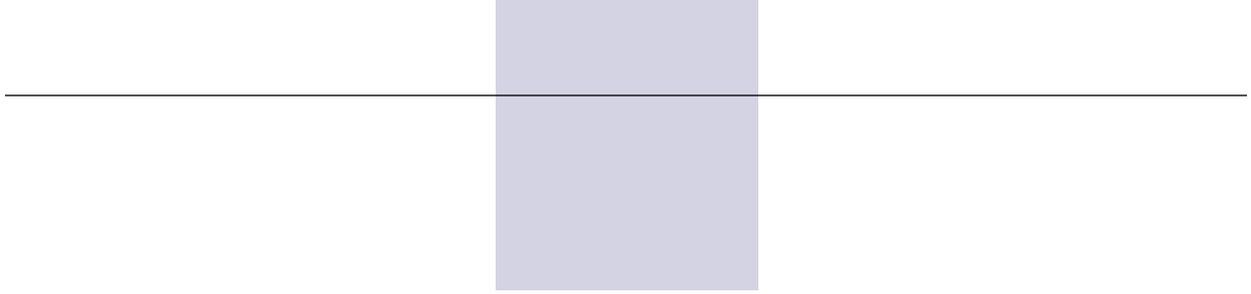


Microemulsion Capsule Technology to Optimise Drug Delivery

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Pharmaceutical Manufacturing and
Packing Sources, Summer 2003
edition, page 45-49

While it seems that a new drug launch draws all the attention to the specific drug substance, it is clear that the authorities only approve a drug product which contains more than just the specific drug substance alone. In reality, the drug product is a combination of the drug, a formulation of functional excipients and their processing. The formulation and processing is critical for the pharmacokinetic profile of the drug substance in vivo, which is part of its efficacy and safety. The optimal efficacy and safety is dependent on the drug concentration at the receptor site, the input rate and the duration of receptor interaction. In a recent draft guideline the FDA addresses the need to evaluate the pharmacokinetic-pharmacodynamic correlation to develop the optimal drug delivery system in terms of maximised efficacy and safety profile for the drug substance¹.

According to the Biopharmaceutics Drug Classification (BCS), drugs are classified according to their aqueous solubility and membrane permeability². Drugs with poor solubility but high permeability are classified as 'Class 2' compounds. Their oral bioavailability can be expected to be dependent on the solubilisation kinetic in the gastric juice of the GI tract.

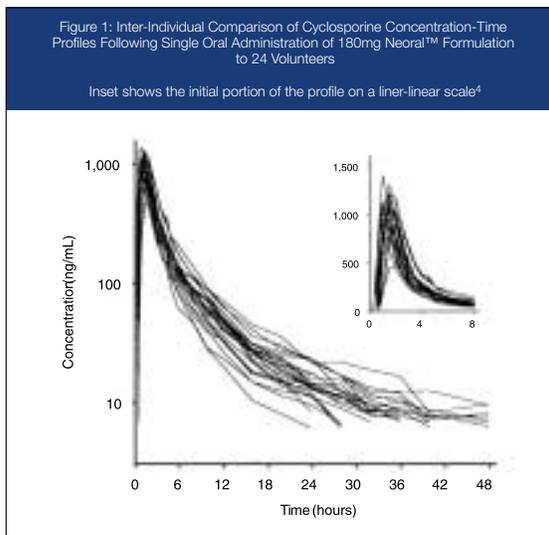
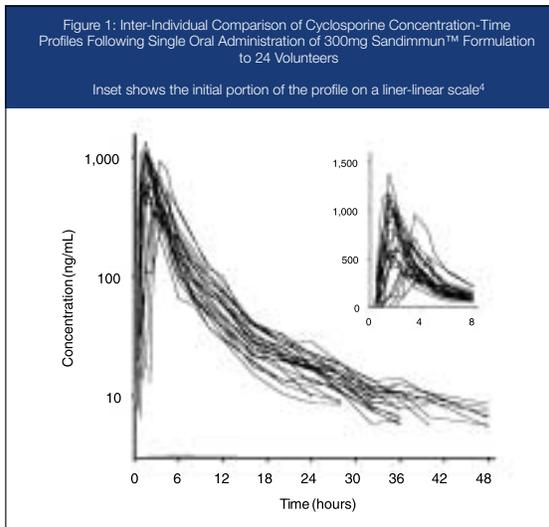
A formulation for a 'Class 2' drug will focus on solubility enhancement or solubilisation to improve the bioavailability and pharmacokinetic profile. Many different technologies have been proposed, especially particle size reduction to the nanometer range and solid dispersions. About a decade ago, self-emulsifying drug delivery systems (DDS) entered into the pharmaceutical development scene as a potential technology to enhance oral bioavailability.

