

# Fixing Form and Formulation for Phase I

**Paul Fagan at Aptuit examines the benefits of identifying pathways and partners to accelerate poorly soluble drug candidates to early clinical studies**



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An ever-increasing number of development candidates brings pressure to bear on development groups who face the need to get new compounds quickly into the clinic. Many drugs are inherently poorly soluble and as such are more difficult to deliver effectively. This article highlights some current approaches for developing such molecules for use in early clinical studies and identifies the key attributes in a service provider which will ensure speed and quality of delivery to the clinic.

The last decade has brought a shift in emphasis within the pharmaceutical industry when faced with the development of candidates for Phase I and IIa studies. Where previously there was a focus on the development of formulated products which allowed rapid scale-up and support of later studies, there is a growing realisation that enabling formulations which allow key decision points to be reached more quickly can be of great value in a drug development strategy.

Such a formulation may be defined as one which will allow the clinical manufacture of the dosage form in numbers sufficient to perform clinical studies through to proof-of-concept, but which will not be scalable or commercialised. It is recognised that the principal benefit of such an approach is that of speed-to-clinic. This is of equal importance to large pharma companies working towards the selection of the best candidates in a burgeoning early development portfolio, and to the smallest biotech keen to ensure that resources are not squandered in developing formulations for what will prove to be ineffective medicines.

Traditionally the effectiveness of this approach has been limited to the development of readily soluble and/or absorbed species. Where this is not the case, and up to 80 per cent of new chemical entities (NCEs) may show solubility problems, the development team are faced with three choices. The first is to modify the drug candidate in a conventional manner such as salt formation to improve solubility; the second is to develop functional formulations to overcome the difficulties associated with a poorly

soluble species, and, where these fail, a third option is to return to the discovery team and identify a new candidate.

Taking the first two of these options as preferable, it is widely recognised that the greater the number of different technology-based approaches available for use, then the greater the chance of success with a poorly soluble compound. Multiple approaches based on both solid state chemistry and formulation science will improve the likelihood of success. This article serves to explore the path to fixing solid form and formulation for Phase I and considers how best to outsource such development.

## THE DOSAGE FORM OF CHOICE

For Phase I studies where a drug is freely soluble and/or readily absorbed, the choice of formulation for development may come down to one of two. The first of these would be the simple presentation of the drug filled by hand into a glass bottle for reconstitution in the clinical setting. Reconstitution fluids are typically water (perhaps flavoured to mask a bitter taste) or a suspending agent such as hydroxypropylmethylcellulose (HPMC) at 0.5 per cent in water to provide for a homogenous distribution where the drug does not dissolve fully and becomes a suspension. Alternatively, other diluents can be prepared which will provide for increased solubilisation of the drug itself. Where this is the case, it is necessary to ensure that: the drug remains stable in such a solution; the compounded product

is sufficiently palatable so as to be dosed and the volumes of diluent used will not produce adverse events on dosing. Note that, where the drug is presented as a suspension, the form and particle size should be known to directly compare results from other studies.

Alternatively, the drug may be presented filled by hand directly into capsules, either solely as an active pharmaceutical ingredient (API) or as a simple blend with lactose or starch, for example. The capsules will typically be made of gelatin or, less commonly, HPMC or one of the newer capsule materials. The advantages and disadvantages of each approach are listed in Table 1. Note that in all cases the choice of solid form is of concern except where reconstitution results in a solution.

On balance it is evident that the drug-in-capsule approach is more attractive than that in the bottle, but this remains limited by the time taken to fill by hand under GMP, the precision in filling (and with it reject rates) and the lower limits of fill weight which are possible. The latter becomes a real issue where the entry dose for studies is less than 0.15mg per kg (or 10mg) per volunteer.

Since 2000, new technologies have come of age which overcome the limitations of hand-filling of capsules for Phase I studies. These technologies can be designated as ‘precision dosing’ methodologies and have found acceptance in the manufacturing suites of many of the most successful pharma companies.

