Drugs Delivery

Enhancing the Bioavailability of Insoluble Drug Compounds

A variety of approaches can be used to meet the challenge posed by poor solubility of drug compounds.

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The better characterisation of biochemical targets increasingly drives drug development; these targets are generally cell-based and access to them in these models is relatively straightforward. This has led to the widely discussed proliferation of highly active compounds that have physicochemical characteristics that are poorly suited to delivery to a whole organism: at the head of this list of undesirable characteristics is poor water solubility. Despite efforts to either chemically modify discovery compounds, or to simply discount those that present difficulties, the putative efficacy of compounds which otherwise have very high affinities for the target is too compelling to ignore – particularly when insoluble compounds make up close to half of the leads generated.

This article focuses on the technologies that have arisen to meet the challenge posed by insoluble compounds and the ways in which these technologies have made a difference. The techniques that are used to overcome poor drug solubility are discussed under the major headings of Size Reduction Technologies, Co-Solvents and Emulsified Systems, Molecular Complexes, Amorphous Drug Forms, and Modification of the Aqueous Microenvironment. Taken together, these cover all of the important approaches.
THE techniques to overcome poor solubility

The description of a technology as ‘solubility enhancing’ can be misleading, since although the phenomenon of super-saturation is real, the techniques used do not increase the solubility of insoluble compounds per se. More accurately, they present the drug in a form which is optimal to its absorption, given its solubility limitations.

It is also important to be aware that water solubility also requires the specification of temperature and pH; many important drugs only exhibit aqueous solubility under certain physiological conditions, and these need to be met at the site of absorption.

Size Reduction Technologies
The techniques of size reduction using various milling processes are well established and these practices are a standard part of formulation development. These techniques work well where compounds have some small solubility in relation to their dose and the aqueous volume of the GI tract; in these cases, the limit imposed by the rate at which the compound dissolves is overcome by effectively increasing its surface area.

The utility of size reduction is illustrated by the development and life-cycle management of Tricor® (fenofibrate). The first product iteration was a 300mg capsule containing particulate drug; the second, a capsule containing 200mg of finely milled drug; the third a 160mg tablet containing finely milled drug and surfactant; and the fourth a 145mg tablet containing nano-particulate drug. All of these formulations are bioequivalent to one another. Progressive size reduction resulted in more than a two-fold increase in bioavailability.

Co-solvents and Emulsified Systems
There are a number of lipid-based presentations which will either self-emulsify through the intrinsic surface activity of the formulation, or become emulsified through the action of bile salts. Examples include: the antivirals, Norvir® (ritonavir) and Fortovase® (saquinavir); and the immune suppressant cyclosporine, presented as Sandimmune® and Sandimmune Neoral®.

The use of a lipid-based system in Fortovase®, as opposed to the powder presentation of saquinavir mesylate in Invirase®, led to more than a 3-fold increase in bioavailability, although it should be remembered that the absolute bioavailability of Invirase® is only 4% (1).

Changes in the nature of the dispersed system are also able to affect bioavailability; the reformulation of the emulsion formulation of cyclosporine in Sandimmune® to the very much smaller particles in the microemulsion formulation of Neoral® also resulted in an increase in bioavailability (2).

Molecular Complexes
In some cases, it is possible to use other molecules, such as cyclodextrins, as carriers for insoluble compounds. Cyclodextrins are water-soluble, but have a hydrophobic centre that is able to accommodate suitable hydrophobic molecular species. The formulation process consists of combining the cycloextrin and drug substance in an aqueous medium over a period of many hours with heat; the drug gradually enters the pore of the cycloextrin and is taken into solution. The final product is either the solution or a dry powder produced through the removal of the water.

Cyclodextrins are effective solubilising agents and are found in several marketed injectable products including Vfend® (voriconazole), Geodon® (zisprasidone mesylate), and Sporanox® (itraconazole) solution for injection and oral use. Cyclodextrins are not inert carriers; the profound change in the properties of the molecular complex – in comparison with the free drug – has led to regulatory bodies considering the complex as a new chemical entity in its own right.

Cyclodextrins are large molecules, which need to be present in molecular excess – the weight of cyclodextrin is necessarily much greater than that of the drug. The weight ratios of cyclodextrin to drug in Sporanox iv®, Vfend® iv, and Geodon® im are 40:1, 16:1 and 14.7:1 respectively (3). Were cyclodextrins used in the dry oral formulation of Sporanox®, more than 4g would need to be administered to deliver a 100mg dose.

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high energy mechanical mill, and a specific type of stabilising agent—generally a polymer. The milling process does not generate appreciable heat and no solvent is used (6). The polymers are also standard GRAS (generally recognised as safe) tablet excipients. The conditions used and energy input can be adjusted such that product can progress from microcrystalline to nano-crystalline to amorphous drug. The polymer is effective in preventing the processed drug—generated by the high energy input—from agglomerating, in the case of nano-crystal formation, or reverting back to the crystalline form, in the case of amorphous drug production. A representation of the Biorise® complex is presented in Figure 1.

The polymer used is generally highly cross-linked and undergoes a reversible deformation of its network during the milling process, providing a system which is able to accommodate drug on a molecular basis. The stability of amorphous drug forms created is consistent with the drug being entrained within the polymer network—re-crystallisation being prevented through physical interactions and constraints on movement within this network. The introduction of this dry powder to an aqueous environment results in a swelling of the polymer network and, through this agency, the drug is able to exit its support. This presents the drug in the form that has the best chance of crossing an absorptive surface, in a manner that bears analogy to a true solution.

In the case of nano-crystalline drug, the polymer is also an effective stabilising agency through an interaction with the crystal surface on a macro scale, effectively inhibiting close approach of the drug particles.