The basic concept of self-emulsifying DDS is to deliver the drug in solution to the site of absorption or to protect the drug from being substantially metabolised in the gastro-intestinal tract or the gut membrane.

Self-Emulsifying Drug Delivery Systems

Self-emulsifying DDS are isotropic pre-concentrates that spontaneously form a fine oil in water emulsions in an aqueous environment under gentle agitation. With a droplet size of less than 100µm, microemulsions form thermodynamically stable translucent, clear solutions. These self-emulsifying pre-concentrates consist of three to five components that might be lipophilic, amphiphilic or hydrophilic in nature. Each excipient provides a certain functionality to the self-emulsifying DDS and is mainly classified as a solvent, surfactant or cosurfactant. Selecting the excipients with the best characteristics for the specific compound as well as for optimal performance in combination with other excipients, is a key challenge in the development of a self-emulsifying drug delivery system.

The first marketed pharmaceutical product formulated as a self-emulsifying DDS was Cyclosporin A, introduced as Neoral™ in Europe (1994) and the US (1995). The challenge for Cyclosporin A was its pre-systemic metabolism and absolute bioavailability of 10-60 per cent. Moreover, Cyclosporin A has a very narrow therapeutic range and requires different blood concentrations for each specific organ transplantation (for example 250-350µg/L for a liver transplant and 80-120µg/L for a kidney transplant)³.



The original market formulation of Cyclosporin (Sandimmun™), launched in 1981 in Europe, was composed of corn oil, dehydrated ethanol and polyglycolzed glycerides (Labrafil M, 1944), which form a coarse emulsion in water. Even if the achieved bioavailability was acceptable, the major issue remained the high inter- and intra-subject variability of 20-60 per cent of this formulation.

The second generation formulation generation of Cyclosporin A (Neoral™) is a composition of a hydrophilic solvent, a hydrophobic solvent and a surfactant, which forms a micro-emulsion with a droplet size of less than 100nm in gastric fluid. As reviewed by Friman &

Bäckman, several clinical studies confirmed that the Neoral formulation significantly increases absorption, which was reflected in the increased C_{max} and AUC, while the t_{max} decreased³. One of the major results of this formulation optimisation led to the desirable dose reduction (see Figure 1 and 2). A dose of 180mg was found to be bioequivalent to the original dose of 300mg.

In addition to the dose reduction, the safety profile could be increased substantially. With the original formulation the high inter- and intra-subject variability led to unpredictable plasma concentration. With its narrow therapeutic range between the minimal effective concentration and the toxic side effect concentration, this improvement was critical to maintain the drug concentration in the therapeutic range and avoid undesirable side effects based on high and low plasma levels⁴.

Another important advantage of the new microemulsion formulation Neoral™ for drug delivery is its bile salt independent absorption. Sandimmun™ was absorbed after pre-digestion of the coarse emulsion by the bile salts. And as demonstrated by Kovarik et al and Freeman et al^{4,5} this led to serious issues for patients with fresh liver transplants as their bile salt flow was interrupted after the transplantation. In this patient population the absorption of Cyclosporin A from Sandimmun™ was insufficient, while the microemulsion formulation (Neoral™) was absorbed independently from the bile salts to give the expected plasma concentrations⁵.

