ORAL DRUG DELIVERY

ON drugDELIVERY

JULY 18TH 2022 • ISSUE N° 135

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ONdrugDelivery Issue N° 135, July 18th, 2022

ORAL DRUG DELIVERY

This edition is one in the ONdrugDelivery series of publications. Each issue focuses on a specific topic within the field of drug delivery, and is supported by industry leaders in that field.

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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.

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2022/23 EDITORIAL CALENDAR

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August 2022	Industrialising Drug Delivery	Deadline passed
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October	Prefilled Syringes & Injection Devices	Sep 8, 2022
Oct/Nov	Drug Delivery & Environmental Sustainability	Sep 15, 2022
November	Pulmonary & Nasal Drug Delivery	Oct 6, 2022
December	Connecting Drug Delivery	Nov 3, 2022
January 2023	Skin Drug Delivery: Dermal, Transdermal & Microneedles	Dec 1, 2022
February	Prefilled Syringes & Injection Devices	Jan 12, 2023
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May	Delivering Injectables: Devices & Formulations	Apr 6, 2023
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July	Novel Oral Delivery Systems	Jun 8, 2023

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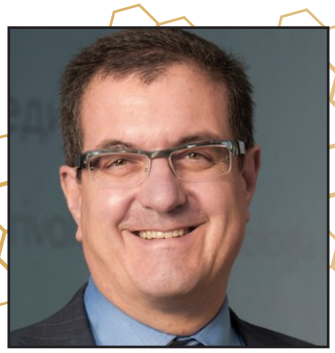

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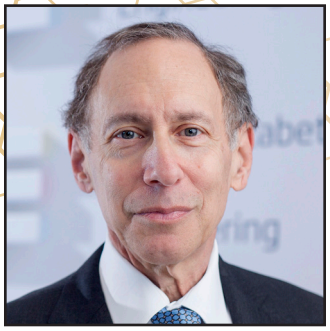

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INFLUENCE OF ADDITIVES ON THE ELECTROSTATIC CHARGE BUILD-UP OF EXCIPIENTS

Here, Aurélien Neveu, PhD, Head of Laboratory and Applications at Granutools, Devang Patel, PhD, Senior Research Scientist at Natoli Engineering Company, and Filip Francqui, Managing Director, Granutools, present a study investigating the influence of additives on the tribocharging behaviour of two excipients using Granutools' GranuCharge instrument.

Good flowability is a key factor for numerous powder processes, with the consistency of the flow directly related to the final product quality. However, when a powder flows, the frictional contact between the particles creates electrostatic charges via the triboelectric effect. This charge build up induces an increase in the strength of the electrostatic cohesive interactions that contribute to the global cohesiveness of the powder and therefore a decrease in its flowability properties.

Moreover, charged particles tend to stick to the surface of pipes and machine parts. A non-negligible amount of material can thus stay trapped in the conveying device, clog pipes and induce undesirable variability of the mass flow. In a 2021 study, Allenspach *et al*[1] demonstrated the correlation between the propensity of powders to accumulate charge during their flow and the sticking of particles at the output of a loss-in-weight feeder. They demonstrated that high charge density leads to heavy sticking and irregular flow, and thus a significant overshoot of the target mass flow. Therefore, the relationship between the sensibility of a powder to tribocharging is directly related to its processing performance.

The addition of additives is a common procedure in the pharmaceutical industry to improve the properties of an excipient and API blend. For example, mesoporous silica has been shown to significantly improve the flowability of excipients by both reducing the capillary bridges between the particles and producing a conductive network to efficiently dissipate the charges throughout the material.[2] However, additives of different nature are generally used and a systematic evaluation of their influence on the electrostatic behaviour of the blend is still lacking.

In this study, the influence of three common additives – Syloid® S244, Magnesium Stearate (MgSt) and Aerosil® 200 – on the tribocharging properties of two excipients

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– microcrystalline cellulose (MCC), Starch 1500® – was investigated. The tribocharging characteristics of the blends were evaluated with the GranuCharge instrument (Granutools), which evaluates the charge build-up due to the flow through a set of SS316L pipes.[3]

EXPERIMENTAL METHOD

The tribocharging properties of the selected excipients were investigated with GranuCharge (Figure 1). The main component of this device is the Faraday cup, specifically designed to measure low electrostatic charges in powders or granular materials. A set of V-shape pipes is used to evaluate the tribocharging sensibility of the powder during a flow. Numerous pipe materials are available (PVC, teflon, copper, etc.) but stainless steel (SS316L) pipes were used in this study. Both the pipes and the operator were grounded during the measurement to avoid influencing the powder charge. A vibrating feeder was used to pour the powder into the pipes.

The measurement protocol was as follows. First, the initial charge density was determined, as it depends on the history of the powder (production, transport, handling), and used as a reference to evaluate the charge build-up after the flow through the pipes. After measuring out 55 mL of the powder, the initial charge density (q0) was measured by pouring the powder directly into the Faraday cup. Then, the powder was extracted from the cup and placed in the vibrating feeder. The sample then flowed through the V-shape stainless steel pipes into the Faraday cup, allowing measurement of the final charge density (qf). The charge density variation (Δq = q0-qf) due to the gain or loss of electrostatic charges during the flow was then determined. The measurement was repeated three times on fresh (unused) samples to assess repeatability. In this study, the average computed over the three tests was reported, with the error bars corresponding to the standard deviation around the mean.