Amorphous Drug Forms

In cases where the compounds have no solubility, or the dose is high relative to solubility, techniques that have some ability to overcome the limits of aqueous media are required. Such techniques involve the production of a stable molecular dispersion of the compound, thus removing the need for dissolution in an aqueous medium to present this form of the drug to the absorptive surfaces.

The best known of these techniques is the production of so-called ‘solid solutions’ containing non-crystalline, or amorphous, drug. In such a formulation, the drug is taken into solution with another material—generally a polymer—either through melting and/or through the use of a solvent. The mixture is then cooled or the solvent evaporated. The presence of the polymer prevents the drug from crystallising and holds it in a molecularly dispersed state, analogous to it being in solution. The drug still needs to exit the bulk of the formulation and to be prevented from agglomerating or re-crystallising. In practice, these are significant limitations; however Prograf® and Sporanox® capsules represent successful commercialised examples of this technology (4,5).

There are two additional major disadvantages associated with these techniques: first, the necessity to use heat and/or solvent; and second, the inherent physical instability of the amorphous form.

BIORISE® TECHNOLOGY

A technology developed by Eurand (called Biorise®) involves the use of a specific type and configuration of
It is also possible to further extend this technology through the incorporation of aspects of the solvent evaporation and cyclodextrin approaches mentioned above. In these cases, the milling process can be used to either: drive complexation of the drug with cyclodextrin in an essentially non-aqueous process; or employ some solvent, or even a solvent vapour only, in cases where this can be tolerated (7).

Two examples of the effectiveness of the Biorise® technology are presented in Figures 2 and 3. Each of these illustrates a different aspect of the technology and the attainment of different desired clinical end-points. Figure 2 is an example in which the milling process and a cross-linked polymer were used: speed of onset and the overall bioavailability of the drug are increased. Figure 3 shows an example in which solvent was used: the bioavailability is greatly increased, but with a much less pronounced effect on the speed of onset. These examples have been selected both to demonstrate the versatility of the technology and to illustrate the degree to which it is possible to tune the pharmacokinetic profile of the drug substance selected.

DIFFUCAP® TECHNOLOGY

As mentioned above, aqueous solubility is also a function of the nature of the aqueous medium and certain important drugs have aqueous solubility under only some of the conditions of pH encountered physiologically. For example, carvedilol and dipyridamole – both of which are soluble in the acidic conditions of the stomach – are effectively insoluble in the neutral/slightly alkaline conditions found in the intestine. This phenomenon is of particular relevance in the development of sustained release forms; although it is possible to produce an immediate release formulation of carvedilol or dipyridamole, a sustained release presentation is a considerable formulation challenge (8,9).

Eurand has developed a proprietary technology (called Diffucap®) that reliably overcomes the problems associated with pH-dependent insolubility, and has combined

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**Figure 2:** Mean plasma concentration of a compound, X, after delivery of a single oral dose of a Biorise® formulation and the commercial reference of a major drug with poor solubility. The study was conducted using healthy volunteers. The milling process and a cross-linked polymer were used to activate the drug (see text).

**Figure 3:** Drug plasma levels of megestrol acetate (a hormone) following administration of a commercial reference and a formulation developed using Biorise® technology. It is important to note that the dose levels in this study were 80mg for the Biorise product versus 160mg for the reference product. This study was conducted using healthy volunteers. Solvent and a cross-linked polymer were used to activate the drug (see text).

**Figure 4:** Artistic representation of the layering techniques used in Diffucaps®; various bead populations and layer compositions can be used to fine-tune release profiles
this with its controlled release technologies to enable long-acting presentations of challenging immediate-release products to be developed.

The most difficult candidates to work with are weakly basic pharmaceutically active ingredients comprising N-containing moieties with a pKa of less than 14, which are practically insoluble (less than 50µg/ml) at a pH>5 and have a daily dosing requirement of over 10mg. However, many of these drugs have appreciable solubility in acid media, and formulations that control the microenvironment pH can be used to produce a soluble drug in a bulk environment in which it would ordinarily be insoluble.

The Diffucap® technology involves a single or a sequential coating of drug-containing core particles – such as beads, pellets, or micro- or mini-tablets provided with an inert seal-coat – with one or more functional polymers to modify drug release. This system is represented in Figure 4. The formulation can be easily engineered to sustain release of drug over several hours after a predetermined lag-time following oral administration (10). The finished dosage form may be a modified-release capsule, a conventional tablet or an orally disintegrating tablet comprising one or more coated spherical bead populations to provide target plasma concentrations suitable for a once- or twice-daily dosing regimen.

The proprietary technology that has been developed for weakly basic drugs involves the incorporation of a pharmaceutically acceptable organic acid or a crystallisation-inhibiting polymer (as discussed above) onto inert cores, and coating the drug-layered beads with proprietary functional polymers. These approaches have enabled Eurand to develop products comprising one or more controlled release bead populations of weakly basic actives for absorption throughout the GI tract. Such formulations are currently in the clinic.

Eurand has thus developed a proprietary technology that reliably overcomes the problems associated with pH-dependent insolubility, and has combined this with its controlled release technologies to allow long-acting presentations of challenging immediate-release products to be developed. The end-results are more convenient dosing schedules and better control of drug levels in the plasma; this in turn means better compliance and fewer side effects.

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References

1. Roche USA, Invirase® Saquinavir Mesylate Capsules and Tablets Prescribing Information.
3. Ortho-McNeil, Sporanox® iv Prescribing Information; Pfizer Vfend iv Prescribing Information; Geodon im Prescribing Information.
7. Lovrecich ML. Supported drugs with increased dissolution rate, and a process for their preparation. US Patent 5449521.