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Solvent-Interactive Transformations of Pharmaceutical Compounds

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1. Introduction

A major factor which determines the overall success of a pharmaceutical product is the solid-state form in which the active pharmaceutical compound exists. It is a well-known fact that most pharmaceuticals possess the ability to exist in different solid forms. The solid-state of a compound significantly influences the physical-, chemical and mechanical properties exhibited by the drug [1, 2]. Subsequently, these properties not only affect the processability and stability of a drug, but also the dissolution and bioavailability thereof [3]. Optimal drug performance depends to a large extent on the solid-state form used in the design and development of a pharmaceutical product. Considering the abovementioned facts it becomes quite evident why it is so important to select the best solid-state form of a given drug to be incorporated into a dosage form. Not only is it imperative that the appropriate solid-state form is chosen, but also to ensure that the specific form will remain unchanged during processing, manufacturing as well as during distribution and storage of the final product [4]. Knowledge of solid-state forms of drugs and the identification of possible transformations have developed from mere scientific interest to matters that must be addressed for every dosage form.

Usually, the most stable solid-state form of a given drug is preferred for incorporation into marketable formulations, because a metastable form may transform to its stable counterpart. Such a transformation may lead to precipitation from solution, physical instability of the dosage form and even changes, and resultant unpredictability, in the bioavailability thereof [5]. Whilst the most stable solid-state forms of drugs offer the best shelf-life for products, they are also always the least soluble forms. This is the reason why there is now a heightened interest in the use of metastable solid-state forms such as metastable polymorphs, amorphous drugs and amorphous solid dispersions, in pharmaceutical products. A decade ago the incorporation of metastable forms in dosage forms was almost unthinkable and a contradiction of pharmaceutical manufacturing guidelines, but it is steadily becoming more commonplace. The

challenge facing pharmaceutical researchers is understanding and preventing/managing the tendency of these metastable forms to invariably revert to their most thermodynamically stable solid-state form, either during processing, storage, distribution or patient administration [3].

Transformations often result from the interaction of a drug with a solvent. These transformations are usually classified as: solvent-mediated, solution-mediated or solvent-exchange processes. A review of current literature quickly shows that these terms, especially the first two, are often used interchangeably and that many authors have different views on which process is involved in a given transformation. It is evident that the different solvent-interactive processes need to be defined more clearly and, by reverting to fundamental principles, this chapter aims to do just that.

2. Overview of solid-state transformations

A solid-state transformation may be defined as any transition from one solid-state form of a compound to another solid-state form resulting in the same composition but different packing arrangement. The phenomena that govern solid-state transformations can be classified as thermodynamic, kinetic and molecular recognition. Competition or reinforcement between these processes is affected by mechanical, thermal and chemical stresses. Molecular recognition determines the number of possible solid-states for any given molecular entity. Thermodynamics control the relative stability and the conditions/direction in which a transformation can occur, but kinetics determines how long a transformation will take [6, 7, 8]. The transformations that may occur in drugs are classified in accordance to the general underlying process(es) of the transformation(s). The following are listed by Zhang *et al.* [4]: solid-solid, solvent-mediated and solution-mediated. All solid-state transformation types will not be discussed in this chapter but for the sake of completeness and to serve as a quick reference guide, Table 1 summarises solid-state transformations, as described in literature, in terms of the type of transformation, possible underlying process(es) as well as processing steps that might induce each transformation. The next few paragraphs will briefly discuss all solid-state transformations. Special attention will be paid to the transitions involving solvent-interactive transformations and these will be discussed in more detail throughout the chapter.

Solid-solid transformations occur as a direct conversion from one solid-state form to another without an intermediate solution or melt phase. Melt-induced transformation occurs when a solid-state form of a drug is melted and subsequently cooled. Parameters such as the cooling rate, nucleation rate and the presence of impurities or seed crystals determine the solid-state form that will be produced. In such a solid-melt-solid process, both the initial form and the resultant form can be either crystalline or amorphous [4]. Solution-mediated and solvent-mediated transformations are typically respectively described only as occurring in solution or in the presence of a solvent (or solvent vapour). Two important facts that should be highlighted here is that almost any environment or processing method can initiate a solid-state transformation and also that it can be extremely difficult to identify the causative agent or process.

