The News Capsule

Issue 11

CAPSUGEL®
Dosage Form Solutions

Powdersize · Xcelience · BEND RESEARCH · encap drug delivery

Xcelodose®

microdosing services expanded in Europe

Our product development and manufacturing site located in Ploërmel, France has complemented its capabilities with the installation of Capsugel Xcelodose® technology for microdosing of powders into capsules (PIC). Capsugel now offers microdosing services for preclinical and clinical studies in Europe and the US. Best practices for microdosing utilizing Xcelodose® systems were developed by Xcelience over the past 10 years, and have now been transferred to the Ploërmel product development team.

An Xcelodose® 600 System has been installed in the cGMP area to support straight-forward preparation of powder filled capsules for First-in-Human clinical studies. A second Xcelodose® 600 System is scheduled to be installed in 2016. Disposable isolator technology has also been implemented around the equipment to allow for the safe handling of highly potent compounds. Onsite Analytical Development and Quality Control teams assure analytical method development and quality controls related to microdosing.

Xcelodose® 600 System

Powder-in-capsule (PIC) studies typically preclude the need for excipient compatibility and dissolution studies for phase I and II evaluations. Proprietary Xcelodose® technology makes PIC studies practical and efficient by providing consistent and accurate powder fill to as low as 100 micrograms with fill accuracy to 1-2% RSD. Xcelience has been successful in reducing product development time by 45% utilizing Xcelodose® technology, saving on average 13 – 17 weeks.

Jan Vertommen
Senior Director
Product Development
and Manufacturing

"This Xcelodose® technology introduction is a further complement to the technologies and services supported at Ploërmel" states Jan Vertommen, Site Director. *"Lipid Multi-Particulates, enTRinsic™ drug delivery, and ionic liquids technologies have complemented our historic capabilities in lipid-based formulation development using soft gel and liquid fill hard capsule technology. We are excited to incorporate microdosing best practices developed by Xcelience as part of our product development service offering."*

The Ploërmel site produces a range of drug products for the pharmaceutical and nutritional market segments, and has successfully passed US FDA, ANSM and ANVISA inspections.

Xcelience and Powdersize

integrated into Capsugel Dosage Form Solutions

Derek Hennecke
President &CEO – Xcelience

Dear Capsugel

Thank you for welcoming me so warmly into the Capsugel fold. After all these years of working together, it is no less of a thrill to be invited to sit at the family table. Our companies have been on a parallel track and, in hindsight, joining forces now seems inevitable.

When it came time to consider the proposal from Capsugel last fall, I went back to the people I trusted inside Capsugel and the legacy companies that had been previously acquired. We would be joining Capsugel's Dosage Form Solutions business unit, an initiative focused on specialty finished dosage form design, development and manufacture – and building upon the Capsugel legacy of best-in-class capsule technologies and a commitment to quality, customer service and continual innovation. And we would be integrating with a team made up of legacy Capsugel folks, as well as Encap Drug Delivery and Bend Research, in continuing to build something special.

Our histories were already intertwined.

I founded Xcelience in 2006, and created a specialized CDMO focused on clinical development and services. A Capsugel technology – your Xcelodose® Precision Powder Microdosing Systems – played an integral role in our preclinical and clinical service offering, and we leveraged these proprietary systems in creating the premier powder-in-capsule service provider in North America. And we used your capsule products in much of our development and clinical work for clients ranging from virtual companies to large biotech. You were a small part of our business, but rock solid, and we stood behind your reputation.

Like you, we listened to our clients closely and continually aligned our investments with their needs – isolator capability for highly potent compounds, flexible and small-scale manufacturing for orphan drugs, clinical supply logistics inclusive of cold chain in the US and Europe, just to name a few.

I also shared your hunger for new technologies, and emulated that pursuit in the purchase of Powdersize – a company that is exceptionally adept at the micronization / particle size engineering it wields – last October.

Now, as we put our first 90 days behind us, I've gotten to know a whole new side of Capsugel. I remain as excited about the future now as I was when this deal was a secret that I couldn't talk about. The synergies in technologies and capabilities are proving greater than expected, and I believe that our rich history together has sown the seeds for a bright future.

We have found in Capsugel a company that will take our clients and the 280 families of Xcelience and Powdersize to the next level.

Liquid Fill Hard Capsules (LFHC)
a simple and versatile tool for life cycle management

In an article published in the March issue of Contract Pharma (March 2016, Pages 62-66, www.contractpharma.com), Stephen Brown (Managing Director) and Wei Tian (Director of Formulation) described the use of liquid fill hard capsule (LFHC) technology as a simple and versatile tool for life cycle management.