MATERIALS

Two excipients (MCC, Starch 1500®) and three additives (Syloid® S244, MgSt, Aerosil® 200) were selected for this study. The blends were produced for each excipient/additive combination for 0.5, 1 and

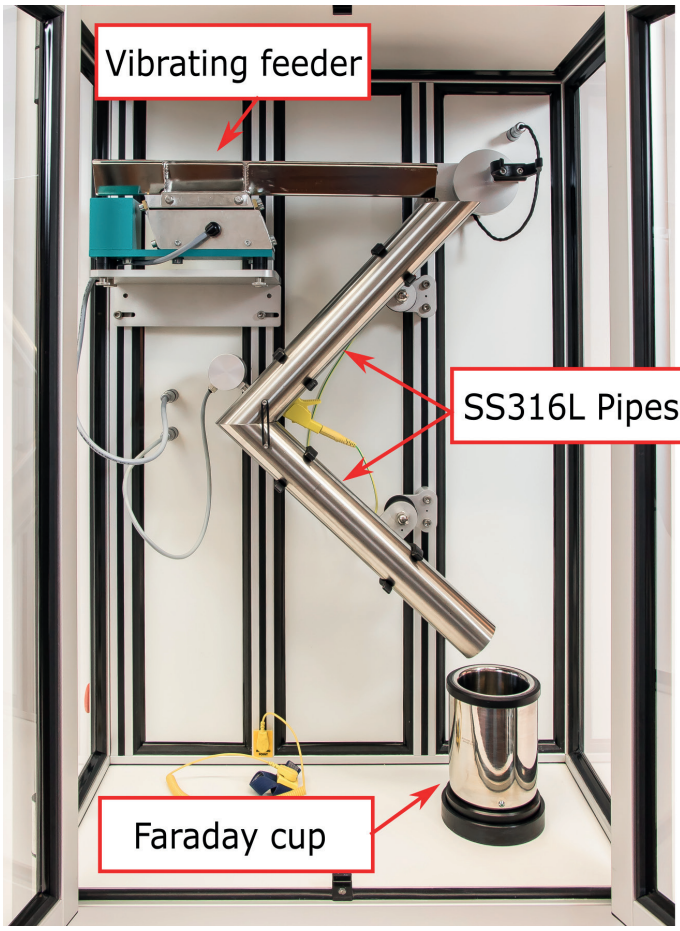

Figure 1: GranuCharge instrument (Granutools).

2% w/w of additives. Therefore, the effect of each additive/exception combination can be evaluated for the tribocharging properties, as well as the influence of the amount of additive. Each excipient additive combination blend was prepared by passing excipient through a #25 mesh screen and additive through a #60 mesh screen and then blended in a V-Blender at 15 RPM for 5 minutes. The resultant blend was then used for further study.

Name	q0 (nC/g)	qf (nC/g)	Δq (nC/g)	Name	q0 (nC/g)	qf (nC/g)	Δq (nC/g)
Starch 1500	-6.62×10^{-1}	-3.49	-2.83	MCC	-4.17×10^{-1}	-4.41	-4.00
Starch + S244 0.5%	-5.61×10^{-1}	-9.70×10^{-1}	-4.08×10^{-1}	MCC + S244 0.5%	-5.99×10^{-1}	-2.45	-1.85
Starch + S244 1%	-5.91×10^{-1}	-5.54×10^{-1}	3.66×10^{-2}	MCC + S244 1%	-1,02	-1.71	-6.86×10^{-1}
Starch + S244 2%	-6.14×10^{-1}	-3.36×10^{-1}	2.77×10^{-1}	MCC + S244 2%	-8.12×10^{-1}	-8.69×10^{-1}	-5.72×10^{-2}
Starch + Mg St 0.5%	-6.03×10^{-1}	-1.73	-1.12	MCC + Mg St 0.5%	-7.21×10^{-1}	-2.79	-2.07
Starch + Mg St 1%	-4.37×10^{-1}	-1.18	-7.46×10^{-1}	MCC + Mg St 1%	-9.41×10^{-1}	-2.25	-1,31
Starch + Mg St 2%	-2.67×10^{-1}	-3.54×10^{-1}	-8.72×10^{-2}	MCC + Mg St 2%	-4.53×10^{-1}	-1.79	-1.34
Starch + Aer 0.5%	-6.50×10^{-1}	-6.97×10^{-1}	-4.62×10^{-2}	MCC + Aer 0.5%	-6.40×10^{-1}	-9.24×10^{-1}	-2.84×10^{-1}
Starch + Aer 1%	-4.80×10^{-1}	-6.99×10^{-1}	-2.19×10^{-1}	MCC + Aer 1%	-4.09×10^{-1}	-3.79×10^{-1}	3.02×10^{-2}
Starch + Aer 2%	-3.22×10^{-1}	-1.03	-7.08×10^{-1}	MCC + Aer 2%	-3.59×10^{-1}	-9.67×10^{-2}	2.63×10^{-1}

Table 1: Initial charge density (q0), final charge density (qf) and total charge build-up (Δq) measured with the GranuCharge for the different blends.

"Reducing the amount of additives is usually beneficial for reducing production costs and easier regulatory compliance."

RESULTS AND DISCUSSION

The obtained initial and final charge densities, as well as the charge build-up, are reported in Table 1 for all excipient/additive combinations. The charge density measured for the raw excipient (without additives) is also shown. The final charge density, obtained after the flow through the stainless steel pipes, is presented in Figure 2. After the flow, the two raw excipients show a high charge density of about -5 nC/g for the MCC and -4 nC/g for the starch. The two excipients demonstrate a high sensibility to tribocharging, which is likely to induce electrostatic-related processability problems. Every combination of excipient/additive leads to a reduction of the final charge density. This reduction can be associated either with a decrease in electrostatic charge generation or a drastic increase in the global conductivity of the material, allowing a more efficient charge dissipation.

To highlight the beneficial influence of the additive, the charge build-up reduction (CBR) is presented in Figure 3. The CBR quantifies the amplitude of the reduction of the charge build-up due to the presence of the additive compared with the charge build-up obtained with only the raw material. Therefore, a CBR of 50% indicates that the charge build-up measured with the additive is 50% lower than the one measured for the excipient alone.

A significant reduction of the charge build-up is observed with CBR >48% for all excipient/additive combinations. This confirms the usefulness of these additives in reducing the electrostatic charging of the blends. However, it was observed that the effect of the additives is not the same for the MCC and the Starch 1500. Indeed, the Syloid S244 shows a stronger CBR when associated with Starch 1500, resulting in at least CBR >80% for the three tested additives. An optimum CBR was obtained for 1% of Syloid S244, but then the effect decreased with increased content. Different behaviour was observed with the MCC, and a clear influence of the content of

