Formulation Strategies for ‘First-Into-Man’ Studies

Deciding on the best approach for taking a new drug into ‘first-into-man’ studies can be a difficult process – but choosing the right formulation is critical in ensuring that a new drug is given the best possible chance of fulfilling its potential in clinical trials.

When a new experimental drug shows great promise in preclinical studies for the treatment of a disease which affects millions of patients worldwide, there is one question that raises significant discussion: What type of formulation would be the most appropriate for testing in man for the first time? ‘Phase 1 clinical trials’ is a critical stage in any drug development project and to reach this stage as quickly as possible is of paramount importance, especially for those companies with limited budgets or key investor milestones to meet. Of equal importance is the need to ensure that the new drug substance is administered in a form that will give it ‘the best chance of success’ in early clinical assessment. A poor choice of formulation can lead to poor clinical data, which in turn can lead to re-formulation and a prolonged Phase 1 clinical programme – or even termination of the project. This article will examine the factors that need to be taken into consideration when deciding how best to take a new drug entity into first-into-man studies, and provides a ‘formulation decision tree’ to offer guidance on deciding which formulation strategy to follow for an orally administered drug.

Defining the Drug Substance

One of the primary aims of preclinical studies should be to identify the physicochemical and biological characteristics of a drug in order to predict oral bioavailability. According to the biopharmaceutics classification system (BCS), drug substances can be classified into four distinct classes based on their aqueous solubility and intestinal permeability (1). When combined with the dissolution rate of the drug and the unit dose required, this information can be used to decide on the most suitable approach to providing a dosage form for the clinic.

More recently, alternative classification systems have been suggested to replace the BCS, since the purpose of the BCS is primarily as a drug development tool to help formulators and sponsors justify requests for biowaivers (2,3). The developability classification system (DCS), which was developed using the BCS as its basis, focuses on intestinal solubility, the compensatory nature of solubility and permeability in the small intestine, and an estimate of the particle size needed to overcome dissolution rate-limited absorption. Observations on test compounds have demonstrated DCS to be of greater value in predicting which factors are critical to in vivo performance compared with the BCS.

Another tool used to predict whether a drug molecule will have oral bioavailability in humans is Lipinski’s ‘Rule of 5’ (4). This states that poor absorption of an orally-administered compound is likely if the compound has a molecular mass greater than 500 Da, high lipophilicity (cLogP greater than 5), more than five hydrogen bond donors and more than ten hydrogen bond acceptors.

If a drug molecule has been predicted to exhibit good oral bioavailability following application of Lipinski’s ‘Rule of 5’ and/or the DCS, then a simple drug-in-capsule or drug-in-bottle unformulated approach could be used. On the other hand, if a drug molecule is predicted to have poor oral bioavailability, alternative formulation strategies will need to be considered.

Choosing a Formulation Strategy

Having defined a drug substance according to its solubility and permeability, the next step is to select the most appropriate strategy for formulating the drug for
use in Phase 1 and possibly Phase 2 clinical trials. Based on the physicochemical and biological characteristics of the drug, different formulation strategies may be applicable. Strategies to consider when formulating a drug for a first-into-man study are summarised in the 'formulation decision tree' shown in Figure 1.

A popular strategy is to manually add the necessary quantity of the drug substance directly into a capsule or bottle for reconstitution with a suitable liquid prior to ingestion. This simple formulation strategy accelerates progression to first-into-man studies, while also being cost-effective. Specialised dosing equipment can be used to facilitate high precision filling of capsules, particularly when dosing potent drug substances (where the required dose is less than 10mg), or when large quantities of capsules are required to be filled.

Although the drug-in-capsule or drug-in-bottle approach is time- and cost-efficient, it is not suitable for all types of drug substance. If a drug substance does not ‘wet’ easily, or if its solubility in water is not sufficient, then it may be poorly absorbed from the gastrointestinal (GI) tract – and this will influence the pharmacokinetic data obtained. For drug substances that have poor water-solubility and have exhibited poor or variable absorption when tested in animal models, a water-solubility enhancing formulation strategy should be considered for Phase 1 clinical evaluation. There are several such strategies that can be implemented, ranging from particle size reduction to using inclusion complexes such as cyclodextrins. The most commonly used strategies are discussed briefly below.

**Particle Size Reduction**
The dissolution rate of the drug substance can be significantly accelerated by reducing the particle size of the active pharmaceutical ingredient (API). Particle size reduction can be efficiently achieved down to 2-10µm through the use of micronising equipment such as fluid energy mills, in which particle size reduction is achieved by collision between the particles at high speed. Over the last 10 to 15 years, the processing of drugs as nanocrystals (<1µm) has rapidly evolved into a reliable drug delivery strategy, enabling the production of formulations with rapid drug dissolution characteristics and enhanced bioavailability after oral administration. Precipitation (‘bottom up’) or wet milling (‘top down’) techniques can be used to produce submicron nanocrystals (5,6).

