

**W**hen, at the end of the 1990s, Chris Lipinski created awareness of the decreasing aqueous solubility and bioavailability of compounds coming out of drug discovery by leading pharmaceutical companies, he implicitly gave direction to drug delivery research and development in the decade of solubility and oral bioavailability enhancing drug delivery technologies. As of 2009, the final year of this decade, many oral drug delivery strategies have been successfully developed and proven, mainly based on amorphous systems, nanoparticles or self-emulsifying drug delivery systems.

### Amorphous delivery

Drug delivery systems where the drug is maintained in amorphous form can be achieved by solid dispersions formed by hot melt extrusion. Maintaining the drug in an amorphous form in the system will facilitate the interaction of the drug with the media upon dissolution of the system. Tashtouch et al (2004) used single excipient systems of either lauryol PEG-32 glycerides or PEG 6000 to prepare a solid dispersion of glibenclamide by a hot melt liquid

### Contributor profile



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capsule filling process, which he compared with the existing Daonil tablet formulation. In-vivo pK studies in healthy volunteers showed that both solid dispersions increased the Cmax as well as the AUC by a factor of two compared to the existing tablet formulation.

### Nanoparticles

Reducing the particle size of the drug to increase the surface area of the crystals is the basic concept of nanoparticles. Wu et al (2004) compared different particle size reduction methods for aprepitant to investigate their impact on the oral availability of the drug. Comparing jet milling with wet-milling as well as with wet-milling followed by spray drying, the AUC could be slightly enhanced by

# DRUG DELIVERY: THE NEXT DECADE

How has drug delivery changed during the first decade of the 21st century and how is it set to continue?

**Sven Stegemann** of Capsugel examines the discoveries and societal effects that will propel the market onwards from 2010.

jet milling and doubled by wet milling compared to the standard suspension. However, the wet-milled and spray-dried formulation showed a five-fold increase in the AUC and a four-fold increase in the C<sub>max</sub>. With the additional advantage of reducing the T<sub>max</sub> from 6.8h to 2.0h the wet-milled and spray dried nanoparticle formulation was launched as Emend capsules on the market.

### Self-emulsifying

Self-emulsifying drug delivery systems are normally liquid or semi-solid mixtures of three to five-component systems. On contact with water, they form thermodynamically stable nano-emulsions in which the drug is dissolved and remains dissolved during absorption, increasing the oral bioavailability of poorly water soluble drugs.

Cyclosporin A, an immunosuppressant drug with a high molecular weight and poor, variable oral bioavailability was brought to the market in self-emulsifying drug delivery system (Sandimmun). However, the system formed a coarse emulsion and was significantly digested leading to high inter-patient variabilities as well as a significant food effect. As the drug has a narrow therapeutic window it was reformulated as a true self-emulsifying system

## Drug delivery systems of the future need the flexibility to serve different dose strengths.

forming a nanoemulsion. Achieving the same C<sub>max</sub> with a 180mg dose instead of a 300mg dose as well as eliminating the food effect, the product was switched to the new formulation (Neoral).

### What's next?

During the past decade, pharmaceutical scientists have seriously challenged their drug discovery as well as lead compound selection processes to address the solubility and potential bioavailability issues very early on through a 'targeted product profiling' step. Drug delivery starts to be considered at the last step of the API synthesis by crystal engineering concepts and already targets the elimination of potential oral bioavailability issues. As a result, many of the first-in-human studies are now performed by a simple powder-in-capsule approach.

The next decade for drug delivery started with the introduction of the Quality by Design (QbD) concept, which draws the attention from a pure end product performance to a real product and process understanding including the relevant critical quality attributes and their control strategies.

The QbD concept was specifically brought forward by the industry to achieve a high degree of flexibility during development and manufacturing allowing continuous process improvements during the product lifecycle with

the aim to achieve a continuous manufacturing process and real-time-release of the batches. It is therefore obvious that the implementation of the QbD concept for future drug delivery system developments and the resulting pharmaceutical products are of critical importance for the pharmaceutical industry to meet some of the major challenges of the upcoming decades.

### Tackling the challenges

Firstly, with the increasing understanding of 'systems biology' and the 'disease networks' combined with modern pharmacogenomics, future drug treatments will be much more individualised, in terms of drug selection but also in terms of dosing regimens. Drug delivery systems of the future therefore need to have the flexibility to serve many different dose strengths that can easily be processed on a large and small scale. Moreover, combinations of two drug products or one product with two different release profiles will come into perspective in future drug delivery systems, creating an even bigger challenge in terms of dose flexibility in development and manufacturing.

Secondly, the demographic situation will increase the major prescription drug user group, the generation of 65 years and older from 204 million to 343 million people in the developed and from 323 million to 1.122 million in the developing countries in the coming decades. It needs to be understood as well that within the senior citizens group, the number of people aged 90 and over will increase most (expected to be fivefold). In fact, drug delivery for this target group needs to take into account not only a series of different dose strengths, but also a clear identification of the final drug product to allow for clear identification by patients that need to take several drugs.

The challenge for drug delivery of the next decade is to provide oral drug delivery systems that are developed through a QbD approach and that can easily be provided at an optimum quality and performance in many different dose strengths, where each can easily be made distinguishable. Drug delivery systems therefore will have to go towards well-established streamlined models. In the ideal case, drug delivery should be as simple as the active, alone or co-processed with one excipient, filled into a capsule, allowing for simple dose strength adjustments and with different color and imprint options for differentiation. However, even more sophisticated drug delivery systems, like self-emulsifying drug delivery systems can serve simplification as they are solutions that are homogeneous by nature, can be prepared by a simple mixing process and filled into capsules (such as Licaps) and sealed by a LEMS sealing process.

Successful drug delivery of the next decade will have to provide solutions to clinically relevant pharmacokinetic challenges of new compounds that are effective and sufficiently understood in terms of their formulation and processing as well as provide a high degree of flexibility in manufacturing a large range of different dose strengths. **WPF**