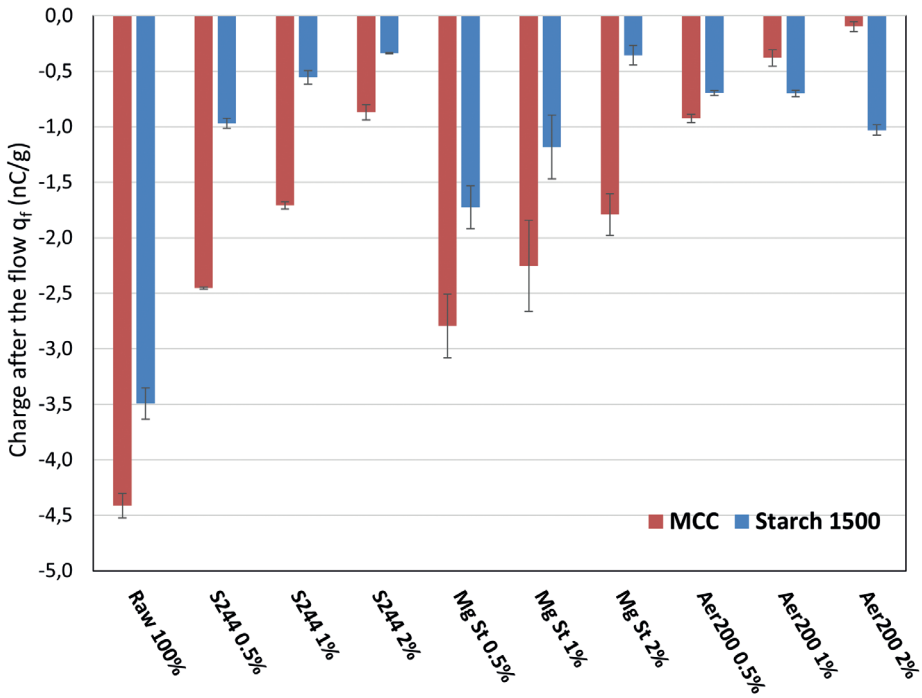

Figure 2: Charge density measured after the flow through the SS316L pipes for different %w/w of the three additives.

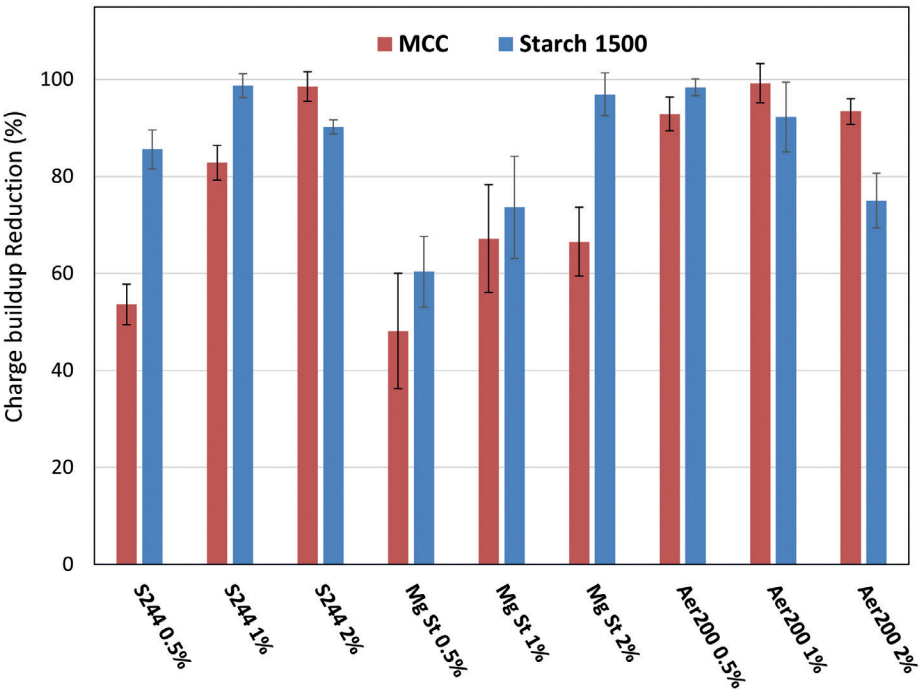

Figure 3: CBR for different %w/w of the three additives.

Syloid S244 was observed. At 0.5% of Syloid S244, the CBR was about 55% but drastically increases to 99% for 2% of Syloid S244.

The MgSt shows a lower CBR for both excipients, except for the Starch 1500 at 2% MgSt. For the MCC, a slight increase in CBR is observed from 0.5% to 1% MgSt but still a lower performance compared with the Syloid S244 and the Aerosil 200. For the Starch 1500, the CBR was strongly dependent on the additive content, with a constant increase up to 97% for 2% of MgSt. Therefore, the performance of the MgSt on the Starch 1500 at a content of 2% is similar to the Syloid S244 and the Aerosil 200.

Finally, the Aerosil 200 had a strong impact on the CBR. In particular, the MCC shows a CBR >90% for all additive content. Reducing the amount of additives is usually beneficial for reducing production costs

and easier regulatory compliance. From these results, it can be determined that the Aerosil 200 is the additive that shows the higher CBR for MCC at the lower content (0.5%). However, for Starch 1500, the effect of the Aerosil 200 is different – at 0.5% of Aerosil 200, a high CBR is observed (>98%), but a subsequent increase of additive content leads to a decrease in the CBR.

CONCLUSION

In this study, the influence of three common additives (Syloid S244, MgSt, Aerosil 200) on the tribocharging behaviour of two excipients (MCC, Starch 1500) was investigated with GranuCharge. A significant reduction in the charge build-up of the blends was observed for all excipient/additive combinations. However, the additives can exhibit different performance in terms of charge reduction depending on the excipient with which they are associated. Furthermore, increasing the additive content does not systematically improve the charge reduction. In some cases, an optimum is observed and higher additive content leads to lower charge reduction.

These results highlight the importance of systematic characterisation of the influence of additives on the triboelectric behaviour of powder blends. Indeed, the complexity of the mechanisms involved in tribocharging powders makes it very difficult to predict what the charge build-up will be. Fortunately, the GranuCharge instrument has demonstrated its ability to evaluate the tribocharging ability of the different blends. This study is a preliminary work that opens up promising outcomes for future investigation. In particular, it is an ongoing study aiming to understand more deeply the interaction between the excipient and the additive particles that leads to the CBR.

> "These results highlight the importance of systematic characterisation of the influence of additives on the triboelectric behaviour of powder blends."

ABOUT THE COMPANIES

Granutools combines decades of experience in scientific instrumentation with fundamental research on powder characterisation to develop and manufacture instruments that measure physical powder characteristics, such as flow, static cohesion, dynamic cohesion, tapped density and tribo-electric charge.