### PRECISION DOSING OPPORTUNITIES

Precision dosing can be defined as the ability to fill very low weights of drug or blend directly into capsules or clinical studies with much enhanced control around filling limits. The Capsugel Xcelodose™ 600 system can, for example, fill to 100µg when coupled with a six-place balance and at speeds of around 200-300 per hour. Notably this is the typical daily output when a manufacturing operative fills capsules by hand. As well as increased speed and lower fill weights the other key attribute of the technologies is centred on the reproducibility of the fill. The comparison between hand fill and automated fill is also shown in Table 1.

Figure 1 serves to illustrate the consistency of dosing between batches of microcrystalline cellulose (1). A typical RSD for all filling ensures that yields are high and drug losses are low.

**Table 1:** Comparison of drug in bottle approach with drug in capsule approach for Phase I dosing

	Drug in a bottle (hand fill)	Drug in a capsule (hand fill)	Drug in a capsule (precision fill)
<b>Dose selection to the point of manufacture</b>	Yes – and post manufacture by adjusting dosing volume	Yes	Yes
<b>Accuracy and reliability of weighing</b>	20mg – 20g with RSD of 5%	10mg – 200mg with RSD of 5%	100ug – 200mg with RSD of 2%
<b>Lower limit for dosing</b>	Depends on solubility of drug	10mg	100µg
<b>Stability</b>	Stability as a reconstituted product must be assessed	Follows API stability unless there is incompatibility with capsule shell	Follows API stability unless there is incompatibility with capsule shell
<b>Homogeneity</b>	May be a problem on reconstitution where full bottles is not dosed	Not a problem	Not a problem
<b>Palatable</b>	May require taste masking	Not a problem	Not a problem
<b>Useful for poorly soluble drugs</b>	Perhaps where the correct reconstitution solvent is chosen	No	No

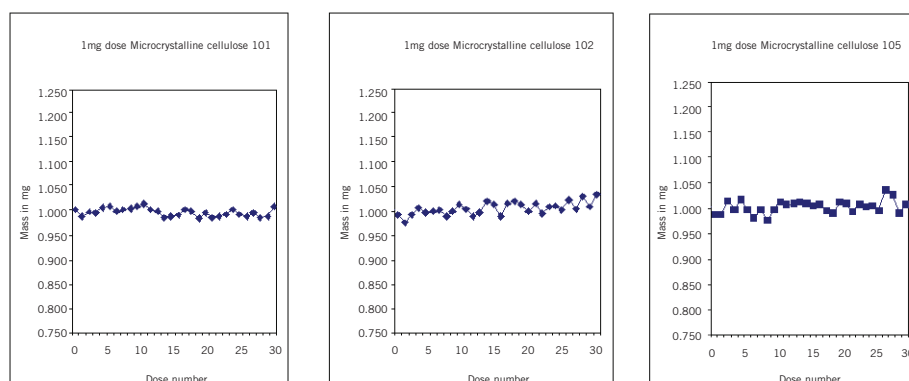
In reviewing these technologies in more detail, it becomes obvious that, where the drug is presented in the correct (soluble) form, the use of drug-in-capsule for delivery to FIM studies will present the quickest, simplest and most cost-effective route to the clinic.

### THE CORRECT SOLID FORM FOR DEVELOPMENT

Standard pharmaceutical texts suggest (and with good reason) that any API for development should demonstrate a consistent series of characteristics. The material should be crystalline (to ensure purity and consistency), soluble (to increase drug absorption), chemically stable (to ensure suitable retest and expiry dates on products) and physically stable to guard against problems in processing, such as moisture uptake. These demands are in effect the acceptance criteria in any solid form selection process, and as such are used to provide a ranking process for different salts, polymorphs, hydrates and solvates.

Conventional wisdom therefore suggests that, where a compound is poorly soluble and where it has an acidic or basic

**Figure 1:** Filling performance of the Xcelodose™ 600 precision dosing system



functional group, salt formation is the logical next step. The majority of pharmaceuticals are, to this end, marketed in the form of a salt which typically will be sodium, calcium or potassium salts of weak acids and chloride, sulphate or bromide forms of weak bases (2). Problems will arise, however, where a NCE does not possess a functional group which can be exploited in this way or where salt selection does not identify a suitable solid form for further development.

