 157.5 min (complete ^{99m}Tc release). Outline of the stomach is drawn for visualisation only.

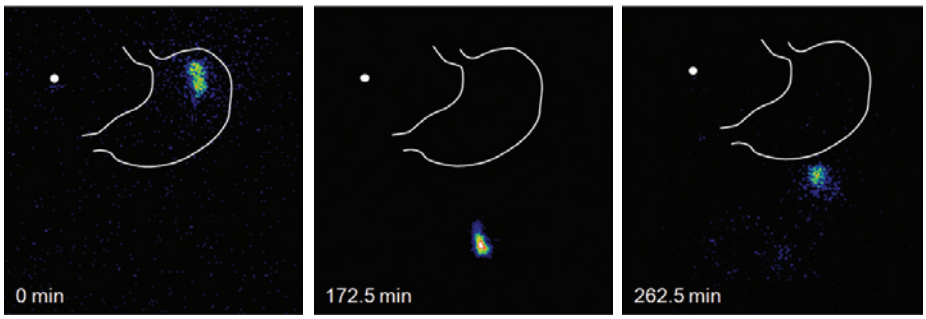

Figure 3: Scintigraphic images of a healthy volunteer at various times post-dose: 0 min (immediately post-dose); 172.5 min (onset of ^{99m}Tc release); and 262.5 min (complete ^{99m}Tc release). Outline of the stomach is drawn for visualisation only.

upon awakening called "the a.m. surge".[2,3] DDi has developed a formulation for the delivery of anti-hypertensive drugs in the middle of the night, prior to wake-up, when the risk of fatal heart attack is greatest.

The formulation provides a delayed release of verapamil. *In vitro*, around 20% of the drug is released 3-5 hours after administration, with the remainder of the drug being released in a sustained manner over the following 4-5 hours, thereby covering the pre-wake-up period of greatest cardiovascular risk. This ensures that peak plasma levels of verapamil are achieved during the night in a targeted manner consistent with the chronopharmacological nature of cardiovascular disease.

This formulation was validated clinically using gamma scintigraphic imaging in six healthy male volunteers, demonstrating delayed sustained release of verapamil *in vivo* (see Figure 3 on previous page).

PAIN THERAPY

People with rheumatoid arthritis suffer significant problems with pain and stiffness upon awakening, severely impacting on their normal daily functions.[4] DDi has developed a formulation that provides an immediate night-time release of diclofenac, followed by a seven-hour delay before pulsatile release of a second dose of the drug. This formulation offers immediate pain relief at night time, allowing pain-free sleep, and subsequently provides delivery of pain-relief prior to waking. This will be particularly useful in the treatment of patients suffering from chronic pain that has a significant inflammatory component.

The formulation has been demonstrated *in vitro* to be highly reproducible. Further studies are being carried out to validate the formulation *in vivo*.

COLON TARGETING

Colon targeting is desirable for treatment of diseases specific to the large intestine.[5-8] Two formulation strategies have previously been proposed for the delivery of drugs to the colon:

1. The use of pH-sensitive coatings that dissolve at specific pHs in the small intestine.
2. The use of microbial flora of the colon to selectively metabolise a portion of the coating.[5-8]

Before employing such strategies it is important to consider the environment in the small intestine and colon in the disease state as the pH and microbial organisms may differ from that understood to be present in the healthy population.

DDI COLON DELIVERY TECHNOLOGY

DDi has developed patented technology for time-delayed formulations based on a detailed understanding of the erosion of dosage forms in the GI tract. The barrier layers developed by DDi operate independently of pH and are relatively unaffected by agitation conditions, leading to excellent *in vitro/in vivo* correlation of erosion performance. However, gastric residence is a very variable event in a population and depends significantly on the fed state of the subject. In the presence of food, gastric emptying is delayed. Since the dietary habit of patients is virtually uncontrollable, gastric emptying will be very variable in a patient population. This means that employing time-delay alone is not a useful technique for the delivery of drugs to the colon, since gastric residence will be variable and will result in delivery to a range of intestinal sites.