Natoli Engineering Company is a global leader in tablet compression tooling and far more. Founded on the uncompromising principle to manufacture and deliver the highest quality products at a fair price with exceptional customer service, Natoli continues to build on a half century of innovation and industry leadership. Natoli is also a leading provider of tablet presses, control system software and premium replacement parts for tablet presses and encapsulation machines. Additionally, Natoli provides formulation development and analytical/testing services, unparalleled technical support and troubleshooting, technical training courses and a comprehensive tablet compression accessories catalogue.

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ABOUT THE AUTHORS

Aurélien Neveu, PhD, focuses primarily on researching the understanding of granular materials at different scales. During his PhD, he developed discrete numerical models to describe fragmentation mechanics of cohesive granular materials by taking the complex microproperties of the grains into account. He then moved to a larger scale to study segregation in gravity-driven rapid flows, as well as aeolian transport of granular materials, with huge implications for natural disasters. He joined Granutools as a particle scientist performing research on powder characterisation, and is now Head of Laboratory & Applications at the company.

Devang Patel, PhD, works as a Senior Research Scientist at Natoli Engineering Company. He uses his experience in resolving or providing guidance on various tableting issues, such as sticking and picking, to provide scientific and technical support for Natoli's customers by generating application data for formulation and tablet tooling. During his PhD, Dr Patel investigated tablet sticking using different metal coupons and a powder rheometer. Some of his notable academic contributions include peer-reviewed papers on formulation and 3D printing.

Filip Francqui is the Managing Director of Granutools and has over 20 years of experience in precision instruments business. Mr Francqui's experience covers the semiconductor, electronic microscopy and nanotechnology fields. Before founding Granutools, he was successively managing the Belgian, Dutch and Indian business for the electronic microscopy subsidiary of Thermo Fisher Scientific known as FEI company, which was famous for high resolution and low voltage imaging. Mr Francqui holds a master's degree in Applied Physics from the Free University of Brussels (Belgium) and an MBA from INSEAD (Singapore). He has numerous publications in scientific journals and holds two patents.

NANOENCAPSULATION: A NEW ERA FOR ORAL SOLID DOSAGE FORMS

In this article, Oksana Lemasson, PharmD, PhD student, and Sandrine Bourgeois, PhD, Associate Professor, both at the Laboratory of Automatic Control, Chemical and Pharmaceutical Engineering at Claude Bernard University Lyon 1, and Vanessa Bourgeaux, PhD, Innovation Leader at Skyepharma Production, discuss the performance of the NanoMicS platform for the oral administration of nanoparticles.

The oral route is the preferred route for drug administration because it allows better patient compliance. However, many factors limit the effectiveness of oral treatments, including the poor bioavailability of some APIs. It is estimated that 60% of new available APIs are rated as Class II and Class IV under the Biopharmaceutics Classification System (BCS) based on their low water solubility. Most of these APIs also have a low oral bioavailability due to extensive hepatic metabolism through cytochromes or high affinity with permeability glycoprotein (P-gp), a transmembrane transporter present in the intestine capable of pushing drugs back into the lumen, thus decreasing their absorption.[1,2]

Nanoencapsulation then appears to be a formulation of choice to overcome those biological barriers and achieve specific properties that are a key differentiating factor from other drugs. Nanoparticles act as a shield for the active molecule, preventing it binding to P-gp and cytochromes and conferring enhanced permeability.[3] Nanoencapsulation can be applied to new chemical entities but also to already-on market APIs (through product lifecycle management). In this latter case, the nano approach gives pharmaceutical companies the opportunity to increase the rentability of active ingredients by developing "premium" drug product generation with enhanced therapeutic efficacy and minimised off-target side effects.

> "While widely used for injectables, nanoparticles remain poorly explored for oral administration."

NANOMICS PLATFORM AT A GLANCE

To answer market needs, Skyepharma – which specialises in oral solid dosage forms and high-pressure homogenisation (HPH) technology – has taken the step to create a nanoformulation platform, NanoMicS, focused on the development of innovative nanoparticle-containing tablets, capsules or micropellets.

Skyepharma has already developed a first HPH-based process capable of producing nano-sized particles of APIs named IDD-Dissocubes™. This top-down technology, resulting in nanocrystals fof API, is currently on the market for the treatment of for lipidic disorders (Triglide®)[4] and has allowed a dramatically reduced food effect and administered dosage of fenofibrate, compared with traditional oral dosage forms. Reinforcing the pipeline of bioavailability-improving solutions with nanoparticles manufactured through HPH is

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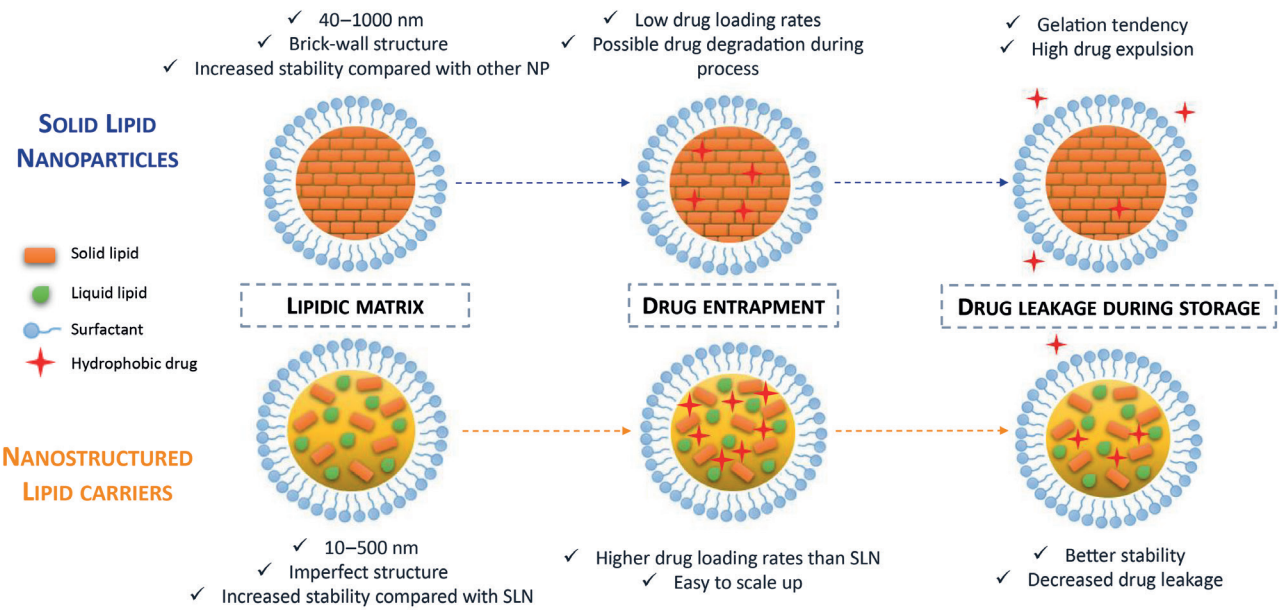

Figure 1: Main characteristics of SLN and NLC.

thus completely in line with Skyepharma's strategy to bring high-value oral solutions to customers and ultimately patients.