## ALTERNATIVE APPROACHES TO SOLID FORM SELECTION

### Cocrystal Development

One novel approach to this challenge is to produce cocrystals of a non-ionisable species to improve solubility. Work from Purdue Pharma and SSCI, for example, serves to highlight this approach wherein cocrystals are produced using a solubilising guest molecule within a crystal lattice of the host drug molecule. Such host/guest interactions exploit the potential for the formation of hydrogen bonding networks between the species. Despite the fact that the intrinsic solubility of the drug molecule is not increased, the cocrystal allows for a more rapid dissolution rate of the host and with it the potential to improve bioavailability.

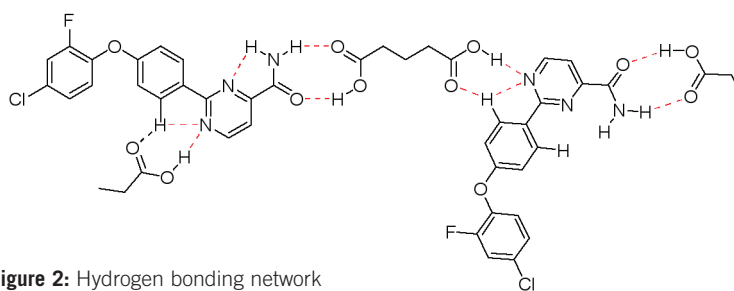
Figure 2 serves to highlight the nature of the host/guest interactions between 2-[4-(4-chloro-2-fluorophenoxy)phenyl]pyrimidine-4-carboxamide and glutaric acid (3). Figure 3 demonstrates a four-fold improvement in bioavailability in dogs, which is related directly to an 18-fold increase in dissolution rate between the cocrystalline material and the API.

Materials produced in this way are shown through solid state analysis to be crystalline and will demonstrate unique x-ray powder diffraction (XRPD) patterns, melting points and other physical behaviours.

### Amorphous Materials for Drug Development

While cocrystals represent a new direction for solid form modification resultant in controllable, crystalline materials, there is a growing awareness that the use of amorphous materials provides an alternative route to increasing the solubility of new chemical entities (NCEs). To pharmaceutical scientists, amorphous materials represent the antithesis of what is necessary to develop solid dosage forms. But are they really as bad as they seem?

Amorphous materials by definition have no long range order, which implies in turn that there is no means of control and consistency. Together this leads to a propensity to be physically unstable and results in a solid form which, on first review, has little appeal for conventional formulation. It is this instability which,



**Figure 2:** Hydrogen bonding network in the 2-[4-(4-chloro-2-fluorophenoxy)phenyl]pyrimidine-4-carboxamide glutaric acid cocrystal system

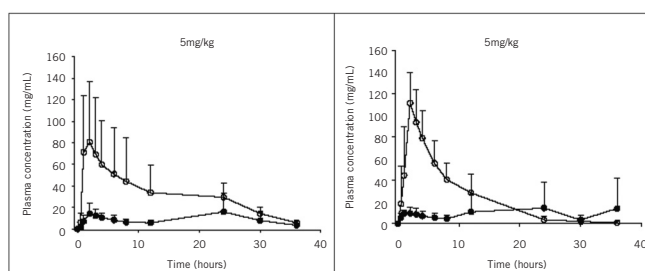
paradoxically, provides beneficial characteristics for the development of such a form in clinical studies.

This lack of long range order, when compared to a more tightly bound crystal lattice, leads to an increase in the rate of solution for a molecule. Furthermore, these materials are often of reduced particle size. Together these aspects lead to an increased rate of solution which, as discussed previously with cocrystals, can result in an increased bioavailability of difficult to solubilise compounds when given orally. Additionally, the use of amorphous materials can provide for intellectual property (IP) extensions over the crystalline material and, by default, can remove the complications of hydrates and polymorphic forms.

Critics of the use of amorphous materials point to concerns over the physical and chemical stability of these materials and a tendency for amorphous materials to recrystallise. Furthermore, there is a lack of understanding regarding the nature of amorphous states can lead to regulatory issues, such as inconsistent materials and irreproducible results and performance. There is also often an absence of reliable QC methodology which can characterise the API and final product.