The addition of a gastroresistant coating to a DDi time-delay formulation successfully eliminates the variability of gastric emptying. The erosion of the time-delay layer only begins following dissolution of the gastroresistant coating, which can only occur in the higher pH environment in the small intestine, following gastric emptying. Since small intestine transit time is very reproducible, at around 3-4 hours, it follows that an enteric coated time-delayed dosage form with a time-delay of around three hours will successfully target the colon.

We have successfully used this strategy for the development of a range of colon-targeting versions of time-delayed dosage forms.

Drug Delivery International Ltd and Bio-Images Research Ltd are part of the Bio-Images Group – providing integrated pharmaceutical development solutions.

REFERENCES

1. *Ohayon MM. "Difficulty in resuming or inability to resume sleep and the links to daytime impairment: definition, prevalence and comorbidity." J Psychiatr Res. 2009 Jul;43(10):934-40. E-pub 2009 Mar 3.*
2. *White WB. "Circadian variation in blood pressure." Blood Press Monit. 1997;2:46-51*
3. *Millar-Craig MW, Bishop CN, Raftery EB. "Circadian variation of blood pressure." Lancet. 1978;1:795-797.*
4. *Yazici, Y; Pincus, T; Kautiainen, H; Sokka, T (2004). "Morning stiffness in patients with early rheumatoid arthritis is associated more strongly with functional disability than with joint swelling and erythrocyte sedimentation rate." J Rheumatol. (2004) 31 (9): 1723–6.*
5. *Stevens HNE. "Pulsincap Technology with Special Reference to Colon Targeting." Progress in Drug Delivery Systems II. pp. 31-45, Pub. Biomedical Research Foundation Tokyo, Japan (1993).*
6. *Binns JS, Stevens HNE, Bakshaee M and Wilson CG. "Colon Targeted Release Using the Pulsincap Delivery System." Proceed. Intern. Symp. Control. Rel. Bioact. Mater., 21, 260-261 (1994).*
7. *Pecek D, Sime KA, Ronaldson VE, Connolly SM, Hodges LA, McInnes FJ, Stevens HNE. "Development of a capsule systems for site specific drug delivery." Proceed. Intern. Symp. Control. Rel. Bioact. Mater (2010).*
8. *Pecek D, Sime KA, Ronaldson VE, Connolly SM, Hodges LA, McInnes FJ, Stevens HNE. "Validation of a targeted release capsule using scintigraphic methods." AAPS, New Orleans, 2010.*

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encap drug delivery

LIQUID-FILL HARD TWO-PIECE CAPSULES:

THE ANSWER TO MANY PRODUCT DEVELOPMENT ISSUES

In this article, Gary Norman, Product Development Manager, Encap Drug Delivery, gives an overview of the various processes and technologies the company employs for the development of capsule-based formulations. Particular advantages of these formulations over traditional presentations are described.

Liquid-fill formulation is one of the fastest growing sectors of the drug delivery market, increasing at a rate of 30% per annum. This is due to the number of highly potent chemical and biological drugs moving through development pipelines today particularly for cancer treatments.

BIOAVAILABILITY ENHANCEMENT

For drugs with low solubility or bioavailability, Encap Drug Delivery has a range of formulation options and technologies which will give drugs the best chance of success. These include solid solutions and solid suspensions of drugs in polymeric vehicles, emulsions and self emulsifying lipidic systems. Liquid and semi-solid filled hard capsule lipidic formulations are also ideally suited to compounds with low aqueous solubility, poor permeability and consequently low or variable bioavailability.

Formulations which increase the solubility of the active or indeed present the drug as a solution can have a significant impact on the bioavailability of such drugs. Lipidic vehicles are generally well absorbed from the GI tract and in many cases this approach can significantly improve the oral bioavailability compared with administration of the solid drug substance.

