A Review of Polymorphism and the Amorphous State in the Formulation Strategy of Medicines and Marketed Drugs

Mahmoud Omar*, Patrick Makary* and Michal Wlodarski

University College London, School of Pharmacy, 29-39 Brunswick Square, London, WC1N 1AX

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Abstract
The different solid physical form of a medicine can affect its formulation and biological activity greatly. For such reasons, modern pharmaceuticals need to pass through extensive solid-state evaluation. Within the recent year, pharmaceutical research became more and more aware with different solid-state as amorphous form, polymorphic salts and co crystals. This review is the short outline for the different solid states giving specific examples for different marketed pharmaceutical products that had to pass through solid-state perforation.

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1 Introduction
Despite the rapidly growing interest in biopharmaceuticals and diagnostics, the solid-phase small drug molecules still dominate the pharmaceutical market. The physical structure of a solid drug is arguably the single most important parameter having a profound effect on drug’s heat capacity, volume, density, viscosity, surface tension, hardness, melting, sublimation, heat of fusion, heat of solution, solubility, dissolution rate, enthalpy of transitions, hygroscopicity, rates of reactions, and many others. Indeed, the solid phase characterisation processes, encompassing techniques of spectroscopy, chromatography, microscopy, and thermal analysis are invariably the core of analytical departments of most pharmaceutical companies.

Solid drug forms can be divided into crystalline and amorphous, the prior experiencing long-range molecular order and the latter having no distinct molecular arrangement in a long-range scale. For the same drug molecule there might be several crystalline forms, depending on their arrangement in the crystal lattice. Moreover, the crystalline form may have solvent molecules incorporated into the lattice structure resulting in solvate formation. If the crystal structure comprises two or more neutral molecules (which are not solvent molecules), then co-crystals are formed. The amorphous form is characterised by a glass temperature, below which it exists in a solid-like, brittle state (termed glass) of a limited molecular mobility. Above that temperature, the form turns into a liquid-like, rubbery state and experiences a sudden increment in molecular mobility that increases the probability of crystallisation.

In regard to the medicinal product development, the solid form characteristics listed previously were of a great importance as they define a number of drug formulation issues. Stability, which in turn affect's product's shelf-life, is greatly affected by the drug structural arrangement and may often pose problems if a metastable form is developed. Similarly, amorphous drugs have to be developed (and subsequently handled) with care, to minimize the risk of crystallisation. The processability of drugs is also largely determined by the solid form as drugs of different molecular arrangements tend to dry, granulate, flow, and compress differently. Finally, drug’s bioavailability may be affected by the solid form choice. Stable polymorphs, of lower lattice energies, have relatively low dissolution rates and may pose drug liberation problems. Conversely, metastable polymorphs may be used to improve solubility; however, the choice has to be compromised against drug’s stability.

The aim of this work, is to set specific examples of drugs in order to demonstrate how the choice of the physical form of the active pharmaceutical ingredient is influenced by its properties, the drug's
therapeutic application, and possible formulation options. In addition, control measures necessary to ensure formulation stabilities were outlined where suitable. A number of crystallines (featuring examples of metastable forms and co-crystals) and amorphous drugs were discussed to ensure a diverse range of physical forms and formulation strategies could be compared.

2 Polymorphism

Polymorphism is defined as the ability of a chemical compound to occur in more than one crystal structures. Molecules in a crystal lattice are held by weak bonds such as van der Waals forces or hydrogen bonds. Variation in intermolecular interaction results in different forms of crystal structure. The unlikeness in crystal structure maybe followed either packing polymorphism where molecules are arranged differently while keeping same conformation to one another, or conformational polymorphism where molecules are more flexible and exist in a distant conformation.