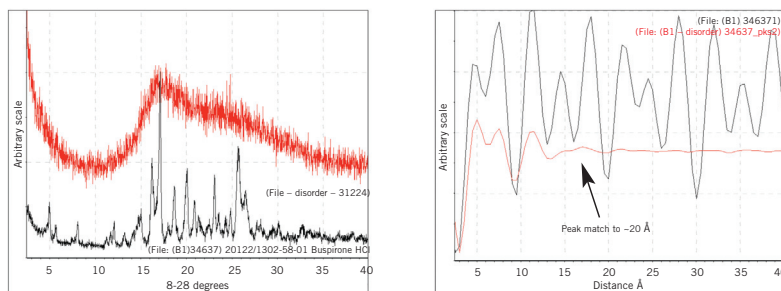
Each of these criticisms in turn are being addressed and specialist providers now offer a routine service which will develop and characterise the amorphous material with often surprising results. Taken together, the use of XRPD and pairwise distribution functions (PDF) (4) can be used to show that there is order in what traditionally was considered a fully disordered system.

**Figure 3:** Plasma levels of 2-[4-(4-chloro-2-fluorophenoxy)phenyl]pyrimidine-4-carboxamide in dogs dosed with API (solid circles) and when dosed as a glutaric acid cocrystal (open circles)



(Source: reproduced from McNamara et al, Pharm Res, 23 (8), pp1,888-1,897, 2006)

**Figure 4:** The XRPD pattern for crystalline and amorphous material and an interpretation of these data via a pairwise distribution



Using buspirone hydrochloride as an example Figure 4 (5) shows how an apparent lack of order as shown in the XRPD pattern can be reinterpreted, through such computational methods, in order to show a short range order characteristic of known and understood forms.

Where this local, short range order for amorphous materials can be determined and characterised against a known standard, it can be used to characterise the bulk drug for further use. Such steps are essential to move forward with any regulatory and quality programme in working with an amorphous API.

Where materials are understood, they can be developed and stabilised further with the use of a stabiliser into the formulation. These stabilisers may include polyvinylpyrrolidone (PVP), HPMC or citric acid, and be presented in the form of a solid dispersion prepared by freeze drying, spray drying, solvent methods or melt extrusion. As with all development studies, the performance and stability of these systems should be assessed to a level which demonstrates the suitability of each as appropriate for the phase of clinical development in which the drug resides. What is now certain is that amorphous materials will have a growing importance in the development of poorly soluble compounds.

Many routes to the production of amorphous materials are possible. Whilst there is much patent protection around some processing steps, opportunities remain to prepare materials through spray drying, solvent evaporation, grinding, melting and crash cooling.

### FORMULATION ALTERNATIVES FOR EARLY PHASE CLINICAL STUDIES

The approach of developing enabling formulations to support Phase I studies is appropriate only where the solid form allows for the use of such development. Where the form does not provide suitable bioavailability, formulation strategies should be employed to overcome the difficulties associated with poor solubility. At this point the formulator has one eye on the future, recognising that decisions made at this stage may have an impact on dose selection strategies later in the programme. With

this in mind, the focus changes to develop a formulation which can be scaled and used in later stage clinical studies. Often this can result in a longer, more involved formulation strategy.

Whilst there are many formulation alternatives available, some of which are readily accessible and others covered by IP protection, the objectives in development remain the same as before – stable, palatable, elegant formulations which can be managed

within a good manufacturing practice (GMP) environment.

Smaller organisations will undoubtedly be concerned that they do not become bound to a specific provider of a technology who will expect royalty payments as the compound progresses. This can make the future sale of their asset less attractive to potential suitors. It is better in this case to use readily available dosage forms which are not bound tightly to current IP if possible and to move to the latter where initial approaches fail. Readily available dosage forms may include oil-filled hard gelatin capsules, melt granulations, those utilising wetting agents and those utilising particle size reduction as part of the manufacturing process. As with solid state modification, the selection of a vendor offering more than one of these alternatives will maximise the chances of success in development.

### OUTSOURCING CONSIDERATIONS WHEN FACED WITH A POORLY-SOLUBLE COMPOUND

Where there is a multitude of formulation and solid state approaches to help improve bioavailability in early clinical studies, it is imperative to consider that there may be no single solution to the challenges described. Against this is carefully balanced the need to rapidly develop a dosage form, allowing flexible dosing to recognised standards of quality and compliance. Further assessments of product characteristics such as dissolution, homogeneity and stability will also be necessary.