Encap has expertise in the use of self-emulsifying vehicles and has developed a number of self-emulsifying drug delivery systems (SEDDS) and self-microemulsifying drug delivery systems (SMEDDS) for the oral administration of drugs with poor water solubility. These are formulations which form emulsions or micro-emulsions spontaneously on contact with aqueous media. An example of a marketed product that uses a SMEDDS type formulation is Neoral, an oral formulation of cyclosporine from Novartis (Basel, Switzerland).

In addition, Encap can offer the possibility to explore formulation screening for this type of formulation using excipients from a range of manufacturers including Gattefossé (Saint-Priest, France). Encap has experience of a wide range of functional "bioavailability-enhancer" excipients which are fully approved from a regulatory perspective and include the screening of such excipients during pre-formulation studies.

A formulation strategy for poorly soluble drugs is the use of solid solutions, which are molecular dispersions of drug molecules in a polymer matrix. This conversion of the drug into the amorphous state produces material which dissolves more rapidly than the corresponding crystalline drug substance. The incorporation of the drug substance into hydrophilic polymeric materials such as polyvinylpyrollidone (PVP) and polyethylene glycol (e.g. PEG6000) can produce additional solubility enhancing effects.

Solid solutions can be prepared by dissolving the drug and the polymer in a suitable volatile solvent. On removing the solvent (by spray drying) an amorphous drug/polymer complex is formed. In some cases it is possible to dissolve the drug in the molten polymer and fill directly into hard capsules. On cooling, the drug is entrapped in an amorphous state within the water-soluble matrix.

In many cases, improvements in drug dissolution and bioavailability can also be achieved using dispersions or suspensions of drugs in appropriate vehicles which are suitable for filling into hard shell capsules.

TARGETED DELIVERY

In addition to the liquid-filled capsule technology Encap has other complimentary technologies such as targeted delivery of capsules. Targeted delivery could be as simple as enteric coating. However, for targeted delivery of capsules to the colon our ENCODE® technology is utilised.

ENCODE is Encap Drug Delivery's umbrella trademark for technologies that deliver cap-

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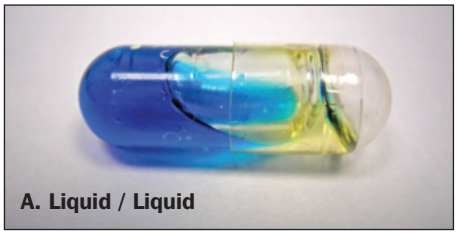

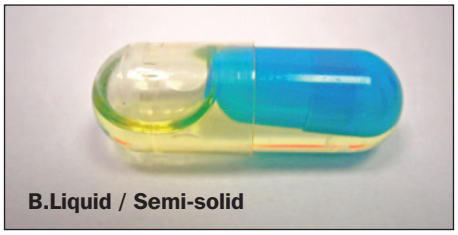

Figure 1: DuoCap: Examples of various fills.

sules to the colon. One such technology in this area is ENCODE$_{pHloral}$, a specialised patented colonic target coating.

ENCODE$_{PHloral}$ is a dual-trigger mechanism, utilising pH and the microbiota in the colon, for delivery of the drug accurately and consistantly to the colon, either for topical delivery such as anti-inflammatory drugs for ulcerative colitus / Crohn's disease. For certain drugs, systemic delivery may be achieved via the colon with increased bioavailability due to lower expression of the PGP efflux mechanism and/or due to the absence of certain enzymes in the colon, such as CYP 3A4, which may degrade a drug if it is a CYP3A4 substrate.

DUOCAP TECHNOLOGY

DuoCap™ is a single, oral-dosage unit that comprises a capsule-in-a-capsule and offers broad therapeutic applications. The inner and outer capsules may contain the same active drug providing multiple release profiles from the dosage unit, for exampe, an immediate-release formulation from the outer capsule and a controlled-release formulation from the inner capsule.

In addition to modifying the release profiles it is also possible to target the inner and outer capsule to different areas of the GI tract (small intestine or colon), with the appropriate coating as discussed earlier. Alternatively, the capsules may contain different actives for use with combination therapies or actives that are incompatible in a single capsule.

