ROUNDTABLE: TRENDS AND INNOVATIONS IN ORAL DRUG DELIVERY

In this roundtable discussion, Michael Morgen, PhD, Director of R&D at Lonza Bend, Torkel Gren, PhD, Senior Director, Technology Officer & Strategic Investments, at Recipharm, and Yogesh Sadhale, PhD, Director, Pharmaceutical Development, at Metrics Contract Services, discuss the current trends and innovations influencing oral drug delivery development and what their respective companies can offer to pharma in this space.

MICHAEL MORGEN

Lonza
Small Molecules

Michael Morgen, PhD, is Director of R&D at Lonza Bend. He has 20 years of experience in pharmaceutical development and has led a number of innovation programmes in oral and non-oral drug delivery. His group currently works primarily in the development of formulation-enabling platforms and the associated characterisation techniques for oral bioavailability enhancement and modified release for small molecule drugs. He received his PhD in Physical Chemistry from the University of California at Berkeley (US) in time-resolved spectroscopy and completed post-doctoral work at the University of Texas at Austin (US) in thin film materials for electronics applications. Dr Morgen has co-authored 30 peer-reviewed research articles, six book chapters and is co-inventor of 10 issued patents in drug delivery technology.

TORKEL GREN

Recipharm

Torkel Gren, PhD, is Senior Director, Technology Officer & Strategic Investments, at Recipharm. He holds degrees in Pharmacy and Business Administration, as well a PhD in Pharmaceutics from Uppsala University (Sweden). He has worked in the pharmaceutical industry since 1988 and has held a number of scientist and manager positions in Europe and the US. He was lead formulator and co-inventor of Detrol OD/Detrusitol SR (tolterodine, Pfizer). Dr Gren is Vice Chairman of the Board of the Swedish Pharmaceutical Society and Board Director of SwedenBio.

YOGESH SADHALE

metrics contract services

Yogesh Sadhale, PhD, is Director, Pharmaceutical Development, at Metrics Contract Services. With 20 years of experience in the pharmaceutical industry, Dr Sadhale previously worked at Patheon Manufacturing Services (NC, US), where he managed pharmaceutics and process development. He holds a PhD in pharmaceutical sciences from the Medical University of South Carolina (US). At Metrics, Dr Sadhale manages all aspects of personnel and operations related to formulating and manufacturing a client's pharmaceutical materials for Phase I, II and III clinical trials. He is responsible for scale up and validation of clinical trial materials, as well as manufacturing and packaging clinical trial batches under current good manufacturing practices guidelines. In addition, Dr Sadhale provides planning and budgeting for pharmaceutical development operations.

Q What are the major trends you currently see determining the demand for innovative oral drug delivery solutions in pharmaceutical company pipelines?

MM Pharma pipelines continue to present oral absorption challenges, with new drug targets and mechanisms of action in recent years driving a shift towards drugs with higher molecular weights, melting points and hydrophobicities, leading to poor bioavailability due to low solubility and/or permeability. Solubilisation technologies, including amorphous solid dispersions (ASDs), micronisation and high-energy salts, can improve bioavailability in formulations limited by solubility or permeability. To address these challenges, we see significant value in an end-to-end offering, from drug synthesis through solid form, formulation and

"Many new APIs are poorly water soluble, posing challenges for traditional OSD formulation technologies, with new approaches needed to optimise oral bioavailability for these APIs."

drug product development to identify problem statements early on and successfully address them in partnership with our clients.

TG Despite significant current interest in parenteral drug delivery formats, driven by the many new biologics moving through the development pipeline, oral dosage forms still have an important role to play due to their obvious advantages in terms of cost and patient convenience.

I think two different drivers are transforming the oral solid dose (OSD) segment. Firstly, many new APIs are poorly water soluble, posing challenges for traditional OSD formulation technologies, with new approaches needed to optimise oral bioavailability for these APIs. We already have powerful tools that can be applied to achieve this for small molecules. On the other hand, in regard to biologics, while there has been progress in certain areas, such as some peptides and oral vaccines, more work is needed to create viable universal solutions to oral bioavailability issues for the majority of large molecule APIs. Unfortunately, this will probably not be realised in the near future.