Polymorphic forms of drugs are known to affect drug’s bioavailability. This might be possible, since different polymorphic forms have unusual dissolution rates and different rates of absorption. The stable crystal form of an organic compound usually provides long shelf-life and high stability. However, in most case it is characterized by low solubility and difficulty in formulation. As a result, during drug development the search for the optimum polymorph is essential. Nevertheless, identifying the stable form may not of supreme importance due to the reasons mentioned above.

Carbamazepine is a widely used antiepileptic drug that was found to have polymorphic structures (I, II and III) and one di-hydrate structure. In a study Carbamazepine, polymorphs showed a wide difference in pharmacokinetic properties. They showed solubility and dissolution of the order form III> form I> dihydrate (Fig. 1) (form II is not used clinically). However, form I is the United States Pharmacopeia (USP) reference form of carbamazepine, although it has lower dissolution than form III. This is because that form III is very hygroscopic (Fig. 2) and quickly transforms into the dihydrate form, which is much less active, in terms of solubility, dissolution, and bioavailability if compared to any of the other two forms. Temperature control during crystallisation and manufacture is important while using form I, since it can transform to III at elevated temperatures.

Within recent years generic carbamazepine having form III was approved by the Food and Drug Administration (FDA). Despite the form III will transform into the dihydrate form in case of interaction with water, its high dissolution rate will make a good tablet provided that care is taken during storage and manufacturing.

Fig 1: The dissolution patterns of CZP polymorphs and dihydrate: form I-■, form III-● and dehydrate-▲

Fig 2: The hygroscopicity study of polymorphs at 40°C and 98% form I-■, form III-●

Nevertheless, the differences between unusual t polymorphs may not be limited to dissolution only. In fact, some forms can show no pharmacological activity. In such cases polymorphic transformation to the undesired inactive form must be inhibited at every level to avoid therapeutic failure.

Mebendazole is a broad-spectrum anthelmintic drug that is used commonly in many parasitic infections. It is present in three crystalline forms (A, B, and C). It was proven clinically that the form C is biologically active while form A produces clinical results that are insignificantly different from the placebo group. However, polymorphic transformation of the form C (formulated as tablets) to other solid forms occurred in South Africa (possibly due to...
excessively high temperatures during any part of the production process). Therefore, care must be taken when processing and handling such material. Although two polymorphs with similar dissolution and bioavailability profiles. May however; result in products with different qualities. Sulfamerazine is a commonly used antibacterial agent, formulated as tablets. It exists in two forms (I and II) both of which are similar in solubility and stability. However, form II is the more stable form at the ambient temperatures. During manufacturing, form II was found to form highly porous tablets with little interparticulate bonding, while processing of the form I resulted in non-porous dosage forms. It was then demonstrated that form I had smaller crystals, which allowed better compression and tableting, while form II comprised large crystals, that adversely affected these parameters (Fig. 3).

Careful choice between polymorphs is especially important in cases where the drug doses are relatively high and therefore, the tablets formed must be characterised by high stability. An example of processing variation between polymorphs is acetaminophen, which exists in two forms and form I is the more stable form. However, when formulating this form into a tablet, the result is a formulation which capes quickly, this may be due to constrains of the crystal structure in form I. For that reason, form II is the chosen for tablet formulations.

In some circumstances, the avoidance of formulating the stable polymorph is not an option. This may be caused by regulatory authorities deferring the authorization due to unsatisfying pre-clinical performance of the metastable forms. For example, Torsemide is a commonly prescribed lipophilic diuretic. It has two polymorphs: form I and form II, and a solvatoporphorphor made of Torsemide and a mixture of water and alcohol (form A). Knowing that the drug is lipophilic and has a low solubility, the difference in polymorphic structure is critical. Form II is three times more soluble than form I, while form I is the more stable form. It was shown that the metastable form II is also sufficiently stable at ambient temperature and would be favoured over the form I. Nevertheless, form II has higher water sorption of 1.2% (compared to 0.2% of the form I), thus form II does not meet the USP requirements of the maximal water sorption (0.5%). For that reason, in this case the choice to use the less soluble is a necessity.

