Problem-solving ingredients for complex drugs

Scientific advancements may be leading to more effective drugs, but the requirement for solubility-enhancing technology, palatability improvements and life-cycle extenders is greater than ever. **Susan Birks** looks at ingredient trends

Drug developers around the world are facing a new set of challenges. Not only are the new active ingredients poorly soluble and site-specific, requiring complex delivery systems, but development costs are rising. Add to this the cost of new initiatives such as QbD and the Falsified Medicines Directive and the profitability of new drugs takes a dive. In addition a high failure rate of new drugs and growing use of generics makes lifecycle extensions a priority.

Topping the list of needs for most drug developers, however, is improving solubility and bioavailability. As one ingredient supplier put it, now that all the easy (small) therapeutic molecules have been discovered, the new molecules coming through are much more complex and suffer from solubility and bioavailability issues. As a result, ingredient suppliers and CMOs are focusing their offerings on improving solubility and bioavailability of actives, through either chemical or mechanical methods, or in terms of enhanced delivery vehicles.

As a global provider of pharmaceutical contract development and manufacturing services, **Patheon** sees improving the bioavailability of poorly soluble new chemical entities as a leading challenge in drug development. According to Ben Bauvalot, Patheon's Director of Global Marketing, around 40% of new chemical entities fall into class II – low solubility drugs. This makes them 'tougher compounds to formulate,' he says.

Built-in bioavailablility

There are many approaches to solving bioavailability issues and Patheon, like others, aims to offer a multi-pronged approach. Two years ago the company launched SoluPath, described as a cost-effective service to identify an optimal drug delivery system for compounds with poor bioavailability. Through a parallel screening approach of technologies, such as solid dispersions, micro-particles or lipid-based formulations, Patheon's programme has 'allowed a consistent three to five times increase in bioavailability and shows 30% save rate for compounds that would have failed due to bioavailability issues'.

With so few new drugs making it onto the market, it is also important for commercial reasons to extend the life span of exiting drugs, notes Bauvalot. 'The patent cliff means companies are looking for lifecycle extensions – the combination of one active with another, such as we see in diabetes drugs, for example.'

Patheon is looking to help formulate this type of drug through its expertise in soft gel technology and its new line of softgel solutions – P-Gels – can also be formulated in tandem with the bioavailability enhancing formulation strategies.

Other technologies in Patheon's armoury are: self-emulsifying drug delivery systems, concentrated micro-emulsion technology, galenic systems that mix hydrophilic and lipophilic phases, or micro-particle technology. The company has also added hot melt extrusion (HME) to the range of technologies utilised by the SoluPath programme.

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Dr Matthias Buceris, Head of Pharma Raw Materials at **Merck Millipore**, also sees bioavailability as a major pinch point in the development of drugs. 'No single technology fits all the challenges,' he says. 'This is why Merck Millipore has built up a portfolio of different technologies for large and small molecules.'

Merck's silica technology, for example, is seen as a means to achieve life cycle management. The company is the largest producer of chromatography silica and has extensive silica knowhow as well as pharma expertise through being part of the Merck group. The company's bimodal porous silica is being promoted as a new tool in increasing the solubility of active pharmaceutical ingredients (APIs).

Amorphous silica has been used in oral applications for decades; this latest product comprises particles that contain mesopores for a large surface area and additional macropores for good access to the surface. The drug is dissolved in organic solvent and then loaded onto the surface of the silica particles. After the solvent is completely removed, the drug substance remains on the surface in its amorphous state. This soluble amorphous state is a key factor for improved solubility and the loading process is optimised to achieve it (see *Manufacturing Chemist*, December 2012, p28-29).

Another key supplier offering help with solubility is Dow Wolf Cellulosics, part of the Dow Company. Its expertise in ingredients has generated a range of renewable, plant-based solutions under its Methocel and Ethocel ranges. The company also offers Polyox products that can help with solubility at several steps in the drug formulation and delivery process. In

addition, it has spray dry and HME knowhow that can help in dealing with solubility issues.

After solubility, the challenge that is important for many of the molecules being developed is palatability. Many new cancer treatments are made with relatively unpalatable actives. For elderly patients on a daily regime of drugs, for example, or where medicines are directed at children, palatability and user-friendly formulations are recognised as important in aiding compliance with treatment regimes.