Self-Emulsifying DDS as a Solid Oral Dosage Form

The solid oral dosage form is known to be the preferred dosage form for patient preference and compliance reasons. Patient compliance is initially judged by ease of application and will then be judged by disease relief and the absence of undesirable side effects later on in the treatment. However, patient compliance is still underestimated as a factor for a successful therapy. If the patient does not feel comfortable with the therapy and becomes in compliant, the drug product will be judged by the physicians as not being effective enough. By improving the efficacy and reducing the side effect profile, the drug delivery system and the final dosage form play a crucial role for compliance.

As described above, self-emulsifying DDS are pre-concentrates of excipients that are liquid or semi-solid in nature. It is obvious that traditional tablet technologies cannot be used for this type of formulation. In contrast,

capsules – either soft or two piece capsules – serve as simple ‘containers’ that can be filled with liquid and semi-solid systems. Capsules are known as a well recognised dosage form that is easy to swallow, and dissolves rapidly in the stomach to deliver the content. Another capsule feature is the possibility of various mono- and bi-colour options that support the identification of the product. Especially for elderly and multi-drug treated patients, identification and differentiation of the product achieved by coloration is important for their compliance⁶⁻⁸. Even patients with moderate Alzheimer’s disease substantially gain from coloration⁹.

In contrast to other DDS, especially for bioenhancement, the liquid formulation and filling technology is an easy scalable process. Excipients and drugs are mixed in a liquid stage, either at ambient temperature or under gentle heating. These liquid solutions are filled directly into soft or two piece capsules without any additional processing.

The differences between soft and two piece capsules lie in the composition of the shell and in the production process. Two piece capsules consist of virtually pure gelatine, while the soft capsules are made of gelatine and approximately 20 to 30 per cent of plasticisers in the form of glycerol or sorbitol. The plasticiser increases the hydrophilicity of the shell, making soft capsules suitable for filling with hydrophilic liquid formulation that may not always be compatible with standard two piece capsules. On the other hand, two piece capsules can be filled at a higher temperature making them more suitable for semi-solid formulations. Due to the differences between soft and two piece capsules, the two technologies can be considered complementary to each other, as each offers unique capabilities. In essence, the chosen capsule technology is not likely to present a technical obstacle to the successful development of a microemulsion formulation.

Another difference between soft and two piece capsules is their manufacturing process. With soft capsules the shell formation, filling and sealing is performed in one step. As the shell has a high moisture content in the beginning stage during filling, the capsules are dried down after the manufacturing for a period of several days to weeks. Two piece capsules are pre-manufactured shells that are delivered in a pre-closed position. These empty shells are rectified, opened, filled and closed on the common capsule filling machine. A significant disadvantage for unsealed two piece capsules

is their tendency to leak at the join between body and cap when filled with liquids. A new hydroalcoholic fusion technology has been developed Capsugel and implemented in pharmaceutical manufacturing in recent years that refers the described ‘sealing’ in the USP capsules monograph.

For large scale sealing of filled two piece capsules the Liquid Encapsulation by MicroSparty (LEMS 30) equipment is available. The LEMS is a standalone sealing machine that can seal 30,000 liquid filled capsules per hour coming online from a filling machine or are fed from a bulk hopper (see Figure 3).



Figure 3: LEMS 30 Machine for Sealing Two Piece Capsules after Filling and Closing

Due to the differences in the manufacturing process soft capsule manufacturing is mainly outsourced to specialised contract manufacturers, while the two piece capsule filling and sealing can be established in-house using common preparation and capsule filling equipment.

Development of Microemulsion DDS

The pharmaceutical industry today focuses their in-house development efforts on their core capabilities. Specific technologies required for a certain period in drug discovery or a certain drug in formulation development are subject to be out-licensed to a specialised company. The development of a microemulsion DDS often requires specific expertise that today is not within most of the pharmaceutical development departments.