3 Co-crystals

Within the group of crystalline drug forms, pharmaceutical co-crystals have recently gained a significant interest and a considerable number of co-crystallised drugs have emerged. This rapid development has been due to a number of factors: recent improvements in design and control of co-crystal structures, reliable and reproducible mechanochemical synthesis of co-crystals, their diverse physicochemical properties, and finally the potential to use co-crystallised forms in drug formulation and development to improve product performance. Moreover, novel solid phase characteristics offered by co-crystal formation may be able to provide valuable intellectual property protection advantages.

A pharmaceutical co-crystal can be simply described as a crystalline solid that is made up of two neutral molecules – for example an active pharmaceutical ingredient and a co-crystal former. Notably, the co-crystal former may serve as an excipient in the formulation or be another drug. In recent years, pharmaceutical co-crystal technology has been used to identify and develop new forms of widely prescribed drugs. It was demonstrated that through co-
crystallisation, improved drug solubility, dissolution rate, stability, hygroscopicity, and compressibility could be achieved without altering its pharmacological properties\textsuperscript{1,3}.

Itraconazole (Fig. 4) is a well-characterised antifungal agent used to treat fungal infections. It is a poorly water-soluble drug, administered both orally and intravenously. To achieve satisfying bioavailability, the formulation strategy involved the amorphous form coated on the surfaces of sucrose beads (marketed by Janssen Pharmaceutical as Sporanox\textsuperscript{®} capsules). Nonetheless, co-administration of acidified cyclodextrin-containing beverages together with administered capsules is required for achieving the maximal absorption of the drug (even though such a co-administration can cause diarrhoea).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig4}
\caption{(a)Molecular structure of itraconazole (b) Co crystal forms of cis-itraconazole (c)Trimer unit of 2b from the single-crystal X-ray structure\textsuperscript{12}}
\end{figure}

A strategy of intraconazole co-crystallisation was evaluated to maintain drug’s crystallinity and stability, and improve the absorption properties. The co-crystal formers were engineered into the drug’s solid phases to match itraconazole’s hydrogen-bond donors and acceptors, considering structural complementarities. In the study, a number of stable itraconazole and dicarboxylic acids co-crystals were synthesized (Fig. 4) with an aid of high-throughput crystallization screen and subsequently characterised with X-Ray crystallography. Each of the co-crystal forms contained one co-crystal former molecule and two drug molecules. It was reported the molecular arrangement was held together by hydrogen bonds formed through carboxylic acid-triazole groups, resulting in a trimeric construction (Fig. 4)\textsuperscript{12}.

In vitro, dissolution testing was performed to give an indication of the solubilities and dissolution profiles of the co-crystallised forms in comparison to the amorphous form. The dissolution (in 0.1 M HCl) of itraconazole co-crystals was similar to the dissolution of the amorphous form, rather than to the crystalline form (95% of all crystalline particles <10 µm) of the drug. The co-crystal forms achieved and sustained from 4- to 20-fold higher concentrations than that achieved from the crystalline drug. It was further noted that the Itraconazole:L-malic acid co-crystal exhibited a similar dissolution profile to that of the marketed formulation\textsuperscript{14}.

In a pharmacokinetic study, a co-crystal formulation of intraconazole was found to yield similar oral bioavailability to the Sporanox\textsuperscript{®} form in the animal trial using a dog model. Furthermore, the co-crystals synthesised varied in morphology and particle size. It was noted that some of the forms, especially the hexagonal plate-like form 2b, presented geometrical properties desirable for efficient filtration and drying to a free flowing powder\textsuperscript{15}.

