A new experimental drug substance shows great promise from pre-clinical studies for the treatment of a disease which afflicts millions of patients worldwide. What is the best strategy for testing the drug in man for the first time? This is a question that all companies developing new drugs face on a regular basis.

Entering Phase I clinical trials is a key milestone in any drug development project and to reach this stage as quickly as possible is of paramount importance – especially for those with limited budgets. Of equal importance is 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 strategy can lead to poor clinical data – which can lead to re-formulation and a prolonged Phase I clinical programme, or even termination of the project.

So how do you decide what is the best formulation for a new drug, assuming at this stage that it is intended for oral administration?

KNOW YOUR DRUG SUBSTANCE

From preclinical studies, there should be sufficient information to be able to define the drug according to its water-solubility and permeability characteristics in accordance with the biopharmaceutics classification system (BCS).1 Also, Lipinski’s “Rule of Five” 2 is a useful tool in predicting the oral bioavailability of drug molecules based on certain molecular attributes.

The BCS has proved a useful tool to formulators for classifying drug substances, but its primary purpose is for establishing criteria for biowaivers, and alternative ‘developability’ classification systems have recently been proposed.3,4

How well a drug is absorbed into the bloodstream from the gastro-intestinal tract (GIT) is governed predominantly by (i) drug solubility in the gastric and intestinal fluids and (ii) permeability through cell lipid bilayers. BCS Class I drugs are freely soluble in GIT fluids and permeate easily through lipid bilayers. These drugs are well absorbed when given orally and present the easiest task when choosing a formulation strategy. BCS Class IV drugs on the other hand are defined as poorly soluble (in GIT fluids) and permeate poorly across lipid bilayers. Consequently, these drugs exhibit poor oral bioavailability and pose the formulator the greatest challenge.

Additional physicochemical and biological factors which can challenge formulators are:

• Drug instability:
  – during processing or in the formulation (e.g. apomorphine)
  – in the GIT (e.g. when drug is acid labile, as with omeprazole).
• Narrow absorption window in the intestine (e.g. acyclovir, captopril).
• Drug metabolism and/or efflux within the intestinal wall (e.g. cyclosporin A).
Drug absorption and metabolism can vary between animal species and therefore it is not always possible to predict the influence of biological factors (e.g. pre-systemic metabolism) on drug uptake in humans from preclinical animal studies.

DETERMINE ON A FORMULATION STRATEGY

For first-into-human studies it is usual to administer the drug either as powder-in-bottle (for reconstitution prior to administration) or in capsules, which offer the greatest flexibility for dose adjustment. Choosing a formulation will depend on the properties of the drug substance and the target dose. Decision trees can be very effective tools in helping select the most appropriate formulation strategy. Figure 1 is an example of a decision tree which can be used to select a suitable formulation strategy for first-into-human clinical trials.

The simplest formulation strategy is not to formulate – just administer the drug substance with no additional excipients. In this case the required quantity of drug active is added directly to a container (for reconstitution with a suitable liquid prior to ingestion) or to a capsule. This approach is widely used within the industry as it significantly reduces the time and cost for progressing to first-into-man studies. For small quantities of units the active is weighed into each capsule or bottle by hand. For large quantities of capsules or where the required dose is < 10 mg, capsule filling can be achieved accurately by use of specialised precision powder dosing equipment (for example, Xcelodose® (Capsugel, Peapack, NJ, US), as shown in Figure 2).

The ‘drug-in-capsule/bottle’ approach is particularly suited for BCS Class I compounds, which are absorbed easily from the GIT. Although there are obvious benefits in adopting a drug-in-capsule/bottle approach, it should be considered with caution if the compound is not BCS Class I. If a drug substance does not wet easily or if its solubility in water is poor the drug may be poorly absorbed from the GIT and hence exhibit poor bioavailability. If there is a known history of poor or variable absorption in animal models then a formulation strategy to enhance water-solubility of the drug substance should be considered.

Two basic principles for enhancing water-solubility of the drug substance are (i) reduction of the particle size of the drug substance and (ii) use of solubility-enhancing vehicles.

Brief descriptions of typical solubility-enhancing formulation strategies are given below. Regardless of the formulation strategy chosen, it is vital to assess drug solubility following dilution of the test formulations in aqueous media. The dissolution test procedures used should simulate both gastric and intestinal conditions (in terms of pH, fluid volume, etc).

Particle size reduction

Increasing the overall surface area of a solid can lead to more rapid dissolution of the drug substance. Micronising equipment (e.g. fluid energy mills) can reduce particle size down to 2-10 μm. Taking the principle of size reduction even further, there are now technologies available to produce submicron ‘nanocrystals’ through precipitation (bottom up) or wet milling (top down) techniques. Following particle size reduction the drug substance can be dispersed into capsules, either as drug alone or as a powder blend (with excipients), depending on the required dose and flow properties of the milled drug substance.

Solubility-enhancing vehicles

For each of the strategies described below the resulting formulation can be filled into capsule shells for administration. Capsule filling machines which are suitable for this purpose include the IN-CAP® (Dott. Bonapace, Limbate, Italy), suitable for powders or liquids/semi-solids, and the CFS 1200 (Capsugel) which is suitable for liquids/semi-solids.

Solution/semi-solid capsule formulations:

If the drug can be dissolved in a suitable pharmaceutically acceptable vehicle then it may be appropriate to consider preparation of a solution of the drug which can be filled into capsules. The main benefit of this approach is that pre-dissolving the compound overcomes the initial rate limiting step of particulate dissolution in the aqueous environment within the GIT.