The study and proper understanding of the types of solid-state transformations is currently seen as imperative within the pharmaceutical industry. Recently more and more attention is

being paid to the identification of solid-state transitions of drugs and excipients. As mentioned earlier, the physical state in which an active pharmaceutical ingredient (API) exists is determinant towards the stability, processability, solubility and bioavailability of the compound [2]. Transformation studies of pharmaceutical compounds will assist in the identification of the type of solid-state transformation that occurs, which in turn will help to identify the mechanism of the transformation process and most importantly the processing step responsible for the transformation. Information obtained through transformation studies will allow pharmaceutical scientists to make appropriate, cost-effective and time saving decisions throughout the manufacturing process of a pharmaceutical product.

Transformation type	Transformation result	Transformation process	Possible processing step involved
Solvation or hydration	• Transformation of an anhydrous crystalline form to a solvate or hydrate	• Solution-mediated • Solvent-mediated	• Crystallisation • Wet granulation • Pelletisation • Exposure to humidity/moisture during manufacturing or storage
Desolvation or dehydration	• Solvate/hydrate to amorphous form • Solvate/hydrate to anhydrous crystalline form	• Solid-solid	• Exposure to dry conditions during manufacturing or storage • Processing steps involving the drying of the drug i.e. spray-drying, freeze-drying or fluid-bed drying
Polymorphic transformation	• Polymorphic form X to polymorphic form Y of a drug	• Solid-solid • Solution-mediated • Solid-melt-solid	• Grinding/milling • Compression • Heating • Recrystallisation • Heating above melting point, followed by cooling • Dissolution or solubility testing of metastable forms
Vitrification	• Crystalline form to amorphous form • Solvate/hydrate to amorphous form	• Solid-solid • Solid-melt-solid	• Milling • Compression • Dehydration of solvates/hydrates • Spray-drying • Freeze-drying • Quench cooling of the melt
Crystallisation	• Amorphous form to crystalline form	• Solution-mediated • Solid-solid	• Heating • Grinding/milling • Humidity or plasticiser-induced crystallisation • Dissolution or solubility testing of amorphous drugs

Table 1. Summary of solid-state transformations of drugs [4, 9]

The unintentional transformation of a solid form to another is an unwanted occurrence within the pharmaceutical industry. If necessary preventative steps aren't put in place, a multitude of unplanned solid-state transitions can occur throughout the manufacturing and processing cycle of a pharmaceutical compound, leading to unexpected and unwanted product properties. One unintended transition can lead to an array of problems that detrimentally affect further processing and development steps. Solid-state transformations may also be advantageous, if they are utilised in a controlled and conscious manner to deliberately obtain alternate solid-state forms.

3. Solvent-interactive transformations

Within the context of solid-state transformations, we propose the use of *"solvent-interactive transformations"* as a collective term for all transformations that are caused or accelerated by the presence of solvent. One often sees the two terms, solvent- or solution-mediated transformations, used interchangeably by many authors when, in fact, they are very different processes. The synonymous use of these two terms can be attributed to a lack of proper understanding of the different pathways that the two transformations follow. This section aims to explain the subtle but extremely significant differences between solvent- and solution-mediated transformations, as well as to put forth a new concept namely *"solvent-catalysed transformation"*.

In an effort to obtain sufficient information to clarify the discrepancies that exist with the current use of the terms solvent- and solution-mediated, a literature study was undertaken. Table 2 provides a summary of some of the misconceptions and overly generalised statements found in literature.

Solvent-mediated transformation	Solution-mediated transformation
-	Always: Metastable form → Stable form
Driving force is the removal of solvent from the system	-
Transformation occurs during drying/removal of solvent	Transformation occurs when metastable form is in contact with the saturated solution of the drug
Transition occur out of solvent	Transition occurs in solvent

Table 2. Summary of some of the misconceptions and overly generalised statements regarding solvent- and solution-mediated transformations, as currently found in literature [4, 5, 9, 10, 11]

Our attempts to extract, from literature, concrete facts and unambiguous definitions that could be applied to explain the difference between solvent- and solution-mediated transformation, has met mostly with failure. To make sense of all the contradictory information that is available in current texts, we have opted for a fresh start in defining the relevant terms based on fundamentals. The first question that needs to be answered is: What does *"mediation"* mean in scientific context?