It was therefore demonstrated that the use of pharmaceutical co-crystals of itraconazole resulted in formation of stable crystalline forms that could be used to improve solubility, bioavailability, and processability of the drug. Despite a rapidly developing interest in pharmaceutical co-crystals and promising pre-clinical studies involving co-crystallised forms of widely prescribed drugs (such as paracetamol, aspirin, ibuprofen, flurbiprofen, carbamazepine, chloramphenicol, fluoxetine, sildenafil, and many others), the industry is still waiting for the first co-crystallised drug to enter the market\textsuperscript{2}.

The research in cocrystals has grown considerably, due to their ability to enhance properties of drugs that could be enhanced by other methods. Example solubility, several drug solubility could not be enhanced by simply salt formation. Some drugs might need to make into a prodrug, or encapsulated in a rather complex form. Formulating such drugs into cocrystal is without drought a great advantage. Molecules such as the smaller biopharmaceutical drugs such as amino acids could benefit greatly from such method. Several papers reported the preparation of methionine, proline, valine, leucine and isoleucine cocrystals utilising their zwitterionic properties\textsuperscript{16}.
4 Amorphous forms

The amorphous materials are solids in which the molecules are not organised in a definite lattice pattern. Their structure can affect several properties as: product stability, storage, processing, compatibility, hygroscopicity and dissolution. In addition, they have the tendency to absorb moisture and other solvents. Many drugs are present on the market in the amorphous form as it may offer many advantages if compared to the crystalline form; examples of these drugs are indomethacin, celecoxib, itraconazole and many other.[17]

The solubility of a molecule contributes critically towards its “drug ability” by influencing the dissolution rate and bioavailability, especially in the case of the biopharmaceutics classification system (BCS) class II and IV drugs. The solid state of the drug, whether crystalline or amorphous, can significantly affect its dissolution rate, claiming solid-state manipulation as a viable avenue for dissolution rate enhancement.[17]

The first study presented in this section was used to evaluate the thermodynamic differences between a stable crystalline and the metastable amorphous phase of a non-steroidal anti-inflammatory drug (NSAID) Celecoxib (marketed as Celebrex® capsules), a BCS class II drug (low solubility and high permeability). This active was chosen to be formulated in the amorphous form as it offers initial enhancement in solubility. However, its rapid solvent-mediated reversion to the crystalline form results in a loss of the solubility advantage. Thus, thermodynamic assessment was used for the prediction of the solubility gain of the amorphous form over the crystalline.

The preparation of the amorphous Celecoxib was achieved by melting the crystalline drug in a stainless steel beaker over a hot plate (448 K) followed by quench-cooling over crushed ice. For estimating the isobaric heat capacity (C_p) the amorphous form of the drug was analysed with a differential scanning calorimeter (DSC).

The amorphous form was shown to be more chemically stable than the crystalline form. According to thermal analyses of both celecoxib form. In order to achieve a separation of the two thermodynamic events (glass transition and enthalpy relaxation), analysis for both the crystalline and the amorphous forms of the drug were performed using modulated DSC. The heat capacity values varied for each form, with higher values obtained for the amorphous form. A characteristic step change around a temperature of 320 K and a thermal overshoot in the range 325 – 335 K was observed (Fig. 5).

According to van’t Hoff plots the solubility of both the crystalline and the amorphous form increased linearly with the increase in temperature, but the amorphous celecoxib was higher than that of its crystalline form (Fig. 6).[18]