Stephen Brown
Managing Director
Encap Drug Delivery

Wei Tian
Director of Formulation
Encap Drug Delivery

Simplicity

The LFHC process is relatively simple in concept, i.e. a typically non-aqueous liquid is filled into the body of the capsule using precision pumps that can deliver a fill weight of 100mg to 1.5 grams as required. The caps are then placed onto the bodies of the capsules. Either a seal or a band is then applied around the join.

The typical LFHC manufacturing process can be summarised as follows: mixing, filling and banding (or sealing), packing. These are well-defined unit operations and, comparatively speaking, "formulation-independent". As such, a distinct advantage of the LFHC process is its scale-ability. With an increasing demand on process understanding from the regulatory authorities, the LFHC technology offers a potentially straightforward path for Technology Transfer and new product introduction.

Versatility

The principle requirement for the LFHC technology is to ensure the formulation is liquid at the time of filling. This can include formulations that are liquid at ambient temperature as well as formulations that are solids or semi-solids at room temperature, but are liquids at an elevated temperature during filling. Therefore, LFHC provides an array of sophisticated solutions for drug formulation and delivery:

- High potency drug manufacturing: once wetted, the potential for airborne and accidental exposure is greatly reduced
- Low dose drug products: dose uniformity is assured through excellent weight control attained by filling with precision pumps (mostly <1% RSD)
- Enhanced drug solubility: LFHC formulations routinely incorporate solubility-enhancing non-aqueous excipients or self-(micro)-emulsifying drug delivery systems (SEDDS / SMEDDS)
- Nano-particulate formulations: a single pot process combining milling and formulation through in-situ size reduction in a non-aqueous medium has been developed that inhibits particle agglomeration
- Abuse deterrent formulations: AD formulations with both sustained release and immediate release profiles have been developed to meet the challenge of substance abuse, especially those of CNS drugs
- Intestinal and colon targeting: functional coatings that typically dissolve over a set pH range (and/or degraded by microflora) can be applied to LFHC to provide targeted release and to promote optimal absorption including biological actives
- Combination products: the delivery of two actives which are otherwise incompatible in a single dosage form can be achieved through a capsule-in-capsule technology
- Variable release profiles through a capsule in capsule design can be achieved to maximise efficacy and minimise side effects recognising the circadian or other rhythmic cycles in diseases such as psychiatric or somatic illness.

At Encap, we have found that the combination of manufacturing simplicity and application versatility makes LFHC technology particularly relevant to modern product life cycle management where there are increased regulatory demands on product and process understanding on the one hand, and ever aggressive generic competition on the other.

design
develop
manufacture

New Approaches for Gut Microbiome

Microbiome and live biotherapeutics, i.e. using a living microorganism that is applicable in the prevention, treatment, and cure of a disease, represent exciting new fields. Microbiome is rapidly growing research area for multiple disease states. In the area of gut microbiome, faecal microbiota transplantation (FMT) has been showing significant promise in a number of areas, e.g. 'decolonizing' carriers of antibiotic resistant bacteria, for some time. Effective oral controlled-release/delivery of microbial flora to the ileum and colon for disease treatment is an urgently unmet medical need to facilitate further development of gut microbiome treatments.

mi·cro·bi·ome
/ ˌ mīkrōˈbīōm/

noun

the microorganisms in a particular environment (including the body or a part of the body).
"We depend on a vast army of microbes to stay alive: a microbiome that protects us against germs, breaks down food to release energy, and produces vitamins"

- **the combined genetic material of the microorganisms in a particular environment**
  "understanding the microbiome—human, animal, and environmental—is as important as the human genome"

Dr. Youngster et al from Harvard Medical School conducted a phase II study at Massachusetts General Hospital (JAMA Oct 2014). The study used Capsugel DRcaps® gastric-resistant hypromellose capsule technology as part of the delivery mechanism. A DRcaps-in-DRcaps (i.e. an inner DRcaps capsule was placed inside a larger DRcaps capsule) approach was used to provide enteric protection and site delivery for FMT) to treat relapsing clostridium difficile infection. A full treatment included 30 "DR-in-DR" capsules per patient given in two days. An overall 90% rate of clinical resolution of diarrhea was achieved – a result comparable with rates reported previously in using colonoscopic or nasogastric tube administration to delivery fresh stool preparations or frozen liquefied inocula.

New enTRinsic™ drug delivery technology, which offers full enteric protection without the use of functional coatings, is another potential approach for FMT and other gut microbiome applications.