To be successful in selecting and co-operating with an outside contractor, different aspects need to be considered. The contractor must have substantial expertise in the development of microemulsion formulation combined with reliability, trust and a win-win partnership deal. A good partner will therefore offer a

focused development contract with clearly defined milestones. At each milestone, either partner can decide to stop or go further in the development without any long-term obligations. Often, the costs associated with each milestone are not an issue for a good partnership, as long as the scope of the work is transparent and the costs are reasonable. Even more critical than the cost considerations is a well-defined and realistic time schedule to which both partners should be committed. Other key ingredients for a successful partnership include: effective project-management, continuous communication, the willingness to understand each other's internal structure, and the flexibility to adjust the project's plan quickly in order to achieve the common goals.

To save valuable time in drug development, a contractor must be able to rapidly provide cGMP batches for stability testing and clinical trials with the option of contract manufacturing after the launch. In principle, this means that the contractor should offer access to both soft capsule and two piece capsule manufacturing. Otherwise, microemulsion development may be viewed as limited due to encapsulation issues, which, as indicated earlier, could likely be addressed by either of the two proven capsule technologies.

As trust is always a matter of choice, a contractor is also judged by his portfolio of options. The most valuable option for a partner is the possibility to develop the microemulsion in-house. To fill the existing gap in suitable laboratory and semi-industrial equipment for the two piece capsule technology, a liquid capsule filling and sealing machine was brought to the market in 2002. The CFS 1000 is a fully automated, cGMP compliant liquid filling and sealing equipment that operates at a maximum speed of 1,000 capsules per hour, which is sufficient for Phase I and II clinical supply. The CFS 1000 can operate all common capsule sizes from 00el-4 with the ability to fill from 0.1-1.2ml. With a minimum recommended batch size of only 20-25ml, the equipment also addresses the need to wisely use the limited drug availability that is common in early development. Also, the use of the same filling and sealing principles utilised by high speed filling and sealing equipment makes scaling up easy even for hot melts filled up to 70°C (see Figure 4).



Figure 4:
Development-Scale
Machine for Filling
Liquid and Semi-
Solid Formulation
into Two Piece
Capsule and Sealing

Due to the differences between soft and two piece capsules, the two technologies can be considered complementary to each other, as each offers unique capabilities. In essence, the chosen capsule technology is not likely to present a technical obstacle to the successful development of a microemulsion formulation.

Conclusion

Microemulsion DDS are pre-concentrates to improve the pharmacokinetic of 'Class 2' drug substances to optimize efficacy and safety. As the pharmaceutical industry is focusing mainly on their core capabilities in drug development, subcontracting of special formulation needs is becoming more commonplace. And given the importance of today's drug programmes, the requirements for formulation contractors is set at a very high level. For any contractor, the challenge is to provide a full service ranging from development of the microemulsion DDS to product launch in a win-win deal. This requires the use of contractors whose offer includes specific expertise in microemulsion development, scaling up and clinical manufacturing, as well as provision of the technology for in-house development and commercial manufacturing.

Without such capabilities in place, the inability to scale-up the technology to reach cost and manufacturability standards might lead to the discontinuation of a technology option for promising new pipeline products before even entering into a contract development agreement.

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About the Author

Sven Stegemann is a Pharmacist by education and gained his PhD in Pharmacology from the University of Frankfurt in 1992 before beginning his work in the pharmaceutical industry. Over the years he has worked in galenical development, production, regulatory affairs and licensing. In 1997 Sven joined Capsugel as a Business Development Manager for Europe, Middle East and Africa. In this position he works closely with the pharmaceutical industry on the development of optimized formulation and drug delivery systems. He is active in various organisations (in positions such as Vice President of the EAPB and Member of the CIR group of the EUFEPS).

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