Mediate: "Exhibiting indirect causation, connection, or relation" [12] or "Connected indirectly through another person or thing" [13]. From these definitions it is clear that only those solvent-interactive transformations in which the initial solid form does not directly transform to a second solid form may be described as being either solvent- or solution-*mediated*.

Mediation may be further elaborated upon by employing, in its most simple form, the concept of a statistical mediation model (Figure 1) [14]. According to such a model, the initial solid form (Form X) is the independent variable, because it is the starting material and its existence is independent of both the transformation itself (B) and the product of transformation (Form Y). In a mediated process, there is no direct causal relationship (C) between the independent variable (starting material) and the dependent variable (product of the transformation). Instead, the relationship between the independent variable and the dependent variable is governed by a mediator variable, which in this case is either a solution or a solid-solvent association.

The product of a mediated transformation may be either more or less stable than the starting material. Dissolution testing of a metastable starting material may cause solution-mediated transformation to a more stable form, but recrystallisation techniques may also be used to produce metastable forms of a stable starting material *via* solution-mediated transformation. It is important to keep in mind that this chapter focusses on but one variable, the role of solvents, but in real-world applications the outcome of a mediated transformation will be dependent on numerous thermodynamic and kinetic variables [6].

Many solid-solid transformations are capable, given enough time, of converting one form to another without the aid of solvent interaction (F), but they occur much more rapidly in the presence of a solvent or solvent vapour (E). To occur without mediation, such transformations need to be thermodynamically favoured and therefore can only result in products that are more stable than the starting material. The fact that solvents can accelerate these transformations is evidence of solid-solvent interaction (solvent-interactive transformation), but direct conversion rules out mediation. In these instances the solvent or solvent vapour acts as a catalyst to transformation by reducing the energy barrier and increasing the rate at which the transformation occurs. This is a purely kinetic phenomenon. We therefore propose the use of the term "*solvent-catalysed transformation*" for cases where a solvent or solvent vapour increases the rate of a non-mediated transformation.

Some authors [4, 9, 10] have described solvent-mediated processes as requiring the removal of the solvent to obtain the transformation product. We believe that this may be ascribed to a failure to distinguish between multiple transformations. It is much more likely that solvent-mediated transformation will have resulted in a metastable form (Form Y) that subsequently transformed, *via* regular non solvent-interactive solid-solid transformation (G), to a more stable form (Form Z). Another possibility is that said metastable form (Form Y) could have undergone solvent-catalysed transformation to a more stable form (Form Z).

From the above discussion, the following definitions were distilled:

Solvent-interactive transformation: A solid-state transformation which is *caused or accelerated* by the presence of solvent in liquid or vapour form.
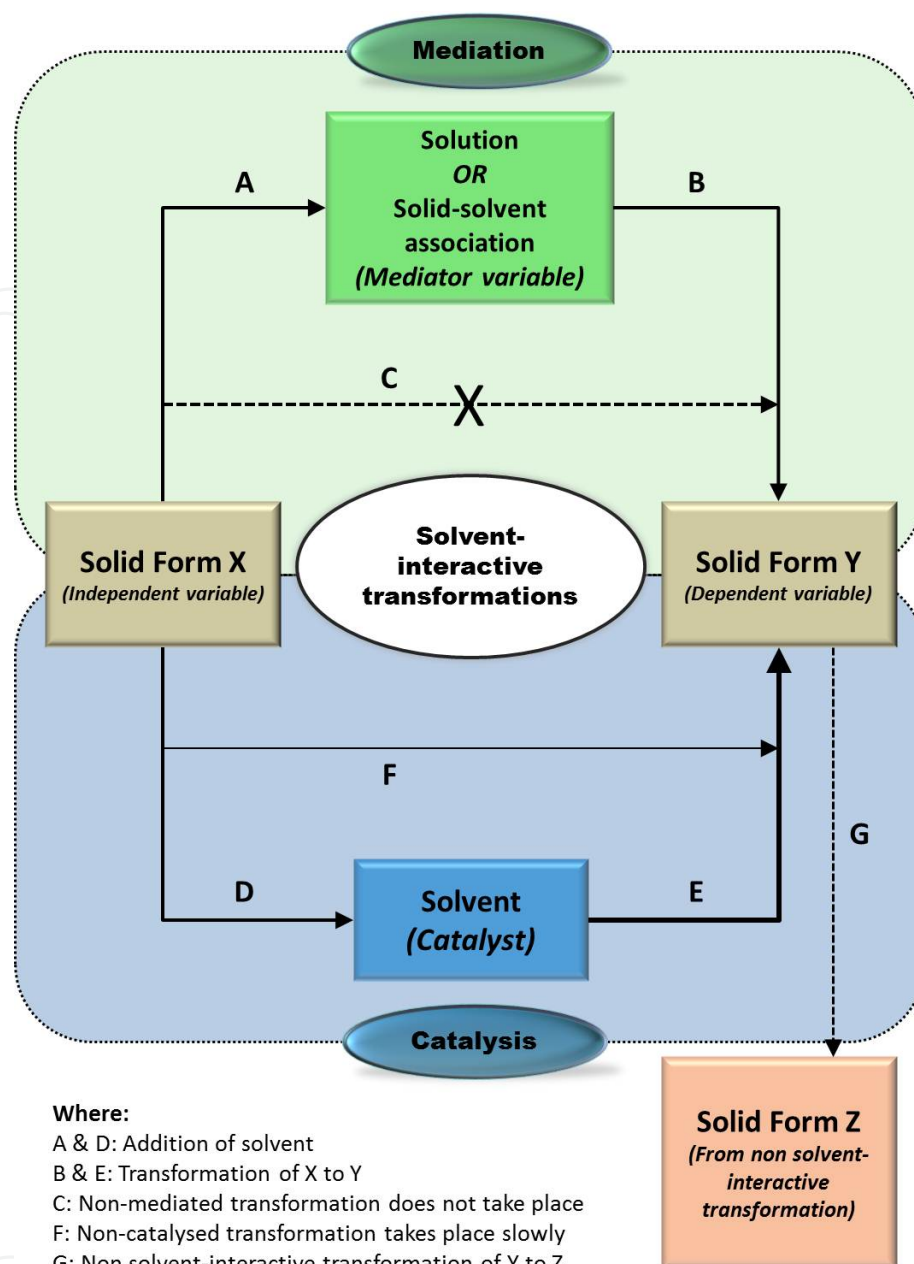
Figure 1. Solvent-interactive transformations.

Three types of solvent-interactive transformation exist:

- **Solution-mediated transformation:** A solid-solution-solid transformation of the solid-state in which *no direct* transformation of the starting material to the product takes place, but which is instead mediated by a *solution* of the starting material in a solvent that was introduced in liquid or vapour state.

  Examples:

  ○ Dissolution: metastable form transforms to stable form

○ Recrystallisation to obtain polymorphs, hydrates and solvates

○ Vapour sorption on the surface of the starting material resulting in deliquescence and subsequent transformation to a hydrate/solvate or more stable polymorph

• **Solvent-mediated transformation:** A solid-solid transformation of the solid-state in which *no direct* transformation of the starting material to the product takes place, but which is instead mediated by an interaction between the *undissolved* starting material and a solvent that was introduced in liquid or vapour state.

Examples:

○ Anhydrous form converting to a hydrate or solvate

○ Solvent exchange resulting in a change of structure

○ Crystallisation of an amorphous form to a *solvate or hydrate*

• **Solvent-catalysed transformation:** A *direct*, *non-mediated*, solid-solid transformation of the solid-state which is accelerated by the *catalytic effect* of a solvent introduced in liquid or vapour state.

Example:

○ Accelerated crystallisation of an amorphous form to an *anhydrous* crystalline form due to plasticisation

With fundamental definitions now having been set, Table 2 should be reconsidered. It is now obvious that the driving force for solvent-mediated transformation cannot be the removal of the solvent and that any transformation subsequently taking place outside of the solvent during drying has to be a non solvent-interactive solid-solid transformation. It is equally obvious that solution-mediated transformation is not limited to metastable forms that convert to more stable forms. The last two statements about solution-mediated transformation in Table 2 are perhaps not erroneous *per se*, but they are vague enough to warrant further discussion. A metastable form will convert to a more stable form *via* solution-mediated transformation if a saturated solution of the metastable form, supersaturated regarding the stable form, exists. Transformation will happen through nucleation and crystal growth of the stable form. This means that continued contact with the metastable form is only required to feed and maintain crystal growth of the stable form. As for the transformation taking place "in solvent", the presence of solvent is most definitely required for a solution of the starting material to be obtained, however the starting material needs not necessarily have been placed "in solvent". If solvent vapour were to adsorb onto the starting material, and said material is sufficiently soluble in that solvent, the solid may deliquesce to create a solution layer around it in which solution-mediated transformation could take place.