This technology employs an entirely novel approach to polymer material science in order to make a capsule-based dosage form that is intrinsically enteric.

There are biomolecules (proteins, peptides) and live organisms (bacteria, viruses) that require enteric protection but have heat-sensitivity which precludes traditional coating and drying processes. Such sensitive applications have therefore relied on non-oral delivery mechanisms, e.g. injections. enTRinsic technology is currently being evaluated by clients to enable the oral delivery of a range of biomolecules, bacteria and LBPs.

The use of these new encapsulation technologies – enTRinsic technology and capsule-in-capsule approaches – are showing great promise in obviating the need for invasive and/or uncomfortable as well as costly procedures for administration. These specialized delivery strategies are expected to develop further as oral biologic delivery systems in the future, further increasing the safety of gut microbiome approaches, such as FMT, by avoiding procedure-associated complications.

ADF guidelines

In March, the U.S. Food and Drug Administration issued a draft guidance intended to support industry in their development of generic versions of approved opioids with abuse-deterrent formulations (ADF) while ensuring that generic ADF opioids are no less abuse-deterrent than the brand-name drug.

This recent draft guidance is among a number of steps the agency recently outlined in an action plan to reassess its approach to opioid medications. The plan is focused on policies aimed at reversing the epidemic, while still providing patients in pain access to effective relief.

In the draft guidance, the agency is encouraging industry efforts to develop pain medicines that are more difficult to abuse. While the FDA recognizes that the ADFs are not failsafe and more data are needed, ADF opioids do have properties expected to deter abuse compared to non-ADFs. Given the lower cost, on average, of generic products, encouraging access to generic forms of ADF opioids is an important step toward balancing the need to reduce opioid abuse with helping to ensure access to appropriate treatment for patients in pain.

The draft guidance (titled "General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products") includes recommendations about the studies that should be conducted to demonstrate that a generic opioid is no less abuse-deterrent than the brand name product, with respect to all potential routes of abuse.

The FDA's actions include initiatives that are likely to spur further use of ADF technologies in and spur further ADF innovation:

- **Expand use of advisory committees:** Starting today, the FDA will convene an expert advisory committee before approving any new drug application for an opioid that does not have abuse-deterrent properties.

- **Expand access to abuse-deterrent formulations (ADFs) to discourage abuse:** ADFs hold promise as their abuse-deterrent qualities continue to improve and as they become more widely available. The FDA has committed to issue draft guidance with its recommendations for the approval standards for generic abuse-deterrent formulations. Release of this guidance is a high priority, since the availability of less costly generic products should accelerate prescribers' uptake of ADFs.

Capsugel's product development pipeline reflects the trend towards increased ADF requirements and market incentives in the US as well as Europe.
A growing number of our client projects are utilizing Liquid Fill Hard Capsule (LFHC) technology to help prevent the misuse of opioids, stimulants, sedatives and antidepressants which may be susceptible to product tampering by the abuser. Our proprietary LFHC technology can be used in formulation development tailored to minimize the risk of a potential abuser's tampering with the dosage unit and render it resistant to crushing, melting and both chemical and physical attempts to extract the active ingredient.

Got a question? Get in touch >

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Event Calendar

Capsugel will be attending/hosting various upcoming events including:

Save the date!

1st Formulation Academy
October 19th – Basel (CH).

Rational Technology selection in addressing Bioavailability challenges

This 1st Capsugel Formulation Academy symposium will focus on solubilizing technologies, their rational and systematic selection, feasibility study, evaluation and development process to achieve the desired pharmacokinetic profile. Based on physicochemical and biopharmaceutical characteristics of a molecule, stratification for the formulation approaches will be discussed and the related feasibility assessment programs proposed. Case studies will be provided on the different delivery technologies successfully applied and scaled up to a commercial stage.

September 5 – 7, 2016

The 7th APS International PharmSci 2016
Technology and Innovation Centre
University of Strathclyde
Glasgow
UK

https://www.ukpharmsci.org/

September 20, 2016

Biotech Outsourcing Strategies 2016
Royal College of Physicians
London
UK

http://www.bio2bevents.com/

September 21 – 22, 2016

8th EuPFI Conference
Novotel Lisboa Avenida José Malhoa
1 1 A 1099-051 Lisboa
Portugal

http://www.eupfi.org/8th-conference/

October 4 – 6, 2016

CPhI 2016
Fira de Barcelona Gran Via
Barcelona
Spain

http://www.cphi.com/europe/

Please see more at:
http://www.capsugel.com/news-events/events

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