Combination therapies are currently of significant interest, demonstrated by the recent launches of Combodart™ (GlaxoSmithKline) and Vimovo™ (Pozen/AstraZeneca).

The inner capsule may contain liquid, semi-solid, powder or pellet formulations and the outer capsule contains liquid or semi-solid formulations (see Figure 1).

Combination drugs have not been as common in the industry as one may think. This may be due to stability issues between the actives. The advent of capsule-in-capsule technology allows both API's to be kept distinctly separate. Therefore, it is likely that combination drugs may become more common in the Pharmaceutical industry. Fewer new drugs are being discovered and developed and current drugs seem to be getting more of the spotlight in terms of being re-formulated for either new indications or extending the shelf life due to patents lapsing.

DELIVERY OF BIO-MOLECULES

Delivering therapeutically active large molecules by the oral route has been a challenge and a goal for several decades. The oral route of administration for these substances is problematic for many reasons: proteolysis by gastric and pancreatic enzymes; high acidity in the stomach; and limited absorption through the GI tract for instance. However the benefits of oral delivery are clear, with the ease of administration and improved patient compliance being the major advantages.

Encap can employ a number of strategies:

- Formulation is designed for optimal biomolecule chemical and conformational stability in a part aqueous environment which is still compatible with capsules
- Avoid exposure to stomach and targeted delivery to small intestine using enteric coating
- Targeted delivery to colon using ENCODE technologies
- As well as delivery of proteins and peptides, our approach can also be used for domain antibodies, oligonucleotides and oral vaccines.

Case Study:

A water-soluble protein which is stable in an aqueous environment, was provided as a concentrate in an aqueous buffer (phosphate buffer solution (PBS)), which was diluted to the required concentration with water. The diluted protein/buffer solution was then incorporated into a novel formulation containing 28% water. A hard-shell gelatine capsule was then filled with the formulation and the capsule was closed and banded. After stability testing, the capsule was found to remain stable without softening or cracking after three months stability storage, and the formulation retained its protein concentration and activity. This therefore provided a viable route for the formulation of proteins (and peptides) in stable aqueous media for administration in capsule form.

FAST CLINICAL DEVELOPMENT

Liquid-fill encapsulation can provide a valuable tool to enable drug developers more rapidly to progress clinical candidates through the development process. The use of powder fill capsules without formulation using equipment such as the Xcelodose (Capsugel, Peapack, NJ, US) has been very well accepted by the industry for first-in-man studies. This has been a valuable innovation. However, a draw-back is that the capsule output makes it difficult to support larger-scale trials without the need for long manufacturing campaigns running into many days for a single batch. Liquid-fill encapsulation provides an alternative route to rapidly progress simple formulations of actives into the clinic which is capable of accommodating batch-to-batch variations in API (particle size, shape, density and flow characteristics) and can scale easily from bench to high speed machines.

WHY CONSIDER A LIQUID FILL FORMULATION FOR A FIRST-IN-MAN STUDY?

For the oral dosing route of administration, there are several dosage form options generally used for first-in-human studies: API in bottle; powder in bottle; API into capsule; and traditional formulations of tablets/capsules. Each approach has associated advantages and disadvantages. In many instances a liquid-filled hard capsule may be a more appropriate formulation for numerous reasons including:

- Best chance bioavailability for API
- Protects hygroscopic and oxidation sensitive compounds including proteins and peptides
- Ideal for cytotoxic APIs
- Removes issues caused by API variability (particle size, shape, crystal habit, density, polymorphic form or moisture)
- Eliminates compatability issues between shell and API
- Provides a scalable formulation that may be suitable up to Proof of Concept and beyond.