Secondly, we are seeing growing demand for OSD technologies designed to enhance convenience for patients in order to optimise adherence. New approaches are being innovated on, designed to achieve more effective modified-release and fixed-dose combinations, to reduce dosing frequencies. We are also seeing advances in taste masking to minimise unpleasant flavours during administration. Smart packs and connectivity solutions are also being pioneered to support patients and healthcare providers in monitoring their administration regimes to prevent missed doses.

All in all, there is a wide array of drug delivery tools available, which is driving a trend of increased use of contract development and manufacturing organisations (CDMOs) and specialised drug delivery companies. Even for big pharma, it is uneconomical to maintain internal access to all the drug delivery technologies available. Collaboration with specialists is an attractive option as it gives access to the best technology for each project at a reasonable cost. On the other hand, outsourcing individual parts of the development process can increase complexity. To manage this complexity, outsourcing of end-to-end development is rapidly gaining traction among pharmaceutical companies.

YS From Metrics' end-to-end perspective, in particular with customers that have advanced novel drug candidates, we continue to be tasked with developing OSD forms to deliver highly complex, poorly soluble APIs to patients safely and effectively.

The APIs of approximately 40% of market-approved drugs and nearly 90% of molecules in the discovery pipeline are poorly water-soluble. Issues associated with poor solubility can lead to low bioavailability and result in suboptimal drug delivery. Most failures in new drug development have been attributed to these reasons. However, although the risk remains that a novel drug can fail in development because bioavailability issues can't be overcome, pharma's contract partners have become adept at applying enabling technologies that can help overcome the pharmacokinetic conflicts of even the most poorly soluble API chemistries.

Experience has proven that disordered ASDs offer distinct advantages over crystalline formulations relative to solubility. It is well understood that changing the solid-state characteristics of the API can help render the molecule more water-soluble. Furthermore, the advent of new techniques to improve the stability of amorphous forms will continue to support the challenges of formulating and processing poorly soluble chemistries into successful commercial products.

Granulation, the technique of particle enlargement by agglomeration, combined with an ASD starting material, is recognised as one of the best ways to manage the pharmacokinetic dynamics of poorly soluble APIs and formulate them for use in OSDs. During the process, small, fine or coarse particles are converted into larger agglomerates otherwise known as granules. This transforms fine powders into free-flowing, dust-free granules that are easy to compress into tablets or fill into capsules with a high level of precision.

As with many enabling technologies delivered by specialist CDMOs, Metrics relies on roller compaction technology from Gerteis (Jona, Switzerland) to accomplish the dry granulation process. We operate two compacting units, serving both clinical and commercial programmes.

Then there's also the US FDA's "priority review" status to consider. Programmes that are given this status by the FDA have shown significant improvements in safety or effectiveness of the treatment of serious conditions when compared with existing treatment options. The FDA's goal is to act on priority review applications within six months (rather than 10 months, as with standard review). The programmes that are assigned priority review status generally have accelerated drug development timelines to take advantage of the faster regulatory review.

Drug sponsors and developers must work with manufacturing partners able to keep pace with accelerated novel drug development programmes. In addition to speed and agility, ensuring product quality is a critical requirement. Metrics has decades of experience working with priority review, breakthrough therapy and fast track designations of novel and highly potent drug programmes.

Lastly, high-throughput screening and advanced drug discovery techniques continue to introduce highly potent compounds – those with therapeutic effects at very low doses (<10 mg/day), have occupational exposure levels (OEL) of less than 10 µg/m^3 and present evidence of reproductive toxicity, irreversible health and/or environmental effects.

Due to concerns around operator safety and cross-contamination, these compounds need to be handled in dedicated facilities, behind isolators or within specialised containment. Most research and discovery-driven pharmaceutical enterprises are not well equipped to handle potent compounds much beyond lab scale. Development, manufacturing and testing of these compounds are often outsourced as a result.

Metrics also considers each highly potent API's properties when determining the level of risk incurred by the amount of API in the formulation (drug load), batch size (Phase I versus Phase II and beyond) and immediate batch size versus projected scale-up considerations. The API's physiochemical properties also contribute to its classification and subsequent risk mitigation strategies.

"Pharma typically outsources the intermediate manufacture of a drug product to an appropriate specialised manufacturing organisation."

Q What advances have there been in our understanding and analysis of oral dosage forms, and how does this benefit current and future development programmes?