The processes and implications of solvent-interactive transformations will be discussed, with reference to practical examples, in the following section.
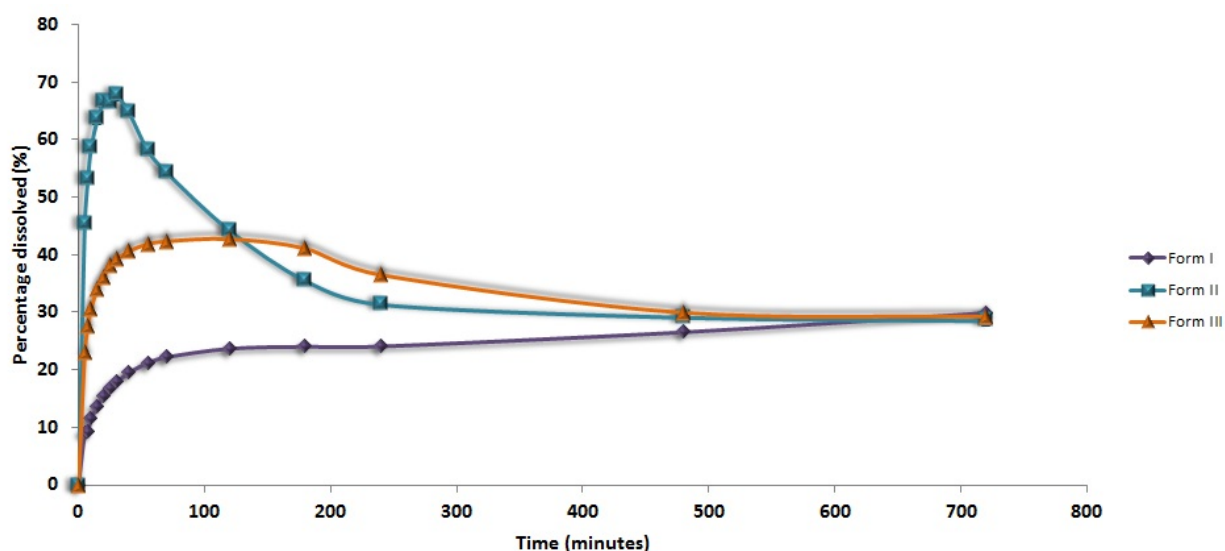
Figure 2. Dissolution profiles obtained from powder dissolution studies of different roxithromycin solid-state forms at 25°C and 100 rpm rotational speed. (Form I=roxithromycin monohydrate; Form II=amorphous roxithromycin; and Form III=roxithromycin anhydrate).

4. Implications of solvent-interactive transformations

Solid-state transformations can affect a significant number of solid dosage form attributes. Aspects like dissolution, bioavailability, stability, appearance, manufacturability, hardness, to name but a few, can be influenced by solid-state transformations [15]. The effect of solvent-interactive transformations on the dissolution and bioavailability of metastable drugs is of particular concern, especially with poorly soluble drugs where a further decrease in solubility or dissolution rate will negatively impact bioavailability and subsequent treatment outcomes [4]. In this section the macrolide antibiotic, roxithromycin, will be used as a model drug to illustrate the effects of solvent-interactive transformations on solid-state properties.

Studies on the physico-chemical properties of roxithromycin showed that solid-state transformations attributable to solvent interaction are possible. Solution-mediated transformation of roxithromycin metastable forms to the thermodynamically favoured form was identified during dissolution studies. Powder dissolution studies were done using three solid-state forms of roxithromycin [16]. During the dissolution studies of the roxithromycin solid-state forms, the solid-state transformation of the metastable forms to the stable monohydrate was demonstrated. Powder dissolution studies were done in distilled water at 25°C with a rotational speed of 100 rpm. No medium replacement was done, because doing so will mask or suppress the transformation. During the dissolution process a steady decline in the dissolved roxithromycin concentration was observed after about 120 minutes for roxithromycin Form III (anhydrate). In comparison, the transformation of the amorphous form of roxithromycin (Form II) to stable Form I resulted in a concentration decrease after approximately 40 minutes (Figure 2).