**Solution Capsule Formulations**
Some drugs can be dissolved in a suitable, pharmaceutically acceptable solvent and the resulting solution can be filled into capsules. The key advantage of pre-dissolving the drug compound is elimination of the initial rate-limiting step of particulate dissolution in the aqueous environment within the GI tract. Nevertheless, this formulation strategy may result in the drug precipitating out of the solution when the formulation disperses in the GI tract, especially in cases when a water-miscible solvent has been used, such as polyethylene glycol.

The problem of precipitation on dilution in the GI tract can be overcome if the drug compound is sufficiently lipophilic to dissolve in a lipid vehicle; in such a case, partitioning kinetics will enable the drug to remain in the lipid droplets. An additional advantage made possible by this approach is that lipidic vehicles are usually well absorbed from the GI tract, resulting in significantly improved oral bioavailability compared with administration of the solid drug substance (7,8). However, the ability of individuals to digest lipid-based
formulations may cause significant inter- and intra-subject variation in drug uptake.

Mixtures of lipidic excipients and surfactants are increasingly being used to produce self-emulsifying drug delivery systems (SEDDS) and self-microemulsifying drug delivery systems (SMEDDS) for oral administration of drugs exhibiting poor water-solubility (9). SEDDS and SMEDDS formulations act by forming emulsions or microemulsions spontaneously on contact with aqueous media. Both of these types of formulation use pharmaceutically acceptable surfactant excipients to achieve self-emulsification. In this way, emulsification of the lipids in the formulation no longer depend on GI secretions such as bile salts, and therefore inter- and intra-subject variability in drug absorption can be reduced.

**Solid Solutions and Dispersions**

Solid solutions are molecular dispersions of drug molecules in a polymer or wax matrix, whereas in the case of solid dispersions, the drug exists in the form of discrete particles dispersed within a polymer or wax matrix – although the terms are often used interchangeably (10). The solid solution strategy employs two separate principles to enhance the water-solubility of a drug: first, conversion of the drug substance into its amorphous state, making it easier for the substance to dissolve; and second, incorporation of the amorphous drug substance in a hydrophilic carrier matrix, such as polyvinyl pyrrolidone (PVP) or polyethylene glycol (PEG 6000). Solid solutions can be prepared either by dissolving the drug directly in molten polymer, or by dissolving both the drug and the polymer in a suitable volatile solvent. When the solvent is removed, an amorphous drug-polymer complex is produced with the drug being trapped in an amorphous state within the solvent or organic solvents, and elimination of the granule drying stage makes the process more time- and energy-efficient (13). As a drug formulation strategy, melt granulation offers several advantages; it does not require the use of water or organic solvents, and elimination of the granule drying stage makes the process more time- and energy-efficient (13). As a drug formulation strategy, melt granulation has proved to be an easy, fast and effective technique for enhancing the dissolution rate of several poorly water-soluble drugs (13,14).

**Cyclodextrins**

Cyclodextrins are doughnut-shaped functional excipients with a lipophilic surface on the inside ring and...
a hydrophilic surface on the outside ring (15). These molecules have been extensively used in pharmaceutical formulation owing to their ability to interact with poorly water-soluble drugs, resulting in an increase in their water-solubility. This formulation strategy works by fitting the poorly soluble drug molecule into the inner ring while the outer hydrophilic surface of the cyclodextrin retains the complex in solution. The inclusion complex can be prepared by dissolving the drug and cyclodextrin in a common solvent, or by solid-state mixing of the materials using a high attrition technique, such as ball milling.

**Conclusion**

Deciding on the best approach for taking a new drug entity into ‘first-into-man’ studies can be a difficult process. The first vital step is to accurately characterise the drug molecule by investigating and determining its physicochemical and biological characteristics. An appropriate delivery strategy can then be selected according to predictions of the oral bioavailability of the drug. The drug-in-capule or drug-in-bottle approach is a simple, cost-effective and time-saving dosing strategy. However, it may not be suitable for drug compounds exhibiting poor water-solubility/bioavailability, as is the case for more than 40 per cent of new drug entities. Poor water-solubility represents a major hurdle in achieving adequate oral bioavailability for a large percentage of drug compounds in development. In these cases, a water-solubility enhancing formulation strategy is necessary in order to give the molecule the best chance of success in clinical evaluation. Different formulation strategies can be implemented based on the characteristics of the specific drug molecule; for example, lipid-based formulations are able to facilitate GI absorption of many poorly water-soluble drugs. The preparation of solid dispersions and solid solutions, as well as the use of melt granulation techniques, can also increase water solubility significantly.

**References**

1. FDA Guidance for Industry, Waiver of in vivo bioavailability and bioequivalence studies for immediate release solid oral dosage forms based on a biopharmaceutics classification system, August, 2000