ENHANCED STABILITY

The chemical stability of oxygen-, moisture- and light-sensitive drugs can be significantly improved by using liquid or semi-solid capsule products. By dissolving the drug in non-aqueous vehicles which are compatible with capsules, this problem of instability can be

Category	Examples
Opioids and Morphine Derivatives	Vicodin, OxyContin, Demerol, Percodan
Depressants	Xanax, Librium, Valium
Stimulants	Ritalin, Adderall, Dexedrine
Anabolic Steroids	Anadrol, Oxandrin

Figure 2: Prescription Drugs of abuse.

reduced or eliminated. Similarly, the amount of moisture present in tablet- or powder-based formulations can be 10-100 times greater than in the oil- or lipid-based formulations used at Encap. This can have a significant impact in improving drug stability.

Vancomycin is one product that was successfully developed as a liquid-fill capsule product in order to achieve acceptable stability.

HIGH POTENTCY PRODUCTS

Liquid-fill, hard-capsule technology is becoming an increasingly attractive approach for both high-potency products and for anticancer agents. Technically, it offers processing convenience in minimising hazards of cross-contamination, minimises the need for complex and expensive plant and assures product uniformity. The approach has also become more attractive commercially with the availability of contract facilities with the relevant specialized full-scale GMP plant .

Low dosage products (under 10mg) can often give rise to low content uniformity. For tablet and powder formulations it is often very difficult to achieve an acceptable uniformity. Liquid-fill formulations, as solutions or suspensions, routinely provide better dose homogeneity and fill accuracy compared with powder-fill capsules, or tablets. They are often the formulation of choice for low-dose products. In addition, liquid-fill capsules generally require less API and excipient compared with other formulations, thus minimising API requirements in both the early stages of drug product development and clinical manufacture. These formulations are also very scalable ensuring a smooth and speedy transition from bench scale to commercial scale when required.

Encap has considerable experience of developing uniform, formulations for doses as low as 250 μg.

Drug products that are intended for use in low doses are generally difficult to produce in a solid oral dosage form. The highly potent nature of such drugs (cytotoxic agents, hormones, etc) means that they carry increased risks of cross contamination and can expose operators to harmful dust during manufacture. Incorporating these APIs into a dust-free liquid or semi-solid formulation is a valid alternative which protects against these risks.

ABUSE RESISTANCE

There is an increasing interest from pharma companies and regulators in the development of abuse resistant formulations. Prescription drug abuse is prevalent globally. Figure 2 provides examples of drugs commonly abused, in various categories. In the US there are about six million users of prescription drugs for non-medical use. Within that six million, the majority of the abuse is of pain relievers; about 4.4 million abusers. There are over 500,000 emergency-room incidents per year. Since 1998 there has been a >100% increase in abuse of controlled prescription drugs. This represents a far greater increase than that in marijuana, cocaine and heroin use. In 2007, 5.2% of 12th-grade students reported to have abused oxycodone, and 9.6% abused Vicodin (hydrocodone + paracetamol).

Methods of abuse tend to be snorting, injection, ingestion (melting or extracting), dose dumping by chewing , abuse of others (covert administration).

The abuse potential of dosage forms such as tablets, capsules (powder fill) and soft gelatin capsule is significant.

Tablets:
- Most popular oral form
- Can be crushed easily to give a high surface area
- Ideal for fast release, extraction, snorting, dose dumping and possibly dissolution and injection

Powder filled capsules:
- Already has a high surface area
- Can contain high-melting-point solids
- Waxy or sticky materials cannot be used
- Similar abuse potential to tablets

Soft gels:
- Contain liquids or near liquid
- Maximum fill temperature of about 35°C.
- Contents can thus be liquefied near body temperature, extracted, dose dumped or directly injected.

Encap's Abusolve™ technology is the application of hard-shell liquid-fill techniques to produce a dosage unit tailored to the required release profile, formulated from excipients chosen to provide the best deterrence to potential routes of abuse. The objective is to provide a useful pharmaceutical to the patient whilst providing resistance to abuse by others.