While widely used for injectables, nanoparticles remain poorly explored for oral administration. Industrial challenges to be met include maintenance of nanoparticle features upon drying and tableting processes, process reproducibility during scale-up, implementation of relevant in-process controls, achievement of satisfactory holding time of nanomaterial and development of efficient cleaning procedures. A good understanding of the natural fate of nanobodies after release from solid forms, the identification of the pathways used to cross the gastrointestinal tract and the elucidation of the mechanism of release of the API from the nanoparticle are areas to be further investigated and mastered to ensure success of the "bench-to market" oral nanoplatform.

Therefore, the NanoMicS platform was developed in partnership with Claude Bernard University Lyon 1's Laboratory of Automatic Control, Chemical and Pharmaceutical Engineering (LAGEPP) – which is highly experienced in nanoparticles and oral formulation processes. The platform started with the development of a generic nanoformulation to improve the solubility of lipophilic drugs, but there are plans to expand the portfolio of nanoformulations further to address all types of molecules, including temperature-sensitive APIs. As ecology matters, all formulations are developed with "green" processes, avoiding the use of volatile organic solvents detrimental to the environment.[5]

> "The manufacturing of nanoproducts requires the control of nanomaterial properties such as size, shape, charge, composition, physicochemical properties and drug-release kinetics."

RECENT SCIENTIFC ADVANCES

First results generated by researchers from LAGEPP on the nanoencapsulation of BCS Class II or IV APIs in solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) were very promising. This innovative strategy, improving the API's solubility in digestive fluids and giving better control of its release and metabolism issues, also has the advantage of being biocompatible and biodegradable. Both SLNs and NLCs contain solid lipid, liquid lipid (Maisine® or Capryol® 90) and surfactant but differ in the whole structure, SLNs presenting a brick-wall structure while NLCs feature a hybrid structure (Figure 1).

For the proof of concept, the selected model drug was spironolactone (SPI), a BCS class II API. The formulation of lipid nanoparticles was developed according to a previous study carried out at LAGEPP by Dumont *et al*,[6] with a nanosuspension composed of two phases: the lipidic (including dissolved SPI) and the aqueous with surfactant and deionised water.[6] The two phases were heated separately and homogenised by high shear agitation. This pre-emulsion was inserted in the Microfluidizer® LM20 (Microfluidics, MA, US) and pumped through the system, inside which high shear forces are applied to the emulsion.

The manufacturing of nanoproducts requires the control of nanomaterial properties such as size, shape, charge, composition, physicochemical properties and drug-release kinetics. Both SLNs' and NLCs' blank formulas provided satisfactory particle size characteristics, with a mean diameter below 200 nm and polydispersity index (PDI) below 0.2 (Table 1).

Property	SLNs	NLC-C90	NLC-MAI
D50 (nm)	192.84 ± 13.92	168.22 ± 32.94	143.37 ± 0.49
PDI	0.174 ± 0.026	0.180 ± 0.042	0.184 ± 0.018

Table 1. Particle size characteristics of blank SLNs and NLCs (n=3), mean ± SEM.

Their observation with transmission electron microscopy (TEM) demonstrated they were all spherical shaped (Figure 2), which is a critical attribute of nanoparticles to cross the gastrointestinal tract. Compared with the blank nanoparticles, the SPI encapsulation did not lead to a significant difference in particle size. However, as shown in Table 2, the NLC formula with Maisine® (NLC-MAI) allowed the highest encapsulation, with 72.8% of SPI encapsulation efficiency, compared with 50.2% for NLC with Capryol® 90 (NLC-C90) and 60.7% for SLN.

A stability study was conducted to ensure a sufficient holding time of the nanosuspension between its formulation and the drying. During seven days at room temperature, the general aspect remained unchanged. Concerning the particle size features, the mean diameter of the lipid nanoparticles increased slightly (from 171 nm to 216 nm, n=3) whereas the polydispersity index was stable (non-significant decrease from 0.18 to 0.16, n=3). These acceptable results confirm that the nanosuspension is stable under conventional storage conditions, without the need for specific precautions. Thus, the demonstrated stability of the nanosuspension allows few days between its formulation with the Microfluidizer® LM20 and its drying for compression.

Drying the nanosuspension presents a double strategic interest. On the one hand, it is well described as an effective way to significantly improve the long-term stability of lipid nanoparticles. On the other hand, this process allows the obtention of powders, which will be compressed into tablets, to offer an innovative oral solid dosage form for patients.

Two drying techniques (spray-drying and wet granulation) were tested to produce an easily compressible and redispersible powder. For both techniques, the nanosuspension was mixed with suitable excipients until the obtention of a satisfactory general aspect of the powder. The two types of dried powder presented satisfactory flow properties, according to the European Pharmacopeia (even "excellent" for the granulated batch) and were easily and successfully dispersed in water.

The powder obtained by wet granulation (Figure 3a) was selected for the preliminary compression study. Two batches of tablets were manufactured, at lab scale (total weight = 150 g) and pilot scale (total weight = 1000 g, Figure 3b). The tablets were easily dispersed in water, with features comparable to the initial powder. Moreover, all the units were compliant with the European Pharmacopeia monographies relative to tablets (mass uniformity, disintegration time, hardness and friability), without any influence of the batch size.