With this in mind, the research teams at **Cargill** have been working hard to prove that ingredients such as its orally dispersible tablet (ODT) excipient, Zerose erythritol, can improve flavour and mouthfeel of unpalatable APIs.

Also working in the area of increasing palatability and user-friendly dosage options, ingredient producer **Roquette** recently developed a fast disintegrating orodispersible film (ODF) with taste-masking effects as an alternative to tablets, syrups or suppositories.

In a recently published study,[1] such an ODF alternative to tablets, syrups or suppositories was developed specifically for treatment of vomiting and nausea in the pediatric population. Roquette's excipients Kleptose HPB (cyclodextrin) or Kleptose Linecaps (maltodextrin) were used as solubilisers and Lycoat RS 720 (modified pea starch polymer) as a film-forming agent. The result was an ODF of dimenhydrinate that was fast disintegrating even in small volumes of liquid. Furthermore, *in vitro* taste assessment by two electronic tongues revealed that the excipients showed taste-masking effects.

New quality initiatives

Another major challenge facing the industry is the concept of Quality by Design (QbD), initiated by the industry regulators. This aims to facilitate the design of products and processes that maximise a product's efficacy and safety profile, while enhancing product manufacturability. As a result of its introduction, companies developing new drugs will, in future, need to prove that their products fit with the concept of QbD – i.e. that they offer better bioavailability, better delivery to the target site, or improved compliance etc.

QbD will have an effect at all levels of process development, says Dr Detlev Haack, Head of R&D, at **Hermes Pharma**.

'Pharmaceutical manufacturers will have to show that they have tested and compared different approaches to a drug's development and chosen the best route and so adhering to the concept of QbD will mean a rise in terms of development costs.'

Among the new formulation challenges arising from QbD suggested by Dr Haack are:

- Making dual tablets to reduce the overall number of tablets needed to be taken.
- Producing effervescent granules – a format that the patient likes to take
- In the case of pain relief, where high doses can be difficult to swallow, turning them into a granulate or soft granulate so that elderly patients can swallow them more easily.

Hermes Pharma specialises in developing and manufacturing user-friendly solid oral dosage forms, including effervescent and chewable tablets, instant drinks and orally disintegrating granules and it aims to help meet these and other future formulations challenges. 'Granulation for effervescent products offers high stability and protection of the ingredients,' says Dr Thomas Hein, Sales and Business Development Director at Hermes. He adds that Hermes has developed several granulation processes, 'including a continuous flow type process for large volume products'.

Exploiting OTC opportunities

Increasing costs and lower profits in the prescription market mean that pharma manufacturers are also looking for new areas to exploit. **Aenova** CEO Heiner Hoppmann says he can see more pharmaceutical companies looking at the OTC market because of the lowering of reimbursements by governments, while the food supplement companies are looking toward the pharma OTC market – thus the markets are coming together.

A specialist in solid dosage forms that was created by the merger of Dragenopharma and Swiss Caps, Aenova has a strong focus in the supplement area. Hoppmann says, 'Alongside our contract development and contract manufacturing portfolio, we will be focusing on our development and production services for effervescent products and our expertise in development of multi-unit-pellet-systems.'

Using innovative technologies, the company manufactures granules and pellets for a wide range of applications. They can be packed into sachets, inserted into capsules, pressed to make conventional tablets or used to manufacture film-coated tablets. The benefits, when compared with other dosage forms, are primarily in the biopharmaceutical field. Depending on the

EXCiPACT signs certification bodies to undertake excipient facility audits

The EXCiPACT Association – a project of the IPEC Federation – has signed agreements with two internationally recognised certification bodies (CBs) to undertake certified audits of excipient suppliers.

The two bodies named are the Stuttgart-based company mdc medical device certification GmbH (working in co-operation with blue inspection body GmbH of Münster) and Geneva-based SGS. The framework agreements are for the certification of the manufacture and distribution of pharmaceutical excipients according to the EXCiPACT Good Manufacturing Practices (GMP) and Good Distribution Practices (GDP) standards.

Auditors employed by these organisations who have completed the formal EXCiPACT training programme will now undertake EXCiPACT-witnessed pilot audits of pharmaceutical excipient suppliers. The independent witnesses will allow EXCiPACT to verify that the standards and the auditor training have been defined and implemented correctly. Once each auditor has been assessed satisfactorily they will then become a fully qualified certified auditor under the EXCiPACT certification scheme.