MM There has been much work recently in improving physiologically based pharmacokinetic models to guide the development of solubilised drug forms. These are particularly useful when used in conjunction with targeted *in vitro* tests designed to measure key parameters related to absorption, such as drug concentration sustainment by excipients, and overcoming pH or fed-fasted effects. The combination of *in silico* and *in vitro* tools helps to accelerate development by minimising the number of formulations that require testing and, therefore, the number of experiments that have to be done.

TG The use of *in silico* prediction is becoming more prevalent and is set to significantly improve development speed for projects with solubility challenges, increasing the chances of successful development. *In silico*-generated absorption and pharmacokinetic data can be powerful tools in guiding the development of new dosage forms, helping to identify solutions to address solubility and other challenges.

YS Recent advancements in understanding disease targets at a molecular level, as well as the impact of high-throughput screening, has resulted in chemistries that are almost always lipophilic. Therefore, to improve aqueous solubility, and therefore bioavailability, specialised enabling technologies are often necessary – a capability that most pharma companies don't have in-house. As such, pharma typically outsources the intermediate manufacture of a drug product to an appropriate specialised manufacturing organisation.

Q The rise of biologic drugs has seen strong competition to the oral delivery route, particularly from parenterals. Do you think there is untapped potential in the oral route for biologics?

MM Although there is enormous interest in delivering biologics orally for reasons of convenience, cost and comfort, achieving high oral absorption with very large, fragile molecules presents a significant challenge. Much effort has been put into protecting them in the gastrointestinal (GI) tract and then augmenting their permeability across the epithelium either chemically or mechanically. Near-term successes are likely to remain very molecule-specific, exemplified by the success of semaglutide. In parallel, improved non-oral delivery approaches are also being sought, with particular interest in inhaled biologics for lung-specific applications.

TG I believe that there is untapped potential in oral biologics. However, the challenges that need to be overcome to realise this potential should not be overestimated. Biologics are a heterogenous group consisting of many different modalities, each with its own development challenges and opportunities. This means that some will be better suited to oral dosage forms, while others will benefit from other delivery routes.

I believe that oral vaccines will become more common over time, as well as oral biologics intended for local effect within the GI tract. However, for other applications, progress will be much slower. Injection will continue to be the dominant administration route for biologics for the near future.

Q Please can you give an overview of your company's offering in the field of novel oral drug delivery systems and oral drug development, as well as how your company works with pharma clients to achieve your shared goals?

MM Broadly speaking, Lonza's oral drug delivery technologies cover solubilisation and modified-release technologies. A significant part of our solubilisation portfolio is based on ASDs manufactured by spray drying or hot melt extrusion. In particular, we have worked hard to innovate in the field of spray drying to make the technology as broadly applicable, robust and scalable as possible. We also use micronisation and salt forms where these are more appropriate. We like to work in close collaboration with our clients to identify the challenges to achieving their desired product profile, with frequent and open communication about the best path forward.

TG At Recipharm, we have an array of formulation technologies and characterisation tools, meaning that we can design an appropriate development plan that is customised to the needs of a wide range of projects. Close discussions with our clients help us define a Target Product Profile and development strategy to help them achieve their goals and ensure success.

YS Metrics Contract Services is a science-led CDMO devoted to helping drug developers take their complex novel OSDs from initial concept to global commercialisation. Metrics works with clients from every corner of pharma development, including virtual, mid-size and large pharma companies, as well as those covering the spectrum of R&D and clinical trials. Providing pharmaceutical development, analytical testing and commercial manufacturing services to more than 100 active clients, we are known for our proactive problem-solving capabilities.

Clients outsource their projects with us for several reasons – formulation, analytical and manufacturing expertise; operational experience; GMP-compliant facilities; highly potent API containment solutions and mastery of complex OSD forms. To a great degree, CDMOs bring the quality and speed developers need to the table, plus the agility to meet tight drug development timelines, all of which are prompting an increase in the demand for outsourcing.

"The rise of biologics does not mean that innovation in the small molecule arena has come to an end; we will continue to see demand for formulation development for new small molecules over the next decade."

Q What do you think are going to be the major areas of growth for oral drug delivery over the coming years?