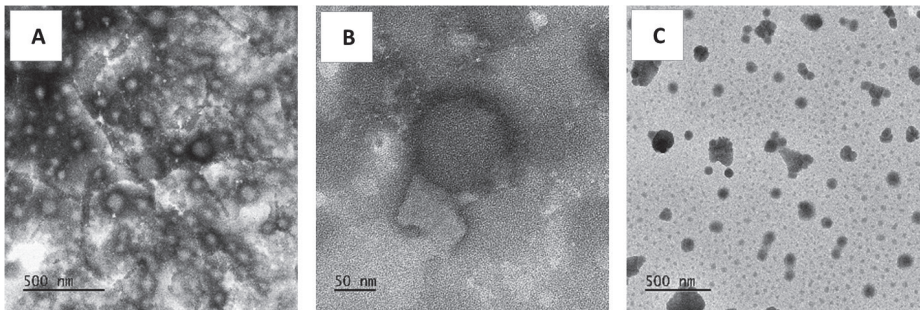

Figure 2. SLN (A&B) and NLC (C) observation by TEM.

Properties	SLNs	NLC-C90	NLC-MAI
D50 (nm)	183.74 ± 33.39	184.97 ± 59.02	176.50 ± 37.53
PDI	0.167 ± 0.055	0.213 ± 0.070	0.217 ± 0.053
EE (%)	60.7 ± 5.3	50.2 ± 18.2	72.8 ± 1.7

Table 2. Particle sizes of SPI-loaded nanoparticles (n=9) and encapsulation efficiency (n=3) for the three types of lipid nanoparticles (SLN, NLC-C90 and NCL-MAI), mean ± SEM.

> "The proof-of-concept confirmed that HPH can be used to manufacture lipid-based nanoparticles with mean diameters lower than 200 nm."

In short, the proof-of-concept confirmed that HPH can be used to manufacture lipid-based nanoparticles with mean diameters lower than 200 nm. While encapsulating the model drug (spironolactone), the addition of a liquid lipid did not have a significant impact on the particle size but significantly improved the entrapment efficiency of the API, especially with the oil Maisine®. *In vitro* investigations are underway to study the release profile of the API as well as the improvement of its cellular permeability when encapsulated in lipid nanoparticles.

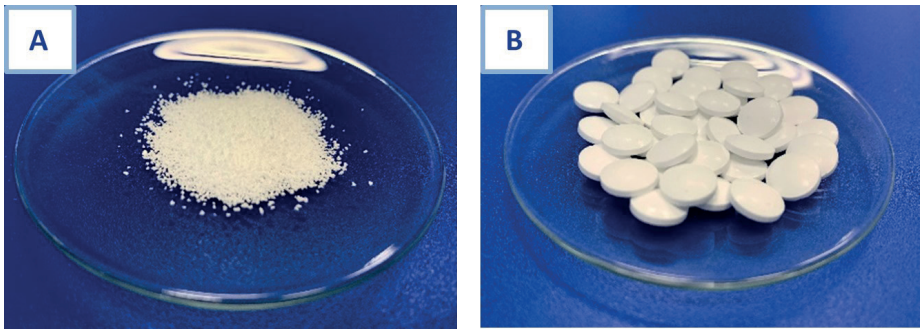

Figure 3. Granulated powder (A) used to produce lipid nanoparticle-based tablets (B).

INDUSTRIAL SCALE-UP AND QUALITY-BY-DESIGN APPROACH

As a contract development and manufacturing organisation (CDMO) and centre of excellence in oral solid dosage form development and industrialisation, Skyepharma is highly experienced in quality-by-design (QbD) and process industrialisation, which are two strong assets for the development of the NanoMicS

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platform. For nanoparticle-containing tablets, attributes such as nanoparticle size, API encapsulation efficiency, polydispersity index and drug-release kinetics come on top of critical quality attributes that are standardly evaluated for tablets (hardness, friability, mean mass and disintegration). To increase manufacturing robustness, the process analytical tool approach should be considered at the industrialisation phase to allow real-time product analysis and continuous feedback on manufacturing.

Defining clearly the attributes of raw materials, their behaviour throughout the process and their quality impact on the final product is also a prerequisite to the successful development of nanoparticles. In the case of solid lipid excipient, for example, changes in surface charge or morphology can alter the therapeutic properties of the API, and its characterisation is as important as the one of the API. Considering those industrial challenges early in development is a key element to reduce drug product development timelines and costs.

"Defining clearly the attributes of raw materials, their behaviour throughout the process and their quality impact on the final product is also a prerequisite to the successful development of nanoparticles."

CONCLUSION

Skyepharma has made the strategic choice to establish itself as a pioneer in the administration of oral nanoparticles. Co-developed with LAGEPP, the NanoMicS platform aims to offer biocompatible delivery system solutions for BCS class II and IV molecules and reduce the number of leads of high therapeutic potential that are given up due to poor solubility issues. The Microfluidizer® technology appears as an eco-friendly solution to enhance oral bioavailability, broadening the spectrum of active molecules that could reach the market in oncology, immunology or infectiology and making patients' daily lives easier.

ABOUT THE COMPANY

Skyepharma Production SAS is a French CDMO specialising in oral solid dosage forms. The company's mission is to provide, thanks to a dedicated and results-oriented team, advanced oral dosage services to the healthcare industry through state-of-the-art facilities and scientific expertise. Skyepharma also provides a range of support services that help client companies from early-stage development (up to Phase III) through scale-up, commercial manufacturing and packaging to market introduction, including controlled substance handling, QbD methodology, troubleshooting, regulatory services, validation, registration and warehousing services.

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ABOUT THE AUTHORS

Oksana Lemasson, PharmD, obtained a double degree in pharmacy and a master's degree in industrial cosmetology, with a specialisation in formulation at the University of Lyon (France). Following her studies, she taught galenics for a year at university to pharmacy students. Wishing to develop her expertise in formulation, she is currently a PhD student at Claude Bernard University Lyon 1's Laboratory of Automatic Control, Chemical and Pharmaceutical Engineering (LAGEPP) (Lyon, France), in partnership with Skyepharma, and works on the development of lipid-based nanoparticles, from proof of concept to manufacturing process optimisation.