The scheme has been made available at a time when the regulators in the EU and US require the holder of the Marketing Authorisation for medicines to ensure that appropriate GMP and GDP is applied to the manufacture and distribution of both APIs and excipients. The requirement for site audits by the FDA and EMA continues to be pressed for pharmaceutical excipients and, as a result, suppliers must be prepared to receive increasing numbers of audits.

EXCiPACT certification can help to avoid some of these additional audits in a cost-effective manner. EXCiPACT expects to register other certifying bodies and auditors in the near future.

The EXCiPACT project consortium was formed back in 2009 by industrial associations from excipient and pharma suppliers including the the EFCG, IPEC Europe, IPEC Americas, FECC and PQG (UK) to jointly develop a set of cGMP and cGDP standards for pharmaceutical excipients. A Global Steering Committee (GSC) was formed to manage the project and it was launched officially in January 2012.

www.mdc-ce.de/index_en.htm
www.blue-inspection.com
www.sgs.com
www.excipact.org

distribution of the active ingredient across various subunits, different reproducible release profiles can be achieved, which enables the bioavailability of the substance to be controlled.

Building partnerships

For most suppliers, the days of customers simply selecting ingredients from a brochure and then shipping samples to the customer in the hope that they will do the job are a distant memory. Suppliers are having to work in long-term partnerships not only with drug developers but also with third parties to develop or select the ingredients and technologies that are suitable. An example is the recent collaboration between independent drug-formulation developer and manufacturer, **Bend Research** and **Dow Chemical Company**. The collaboration is in science-based spray-dried dispersion (SDD) solutions and select enabling of new polymers for poorly soluble oral drugs.

"Excipient properties are critical to delivering spray drying. To get it right requires a partnership between ingredient supplier and pharmaceutical customer"

The two companies will work together to provide the industry with fully characterised polymers supported by QbD principles and the ability to tailor materials to meet the performance needs of specific drugs. They will also develop new materials for SDDs that address technology gaps in manufacturability and delivery, providing better therapeutic performance.

Dow will provide hypromellose and hypromellose acetate succinate, as well as options to tailor these materials, and next-generation cellulosic and noncellulosic polymers for enhanced performance.

The partners believe such collaborations will reduce drug development risk by combining both materials development and optimisation early in the formulation development process for SDDs to achieve optimal clinical outcomes and robust product manufacturing processes.

Dow is fully supporting this collaboration with an array of technologies, including: high-throughput polymer synthesis and API solubility screening; lab-scale product development and structure-property optimisation; as well as a fully cGMP market-development plant capable of supporting clinical development of optimized solution.

Senior R&D Director for Dow, Bob Maughon says, 'New drug delivery technologies are all about making the drugs available to the body and the excipient properties are critical to delivering spray drying. To get it right requires a partnership between ingredient supplier and pharmaceutical customer.'

For example, in new process technologies such as SDD or HME, the ingredient has to be tailored to the application. In ongoing developments with customers, Dow has demonstrated the ability to double the throughput in spray drying with improved excipients, and it can help manufacturers on costs and performance too.

'Employing QbD will also save costs in the scale-up,' he adds.

Regulatory burden and supply chain security

It is increasingly important for pharmaceutical developers to ensure that they have the all right regulatory information and back up for speedy Market Authorisation. Marc Van Gerwen, Global Marketing and Sales Director, Dow Wolff Cellulosics, says: 'What we are doing is making sure we have reliability in supply, sample libraries readily available, good case studies, and technical expertise and help available to ensure companies can get the formulation studies done rapidly for the FDA.'

With adulterated ingredients and counterfeit products hitting the headlines, reliability in the supply chain is another big

Companies are looking for better palatability and more user-friendly dosage formats

issue. As a result, says Maughon, Dow has sought to provide greater transparency of how it sources and makes products and provides safety assurance, for generics as well as new drugs. 'Reliability is so important for a low cost [generic] product, so we must have tighter control over the process. We ensure that we have multiple trains that can produce products for consistency of supply and global reach.'

He cites gelatin as an example. 'Gelatin is an animal product. With hydroxypropyl methyl cellulose (HPMC), a vegetarian alternative to gelatin, Dow can offer more assurance around the quality and the supply chain. In addition, when applying QbD principle HPMC can provide much better product reliability and formulation consistency.'

Just as there has been a step change in drug development, ingredient suppliers are also looking to raise their game and strategic collaborations are becoming vital to solve solubility, palatability and deliverability issues presented new medicines.

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