MM There seems to be no slowing in the industry's drive towards larger molecules, whether these are biologics, peptides or larger "small" molecules, thanks to the demands of the target therapeutic areas now being investigated. There will, therefore, continue to be an emphasis on technologies to facilitate solubilisation, permeation and protection from degradation to allow the chemical space of orally deliverable drugs to be expanded. I also expect that technologies that allow the pharmacokinetic profile to be modified will also be important in the coming years.

TG The rise of biologics does not mean that innovation in the small molecule arena has come to an end; we will continue to see demand for formulation development for new small molecules over the next decade. This will entail continued interest in conventional OSD formulations for the foreseeable future.

In addition, we can expect growing interest in technologies designed to support the repurposing of existing molecules, such as modified-release and advanced fixed-dose combination drugs. There is still considerable opportunity for us to optimise the use of existing molecules – not just to use them more effectively in current indications but to harness them for new indications as well.

YS One OSD form Metrics is experiencing an increased demand for is mini-tablets, targeted for both paediatric and geriatric patient populations – a trend being driven by recent regulatory guidance. To help drive paediatric drug development, the FDA has issued guidance several times over recent years, such as the "General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products", and regulations in the EU reflect current guidance trends for paediatric formulations as well.

For example, EU Regulation 1901/2006 on medicinal products for paediatric use states that "children are not simply small adults" and that "paediatric treatments must thus be tailored to the specific needs of children of various age groups". Regulatory guidance and development trials continue to introduce new, approved and improved paediatric therapeutics. According to a 2020 study, there were more than 840 small molecule and biologic products in development for paediatric indications.

Inherently patient-friendly and convenient, mini-tablets can be dispensed easily and sent home with patients to be self-administered. In addition, mini-tablets are simple, stable, flexible, portable and cost-effective to produce and ship compared with other OSD forms and parenterals. Typically compressed to a diameter of 2 mm, mini-tablets can simplify the administration of multiple APIs or manage different release profiles of the same API in a single dose. Metrics offers comprehensive mini-tableting capabilities, including compression, coating, encapsulation and packaging, to suit a variety of therapeutic performance and patient-centric dosing goals.

ABOUT THE COMPANIES

At **Lonza Small Molecules**, the company's connected experts work together to provide contract development and manufacturing services that help pharma and small biotech companies deliver their medicines to patients in need. From the earliest stages of discovery to the final drug product, Lonza can simplify the outsourcing experience with its reliable, timely service, anticipating risks and solving problems. Whether you are developing a pioneering therapy or creating a new oral solid dosage form, Lonza is the only CDMO partner you need. Throughout a molecule's journey from early development to commercial product, Lonza works together with its clients as one.

Recipharm is a leading CDMO headquartered in Stockholm, Sweden. The company operates development and manufacturing facilities in France, Germany, India, Israel, Italy, Portugal, Spain, Sweden, the UK and the US, and is continuing to grow and expand its offering for its customers. Employing around 9,000 people, Recipharm is focused on supporting pharmaceutical companies with its full-service offering, taking products from early development through to commercial production. For over 25 years, Recipharm has been there for its clients throughout the entire product lifecycle, providing pharmaceutical expertise and managing complexity, time and time again. Despite its growing global footprint, Recipharm conducts its business as it always has and continues to deliver value for money with each customer's needs firmly at the heart of all that it does. That's the Recipharm way.

Metric Contract Services, founded in 1994, now a division of Mayne Pharma, is an oral solid dosage form CDMO providing formulation development, analytical testing and commercial manufacturing services to support drug development from concept to global commercialisation.

Michael Morgan
Director of Research & Development
T: +1 541 382 4100
E: small.molecules@lonza.com

Lonza Small Molecules

Lonza
Muenchensteinrstrasse 38
Basel 4002
Switzerland

www.lonza.com

Torkel Gren
Senior Director, Technology Officer & Strategic Investments
T: +46 8 602 52 00
E: torkel.gren@recipharm.com

Recipharm

Recipharm AB
Box 603
SE-101 32 Stockholm
Sweden

www.recipharm.com

Yogesh Sadhale
Director, Pharmaceutical Development
E: highpotency@maynepharma.com

metrics contract services

Metrics Contract Services
1240 Sugg Pkwy
Greenville
NC 27834
United States

www.metricscontractservices.com