Sandrine Bourgeois, PhD, is Associate Professor in Pharmaceutical Technology at the School of Pharmacy of the Claude Bernard University Lyon 1 (France). After graduating in pharmacy, she obtained a PhD in pharmaceutical technology at Paris-Saclay University (France). She conducts research at the Laboratory of Automatic Control, Chemical and Pharmaceutical Engineering (LAGEPP) on the development and characterisation of new drug delivery systems for oral and mucosal administration. Dr Bourgeois is the author of 28 publications, three patents and has supervised 10 PhD students.

Vanessa Bourgeaux, PhD, brings 15 years of experience in research and development, and pharmaceutical development. She started her career at Erytech Pharma (Lyon, France), where she held the position of global project leader and actively contributed to the development of erythrocytes as drug carriers for oncology and sickle cell disease. In 2020, Dr Borgeaux joined Skyepharma. As Project Manager in the New Product Introduction department, her mission is oriented towards innovation and collaborative partnerships. Dr Bourgeaux graduated in organic chemistry and holds a PhD in biochemistry and cellular biology. She is the author of 13 publications and 12 patents.

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FORMULATING SUPERIOR ORAL SUSPENSIONS FOR BETTER PATIENT COMPLIANCE

In this article, Rina Chokshi, PhD, Global Commercial Marketing Manager, and Dago Caceres, Global Strategy Director, both of IFF Pharma Solutions, discuss how leveraging key ingredients in oral suspensions can enhance stability and sensory attributes, as well as encourage patient compliance.

For many drug formulators and manufacturers, patient compliance remains a key area of focus. With around half of treatment failures attributed to low patient compliance, better drug design and improved delivery options could increase the likelihood that patients will take their medications as prescribed, potentially improving outcomes and reducing healthcare expenditure.

Chewable tablets, orally disintegrating tablets and liquid formulations may all lead to higher rates of patient compliance – particularly in populations that have difficulty swallowing, such as paediatrics, geriatrics and patients with dysphagia. These patients often require alternative drug formats to traditional tablets and capsules, and frequently show the greatest preference for oral liquid formulations.

Research has identified oral suspensions as one of the top delivery formats in the liquid formulations space. The key advantage of an oral suspension is its ability to preserve the structure of the APIs within it without any dissolution, while also providing the patient with an easy-to-swallow liquid format. The fact that the API is not completely dissolved allows the suspension to deliver a higher drug concentration than an equivalent volume of liquid solution.

Demand for suspensions has grown, largely due to their increased bioavailability and ability to contain high doses of APIs. Suspensions also enable easier customisation, allowing for appropriate dosing for all patients, regardless of age or weight. Additionally, suspensions are easy to taste-mask; formulators can overcome any unpleasant tastes from the active ingredient by limiting the amount of drug in solution and by adding flavourings to the liquid vehicle. After all, sensory enhancement of the drug experience goes hand in hand with achieving better rates of patient compliance.

> "Demand for suspensions has grown, largely due to their increased bioavailability and ability to contain high doses of APIs."

CONSIDERATIONS FOR OPTIMAL SUSPENSION FORMULATIONS

Suspensions are finely divided, undissolved drugs that are dispersed in liquid vehicles. They appear in two forms, ready-to-use liquid suspensions and dry powder reconstitutable suspensions, which are dispersed into water by the patient, caregiver or pharmacist before use. They are not to be confused with solutions, which are liquid preparations in which the drug and the various excipients are dissolved in a suitable solvent or aqueous system.

Oral suspensions require a careful balance of ingredients to ensure both drug efficacy and a positive sensory experience. In a suspension formulation, alongside the API, there are multiple excipients included to ensure a stable, uniform drug product with pleasant taste and mouthfeel. A suspending agent, protective colloid and viscosifier are commonly applied as critical functional excipients.

As with any drug format, formulators must overcome a number of challenges when creating suspensions. While it is necessary to source consistently safe, high-quality ingredients, manufacturers must also consider how ingredients may contribute to viscosity, pourability and pleasant sensory attributes. There is also often a need to overcome turbidity, clumping and concerns around the API settling. Suppliers experienced with suspensions can offer both product solutions and expertise in navigating the complex regulatory landscape.

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UNDERSTANDING KEY INGREDIENTS

Suspending agents create a gel-like network, allowing for uniform dispersion of API while remaining stable over extended periods of storage. Often, suspending agents are not used alone, as each has its own unique strengths and weaknesses. For example, colloidal microcrystalline cellulose (cMCC) is a well-established and versatile excipient comprised of co-processed microcrystalline cellulose and sodium carboxymethyl cellulose (NaCMC). It offers several key properties and functionalities that make it an ideal suspending agent, including its thixotropic behaviour for stabilising suspensions and its ability to stabilise reconstitutable dry suspension formulations. cMCC forms a gel-like network and remains stable over a broad range of pH and temperatures.

Despite these strengths, there can be challenges when it comes to activating cMCC. Once dispersed in an aqueous medium, cMCC must be activated so that individual particles deagglomerate and provide optimal suspension properties. To activate it, producers may use water during the milling stage or use high shear agitation. Once activated, cMCC is stable under a wide range of temperature conditions.

Xanthan gum is another common stabilising agent – it is efficient, readily soluble and provides the necessary rheological properties and formulation homogeneity at very low use levels. Xanthan gum is most typically used in formulating reconstitutable dry powder suspensions, although it can also serve as a viscosifier in liquid formulations, typically in combination with cMCC to further aid formulation stability. Furthermore, the desired viscosities and textures can often be provided with only a low level of xanthan gum. At the same time, its pronounced shear-thinning behaviour enables handling of even highly viscous solutions.

Frequently, producers may choose food-ingredient suppliers that are able to generate a pharmaceutical-grade xanthan gum as a supplier. However, this may compromise quality. Manufacturers should preferentially obtain pharmaceutical-grade xanthan gum from a trusted supplier with expertise in pharmaceutical drug formulation.

Lastly, highly purified NaCMC forms clear solutions in water at all temperatures and has exceptional water-binding properties, with the benefit of being available in a wide range of viscosity grades. It can function as a thickener, stabiliser, binder or protective agent in suspension formulations.

> "While cMCC can act as a standalone suspending agent, it can also be synergistically incorporated with xanthan gum or NaCMC to allow for a wide range of functionalities."

While cMCC can act as a standalone suspending agent, it can also be synergistically incorporated with xanthan gum or NaCMC to allow for a wide range of functionalities. When used properly, these ingredients work together to enhance the sensory experience of the drug product. Appropriate use of functional ingredients, excipients and polymers can help ensure an effective and appealing suspension drug product.