The second example shows an evaluation of the effect of the in vitro solubility advantage of amorphous versus crystalline nanoparticulate formulations of poorly water-soluble drug and there in vivo bioavailability following pulmonary administration. The study showed that the supersaturation produced by inhaled amorphous nanoparticles of a poorly water-soluble drug will produce a higher systemic absorption and thereby enhanced bioavailability, if compared to the nanocrystalline form’s bioavailability. Itraconazole was used in the study because of its high lipophilicity and poor water solubility.
concentration profiles in the lung and blood after a single-inhalation is presented in Fig. 7. The pharmacokinetic parameters reported are summarized in the Table 1. Maximal plasma concentrations (C_{max}) for wet-milled ITZ and URF-ITZ dosing groups were 50 and 180 ng/mL at 2.7 and 4.0 h after dosing, respectively. The AUCs for the period 0–24 hours of wet-milled ITZ and URF–ITZ was 662 and 2543 ng h/mL, respectively. In the URF–ITZ dosing group, after reaching the C_{max}, a plateau of the high ITZ level was maintained from 2.5 to 6.0 h, showing similarity to a sustained-release profile. At all the sampling time points, the ITZ levels in rats inhaled with URF–ITZ was significantly higher than those achieved with the inhaled wet-milled ITZ form. The results show that the cumulative ITZ concentrations absorbed into blood from rats was about 3.8 times higher for the URF–ITZ versus the wet-milled ITZ (see also Table 1).

The superior dissolution rate the amorphous over crystalline ITZ which was an advantage in the oral formulation of the drug. The formulation involved the drug coated on the surfaces of sucrose beads (marketed as Sporanox® capsules) and required co-administration of particular beverages for the optimal effect as outlined in the previous section.

Another example is atorvastatin calcium known (marketed as Lipitor® tablets containing the trihydrate crystalline form) successfully prepared by the spray-drying and super critical anti-solvent process. Physicochemical properties and bioavailability were evaluated for both forms. Through the physicochemical assessment, it was demonstrated that the amorphous atorvastatin exhibited an enhanced dissolution rate and higher solubility due to its compared to the crystalline (trihydrate) atorvastatin. Nonetheless, the amorphous form had a significant enhancement in the oral bioavailability. The enhancement in oral bioavailability of amorphous atorvastatin was attributed to a combination of higher apparent solubility and higher dissolution rate due to the amorphous nature.

5 Conclusions

In the pharmaceutical development field, choosing the polymorph of optimal bioavailability, processability, and stability is the goal of every medicinal product developer. However, sensible approach is needed as for example a fast dissolving material can be highly hygroscopic and less favoured – as happened to carbamazepine, where the most soluble form III was not the preferred one due to its high hygroscopicity. In case of torsemide, despite the form II being three times more soluble than form I, the form II was not accepted by the regulatory body due to its suboptimal water sorption characteristics. Sometimes the bioavailabilities of polymorphs are more apparent when tested clinically. Mebendazole was found to exist in multiple crystalline forms. However, the form C is the only form favoured clinically. Thus, it is difficult to consider any other polymorphs in such a case. Many polymorphic forms differ in their processing characteristics. Sulfamerazine was reported to have two polymorphs, both of which had similar solubility; however, they differed in tabletting properties (form I have better compressibility parameters).

Pharmaceutical co-crystals become increasingly useful in the development of medicinal products. Itraconazole – a drug traditionally formulated in the amorphous form – was demonstrated to benefit from co-crystallisation. Of the co-crystals formed, all experienced higher in vitro dissolution rates than the crystalline forms and one of the co-crystals resulted in a better dissolution rate than the marketed amorphous form. In addition, co-crystallised itraconazole demonstrated promising processability parameters, especially in regard to filtration and drying.

The amorphous form of a substance is usually characterized by higher values of thermodynamic properties (such as enthalpy, entropy, free energy) in comparison to its crystalline form. These properties are useful in estimating the stability as well as the
probable solubility advantage of amorphous forms. This was the case with the amorphous form of Celecoxib which has a higher heat capacity than its crystalline form. Another example showed that pulmonary delivery of amorphous nanoparticle formulations of extremely poorly water soluble drugs (especially for high-dose drugs as shown for itraconazole), is beneficial for both local and systemic therapy.

As demonstrated with a number of examples, the solid form of a drug can have a dramatic influence on its physico-chemical properties. As a result, choosing the solid form of an active pharmaceutical ingredient will influence the formulation strategies and the manufacturing process characteristics as well as define the storage and handling requirements of medicinal products.

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7 References