However, a potential problem is that the drug may precipitate out of solution when the formulation disperses in the GIT, particularly if the solvent is miscible with water (e.g. polyethylene glycol). If the drug is sufficiently lipophilic to dissolve in a lipid vehicle there is less potential for precipitation on dilution in the GIT, as partitioning kinetics will favour the drug remaining in the lipid drop-
In recent years there have been significant advances in the use of lipidic excipients and surfactants to produce self-emulsifying drug delivery systems (SEDDS) and self-micro-emulsifying drug delivery systems (SMEDDS) for oral drug delivery. These formulations form emulsions or micro-emulsions spontaneously on contact with aqueous media. Both SEDDS and SMEDDS use pharmaceutically acceptable surfactant excipients to achieve self-emulsification, therefore eliminating the reliance on the gastro-intestinal secretions (such as bile salts) to emulsify the lipids in the formulation.

Solid solutions
Solid solutions (also sometimes described as solid dispersions) are molecular dispersions of the drug molecules in a polymer matrix. This approach combines two principles to enhance water solubility of a drug:

1. Conversion of the drug material into its amorphous state – generally, a drug substance is easier to dissolve when in the amorphous state compared with the crystalline state, due to absence of ordered intermolecular bonds.
2. Incorporation of the amorphous drug substance in a hydrophilic polymeric matrix – a number of hydrophilic, polymeric materials have been used as solubility-enhancing matrices for drug substances. For example, polyvinyl pyrrolidone (PVP) and polyethylene glycol (PEG 6000) have been used for preparing solid solutions containing poorly soluble drugs.

Solid solutions can be prepared by dissolving both the drug compound and the polymer in a suitable volatile solvent. On removing the solvent (e.g. by spray drying) an amorphous drug-polymer complex is produced. On cooling, the drug is then trapped in an amorphous state within the water-soluble polymer matrix, thus enhancing the water-solubility of the drug.

One potential problem with this type of formulation is that the drug may favour a more thermodynamically stable crystalline state, which can result in the drug compound crystallising in the polymer matrix. Therefore the physical stability of such formulations needs to be assessed using techniques such as differential scanning calorimetry (DSC) and X-ray crystallography.

For formulations in which the drug is to be dissolved (in liquid or solid vehicles) miscibility of the drug substance with the vehicle is a key requirement – to maximise water-solubility of the drug and to maintain the physical stability of the formulation (i.e. prevent drug precipitation). A comparison of the solubility parameters for drug and excipients can be used to predict miscibility of the drug the excipients. The closer together the solubility parameters are between drug and excipient the higher the probability of the drug and excipient being miscible. An example of how this information can be used to gauge miscibility of drug with excipients is illustrated in Figure 3. The graph shows that the polymer with the closest spatial proximity to acetaminophen is HPMC and we would therefore expect there to be a high probability that the drug will be miscible in this polymer.

**SOLID DISPERSIONS**

Solid dispersions are similar to solid solution formulations, except that the drug exists in the form of discrete particles dispersed within a polymer or wax matrix.

**MELT EXTRUSION**

This technique is an extension of the ‘solid solution’ approach described previously. It consists of extruding a co-melt of the drug substance and a polymer through a heated screw to produce a solid extrudate which can then be milled to produce granules (for encapsulation or compression into tablets). As with the solid solution approach, the production of a melt extruded drug/polymer matrix is an effective method of increasing the water solubility of a poorly water-soluble drug substance. The effectiveness of this approach depends on miscibility of drug and polymer substances and on the drug substance and the polymer exhibiting similar melting points.

**MELT GRANULATION**

With this approach a water soluble polymer is used as a binding agent in a powder mixture to produce a granule blend. The blend is heated to a temperature at which the polymer binding agent softens (without completely melting) which results in formation of aggregates comprised of the drug and excipients. The granule mass is then cooled, sieved and is then suitable
for either encapsulation or compression into tablets. This technique has proved to be effective in enhancing water-solubility of several drugs.16,19

INCLUSION COMPLEXES SUCH AS CYCLODEXTRINS

Cyclodextrins 20 are doughnut-shaped molecules with a lipophilic surface on the inside ring and a hydrophilic surface on the outer surface of the ring. The principle behind this strategy is that the poorly soluble drug molecule fits into the inner ring and the outer hydrophilic surface of the cyclodextrin holds 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

In conclusion, a number of factors need to be taken into consideration in deciding how best to take a new drug entity into first-into-man studies. The drug-in-capsule approach is often seen as a cost effective and time saving option for testing a drug in Phase I studies. Indeed, it can significantly reduce the complexity of early stage development and progression from drug substance to a Phase I clinical trial can be achieved within weeks. However, if the drug substance has known solubility/bioavailability limitations (as is the case for more than 40% of NCEs) then due consideration should be given to formulation strategies which can enhance drug solubility in the GIT.

Developing a suitable drug formulation for first-into-human studies can be problematic and time consuming, especially for poorly water-soluble drugs. By predicting drug-excipient miscibility (through comparison of solubility parameters) and subsequently using a decision tree approach for choosing an appropriate formulation strategy, it is possible to eliminate a significant proportion of trial and error from a drug formulation development project. This rational approach to formulation development offers obvious advantages in reducing time for project completion and maximising the effectiveness of formulations for Phase I studies.

REFERENCES