Release profiles can be tailored to give immediate (e.g. 100% in 30 minutes), controlled, delayed or sustained release (e.g. 100% release in 40+ hours). The release profiles can be manipulated by selecting the appropriate excipients, size of the capsule and the active concentration

The abuse resistance can be achieved through use of:
- High melting excipients to prevent melting and injection
- Waxy materials, which prevent powdering at room temperature and resistance to snorting
- Unpleasant tasting excipients + taste modifiers
- Thickening agents which make it difficult to extract and inject active
- Capsule banding.

IP PROTECTION

One other often overlooked advantage of liquid-filled hard capsule formulations is that of patent protection or patent avoidance.

Various products have been manufactured using a LFHC formulation avoiding current IP protection. As an example a patent may specify a certain particle size distribution for an active. Using an array of solubilisers this issue is avoided by solubilising the active.

CONCLUSION

Liquid-filled, hard two-piece capsule formulations are an excellent choice to overcome various technical and patent issues that arise in the formulation development of a drug product.

Benefits Summary:
- Enhanced Bio-availability
- Enhanced Stability
- Targeted Delivery
- Fast to Clinic formulations
- Abuse Resistance formulations
- Low dose /potent API Uniformity
- Oral Bio-molecule delivery
- IP avoidance.

Encap is no novice when it comes to the development and commercial manufacture of liquid-filled, hard two-piece capsule (LFHC) technology. In fact, Encap, with over 20 years' experience and more than 60 dedicated staff, is the number one in the liquid-fill hard-capsule field.

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MULTI-TIP TOOLING: A GUIDE

In this piece, Dale Natoli, Vice-President, Natoli Engineering Company, Inc, provides a brief overview of multi-tip tooling for tablet presses, and provides some guidelines for selecting the most appropriate equipment.

Multi-tip tooling isn't new to the pharmaceutical industry; the unique tool configuration has been used for more than 150 years. At the start of the tablet compression industry, single-station tablet presses were used in production and were commonly outfitted with multi-tip tooling to increase tablet production and reduce labour, maintenance, energy, space requirements and the number of presses. When the high-speed 16-station rotary tablet press was introduced in the late 1800s, the single-station press and multi-tip tooling lost popularity.

Soon after the introduction of the rotary tablet press, the industrial, confectionery, and food industries implemented multi-tip tooling, and today the pharmaceutical industry is following suit.

Multi-tip tooling is available in two common configurations: assembly (or multi-piece), and solid. When choosing the configuration, consider the tool type, tablet size, and the number of tips per punch. Also consider tool handling practices, cleaning, and inspection. The supplier will help you decide which configuration is best. Most tooling suppliers have selection guidelines for each tool type.

The assembly configuration consists of the punch body, cap, and individual punch tips (see Figure 1). The biggest advantage of the assembly is the removable punch tips. If one of the punch tips is damaged, it can easily be replaced so the punch can return to service. If a punch tip on the solid configuration (Figure 2) is damaged, the entire tool must be replaced, which is costly.

Cleaning and sanitising the assembly configuration requires disassembling the punch tips from the punch body, cleaning and drying each component, and reassembling. Although reassembly should be quick and easy, if any of the mating parts become damaged or even nicked, or if a slight amount of debris or corrosion interferes, the punch tips won't align. If the punch tips don't align properly and the punch is returned to service, the tooling may fail prematurely or damage the press.

The solid multi-tip configuration (Figure 2), which is machined from a single piece, is becoming more popular. It requires no disassembly for cleaning, eliminating reassembly and ensuring proper alignment of punch tips in the die. However, it allows fewer punch tips in relation to tablet size.

Before investing in multi-tip tooling, verify that your tablet press has turret punch guides and die sockets that are in good condition, with no excessive wear. Worn guides and/or worn die pockets can create punch-tip misalignment, which in turn causes premature tip wear, excessive head and cam wear, and tool binding in the punch guide and tip binding in the die. You can easily check the condition of the turret with a turret inspection kit, which is available from most tooling manufacturers. Inspect the turret for wear periodically, regardless whether single-tip or multi-tip tools are used. Inspection will alert you to premature tool wear and tooling failure.