ACHIEVING FORMULATION STABILITY

Formulation stability is critical for an efficacious drug product. When not paired with the right thickening and suspending agents, APIs can agglomerate, resulting in unstable formulations that do not perform as intended. Formulation stability can be affected by several factors, such as pH level, salt content or various ions.

In a suspension formulation, all ingredients must disperse uniformly to function fully and allow accurate dosing. Achieving this outcome depends on the stability of the suspension formulation. Formulation stability largely depends on selecting the right suspending agent.

For formulation stability, it is often recommended that formulators turn to cMCC as an effective suspending agent. Its activated aqueous dispersion forms a strong, gel-like network and functions as a structured vehicle to effectively suspend the active pharmaceutical ingredient in the formulation. Xanthan gum can also be considered, specifically for facilitating reconstitutable suspension formulations, as it remains stable across a wide pH range, when heated and in the presence of salts or acids. Xanthan gum also contributes to the stability of undissolved APIs in the suspension and can be used to fine-tune the rheological features of a formulation.

> "The right combination of polymers is critical to ensure that viscosity and thickness meet the most stringent standards, while also appealing to patients."

In one study, liquid model suspensions were prepared with these excipients, and their rheological properties and stability were evaluated.[1] The findings indicated that cMCC formulations are very stable during four-week storage at room temperature, while xanthan gum formulations are relatively stable to begin with but show slight phase separation in week four. NaCMC formulations are the least stable, with the API settling within one week. This research confirms that cMCC provides optimal stability for oral suspensions, although formulators can consider pairing it with xanthan gum, as needed.

MAINTAINING VISCOSITY AND POURABILITY

For liquid oral suspensions, formulators must consider viscosity and pourability. The viscosity of a suspension at rest and when being poured is critical to the efficacy of the drug. Liquid suspensions at rest will need higher viscosity to help stabilise the API within the suspension to prevent sedimentation and aggregation of the particles. However, during administration, the liquid suspension must become less viscous upon shear for pourability, while retaining pleasant sensory attributes. The right combination of polymers is critical to ensure that viscosity and thickness meet the most stringent standards, while also appealing to patients.

Xanthan gum is efficient and robust as a singular suspending agent at low use levels. At the same time, its pronounced shear-thinning behaviour enables handling of even highly viscous solutions. It can also be used as a secondary ingredient to another suspending agent, such as cMCC, especially as a viscosifier, while also aiding with the stability of oral liquid formulations.

Formulators can boost viscosity with a combination of xanthan gum and NaCMC.[1] The research shows that, at about pH 3.5, suspensions containing only cMCC are not stable, showing phase separation in week four. However, the addition of NaCMC stabilises the suspension, showing a strong synergistic effect.

SENSORY ENHANCEMENT OF THE DRUG EXPERIENCE

Oral liquid suspensions tend to achieve greater patient compliance due to their ability to enhance the sensory attributes of the drug product. Taste, smell, texture and appearance must all appeal to patients, or manufacturers run the risk of poor compliance.

Oftentimes, ingredients in a suspension work against each other to create an end product that can be too gritty or result in a chalky mouthfeel. Formulators can overcome these challenges by selecting the right functional excipients and taste-masking agents at varying levels. Low use levels of xanthan gum can effectively provide desirable textures to improve mouthfeel. Most often, the use levels (in liquids) are 0.05–0.5%. NaCMC can also modify the texture of suspensions for a more appealing mouthfeel. Additionally, carrageenan can offer a natural solution for gelling and thickening.

The appearance of a drug can also impact patient compliance, especially with paediatrics. To achieve the desired visual appeal for suspension formulations, selecting an excipient that has little-to-no colouring is ideal. NaCMC provides a clear suspension vehicle, while xanthan gum offers a translucent or turbid suspension vehicle. On the other hand, cMCC allows for an opaque suspension vehicle.

To help mask unpleasant tastes, formulators may use selective hydrophobic polymers that may also contribute to coating capabilities, such as moisture protection and sustained release. Adding sweeteners can enhance palatability and contribute to viscosity. However, in suspensions intended for paediatric use, the sweetening agent must be less than 5 mg/kg of patient body weight. While taste-masking agents can overcome unpleasant tastes in suspensions, xanthan and NaCMC are flavourless and odourless, making them virtually impossible to detect on their own.

Formulators have a myriad of possible ingredient combinations to choose from that can contribute to specific sensory characteristics, such as texture and taste. Prioritising sensory enhancement, alongside stability and viscosity, can help ensure patient compliance and, in so doing, a drug's effectiveness.

SUPERIOR SUSPENSIONS REQUIRE REGULATORY EXPERTISE

Superior suspensions require manufacturers to consider the regulatory aspect of each ingredient in the formulation. This includes standard excipients, flavouring agents and colourants. It becomes even trickier when taking the global, often unharmonised, regulatory environment into consideration, such as when catering to the growing demand for oral suspensions in China, due to its ever-growing geriatric population.

While there are several high-quality suppliers of any given pharmaceutical excipient, it is not guaranteed that they understand the complex regulatory environment and intricacies of oral suspension formulations. From the complexities of the US FDA's Inactive Ingredient Database to the intricacies of excipient regulations in countries like China, partnering with an ingredient supplier with extensive experience in the field can help formulators navigate these markets and overcome regulatory challenges.

It is anticipated that demand for suspensions will continue to rise in the coming years, specifically for liquid oral formulations. This demand will likely be especially pronounced in countries with large paediatric and geriatric populations, such as the US and China. It is also expected that demand for suspensions will be driven by over-the-counter medications, such as ibuprofen, and antibiotics, such as amoxicillin. A solid supply partner with expertise in the field can help manufacturers navigate common formulation challenges to achieve superior suspensions that will appeal to patients and increase compliance rates in low-compliance populations.

ABOUT THE COMPANY

IFF Pharma Solutions is a global leader in food, beverage, health, biosciences and sensorial experiences. For more than 130 years, the company has been focused on finding the most innovative solutions to help bring "better for you" products to market. While it has grown over the years, IFF remains agile in its approach and puts its customers' needs at the forefront of the company's thinking. IFF's product portfolio includes the taste, texture, scent, nutrition, enzyme, culture, soy protein and probiotic categories.

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