With the pressures of time and cost it is often tempting to take the first solution presented by a prospective vendor. Should this fail there is often no back up strategy in place and contractors may spend more time than necessary to force-fit a solution. A more appropriate strategy is to identify a vendor who can provide multiple approaches, ideally in both the solid state and through formulation design, and who has the necessary process and project management disciplines in place to allow rapid responses to evolving development. In this context, it is important that they recognise where a change in technical direction is required. Furthermore, the identification of a project leader who can harness each of the disciplines involved in development (including preclinical support and API scale up) will allow for a broader approach to be taken to the challenge. Where this is not possible within a vendor, it may be prudent to

look for a suitably qualified consultant to act on your behalf in this capacity. Table 2 lists some of the key criteria for evaluating potential vendors in the development of a poorly soluble compound for early clinical studies.

Establishing a contract with a prospective vendor should reflect the flexibility necessary in early development. It is a common failing at this stage for the client to expect a fully defined programme of work which will wholly anticipate the solid form and formulation chosen. The reality is that these can be defined only as a result of good science and skilled product development. On the other hand it is necessary, as with all programmes, not to present a contractor with an open-ended ‘blank cheque’ as the time and cost can escalate out of control. A compromise is to define a likely experimental pathway with decision points, and an estimate of likely time and costs associated with each. This pathway should anticipate the first decision points around solid form and formulation development and speculate on the latter stages, such that the proposal may anticipate (for example) clinical manufacture of a fixed number of batches of a certain size and make calculated assumptions about testing, which can be refined at a later stage.

Upon signature of the contract the normal processes relating to successful vendor/client relationships apply. These include: appropriate goal setting and project planning; definition of roles and responsibilities; establishing a communication network; and agreeing appropriate review and reporting strategies. It is most important in this situation to share data as they emerge in a clearly presented manner, and from the vendor’s perspective provide interpretation and meaningful insights as to what this means for the development strategy and timelines. The best vendors will respond to these data and adjust the technical programme whilst minimising the delays to the clinical start.

## CONCLUSION

The development of poorly soluble compounds for Phase I dosing is an ever-present challenge in drug development. Overcoming it will require a multi-faceted approach to solid form and solid form selection. As such, it is necessary to expect some setbacks in the development strategy as the first approach will not always succeed. Working with a vendor who offers a range of solutions will minimise the impact of initial failures. As noted in a previous article, “successful outsourcing is based on ensuring that the right scientific, management and technical resources are applied; getting the mix of these right will realise the benefits of more rapid drug development” (6). This is especially true in this case where technical ability may dominate the decision making criteria in selecting a vendor to get a compound to Phase I. ♦

**Table 2:** Initial selection criteria for vendor selection

Selection criteria	Ranking	Why does this matter?
Technical development skills	Mandatory	Necessary to overcome the challenges of solid state development or formulation development for poorly soluble compounds
Equipment	Mandatory	It is vital that the vendor has the necessary equipment to develop and manufacture such a product
Facility	Mandatory	Laboratories and development areas must be suitably designed for the development and manufacture of these products
Quality systems	Mandatory	It is a basic requirement that each group claim standard commitment to meeting the GLP/GMP requirements of the development programme. For studies in the EU the ability to offer QP release is advantageous
Scientific direction	High	The presence of a key individual(s) to provide technical leadership and overview to the programme will allow for considered responses to rapid evolving data sets to be made
Analytical capability	High	To minimise delays to the programme, the ability to develop and employ analytical methods for development and stability assessment is best located within the same provider. Specifically the laboratory should be experienced in the development of dissolution methods to allow comparison between potential dosage forms
Manufacturing capability	High	To minimise delays to the programme a manufacturing site should be immediately available – subcontracting would only be allowed in exceptional, well-controlled circumstances
Project Delivery	High	Must provide competitive timings and budget for delivery of the early clinical products
Location	High	It is often preferable to work with a regional provider who understands specific needs for working in a particular territory; however, a global provider who can call upon expertise across a range of locations can sometimes be a better choice
Flexibility	High	Must be able to respond to emerging data from solid state programme and realign development objectives

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