For tablet presses with tablet rejection systems, many companies use validation punches, which are identical to the other punches except for a slight deviation in their working and overall lengths. The validation punch verifies the operation of the reject system by producing tablets of different hardness, thickness, and weight. While some pharmaceutical companies are turning to multi-tip tooling, other companies are more reticent, investigating the effect on product flow, compression and ejection forces, and tablet reject systems, among others.

But multi-tip tooling can definitely pay off. For example, a US pharmaceutical company I worked with produced approximately 8,540 pellets per minute using single-tip tooling. When they switched to nine-tip tooling, production reached approximately 76,860 pellets per minute. That's an 800 percent increase without additional personnel or equipment!

Is your product a candidate for multi-tip tooling? Check with your supplier. In today's economy, increasing tablet production while cutting operating costs is especially attractive.

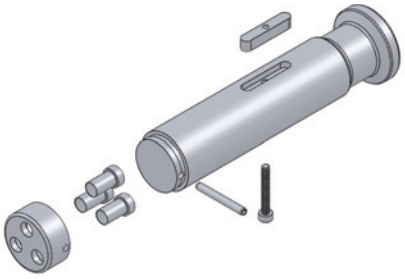

Figure 1: Assembly configuration comprising the punch body, cap, and individual punch tips.

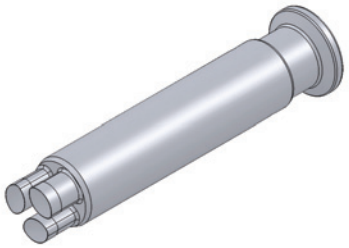

Figure 2: Solid configuration, machined from a single piece.

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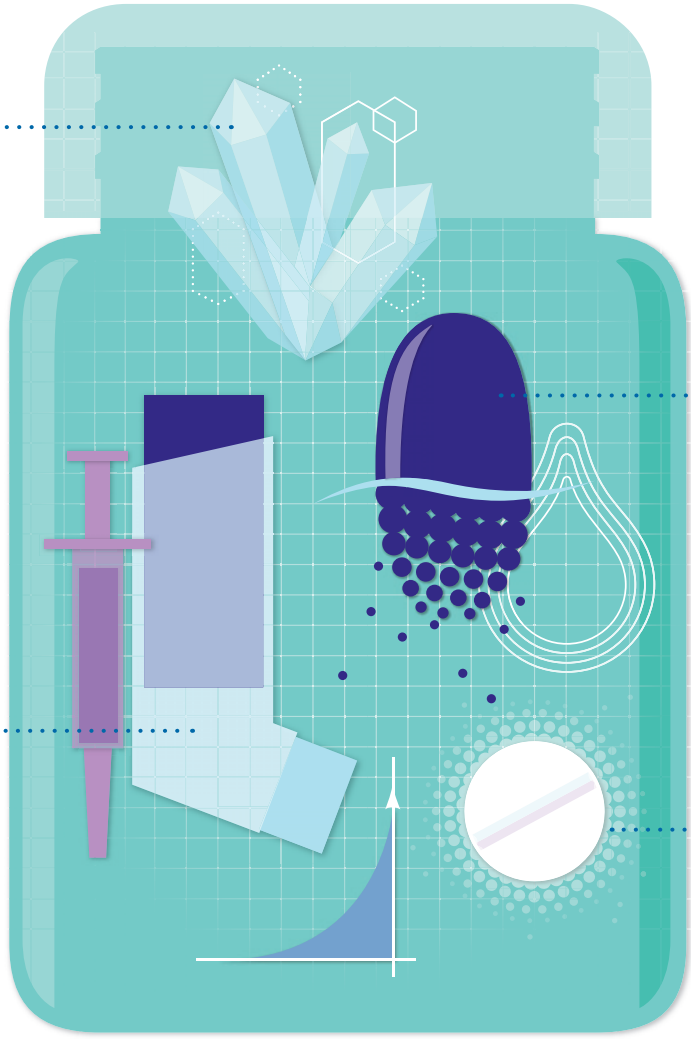

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