Further studies of the solution-mediated transformation process of roxithromycin solid-state forms were done utilising X-ray powder diffraction (XRPD) and subsequent principal

component analysis (PCA). During the XRPD experiments anhydrous and amorphous roxithromycin (Form III and II, respectively) were separately exposed to a sufficient amount of distilled water to allow dissolution, resulting in the nucleation and crystal growth of Form I. This experiment was performed at 25°C (± 2°C). From the experimental data of the transformation process of Form III to Form I it was possible to quantify the transformation process. This was done by following either the decrease or increase of a particular Bragg peak, characteristic to the solid-state forms under investigation. This method was investigated and established as an accepted technique to determine phase transformations by Klug and Alexander in 1974 [17].

The decrease of the anhydrous portion and subsequent increase of the monohydrate form of roxithromycin is plotted *versus* time in Figure 3. With the help of the phase proportion graph the investigators were able to determine the time required for Form III to completely disappear [16].

The XRPD cluster analysis of amorphous roxithromycin is depicted in Figure 4. The plot shows a 25% conversion from cluster 1 to cluster 23 and further cluster analysis eventually showed a 100% conversion of Form II to stable Form I as depicted in Figure 5.
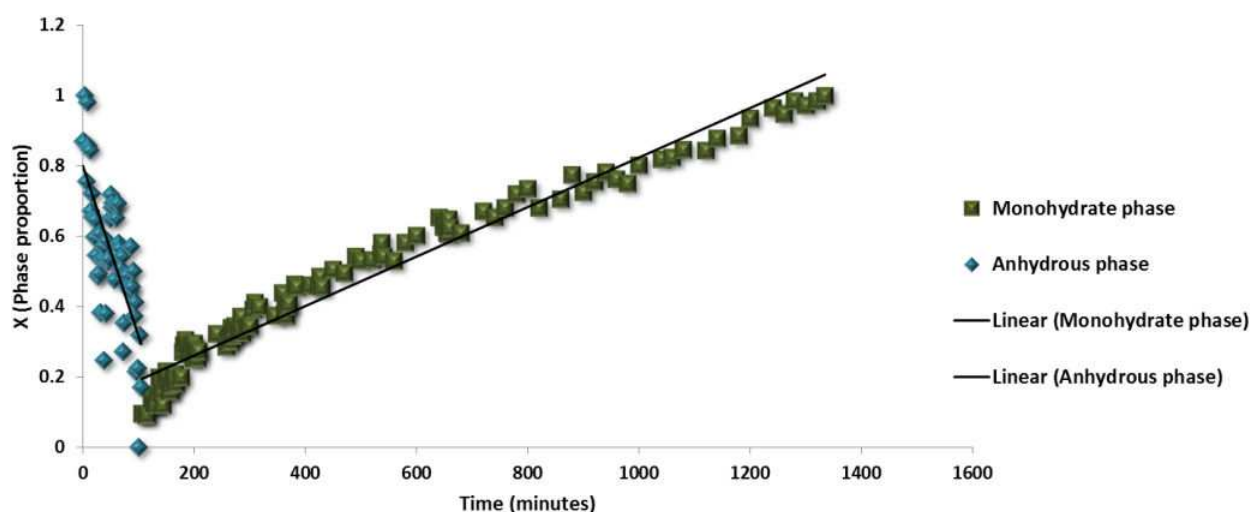

Figure 3. Phase conversion of anhydrous roxithromycin (Form III) to the stable monohydrate (Form I) at 25°C (± 2°C). Adapted, with permission from [16].

The pharmaceutical impact of such a solid-state transformation can be significant. Currently, the incorporation of metastable forms of drugs into solid dosage forms is at the order of the day due to their improved dissolution and solubility properties. When considering a solution-mediated transformation such as described above, one can see that it will lead to a decrease in the solubility and dissolution rate of a drug, which will ultimately influence the bioavailability negatively. At this time no reports could be found on solution-mediated transformations that have occurred *in vivo*, but we could also not find any mention of it yet having been investigated at all. In theory it could happen that the *in vivo* rate of dissolution of an orally administered solid metastable form might exceed the maximum possible rate of absorption for that specific
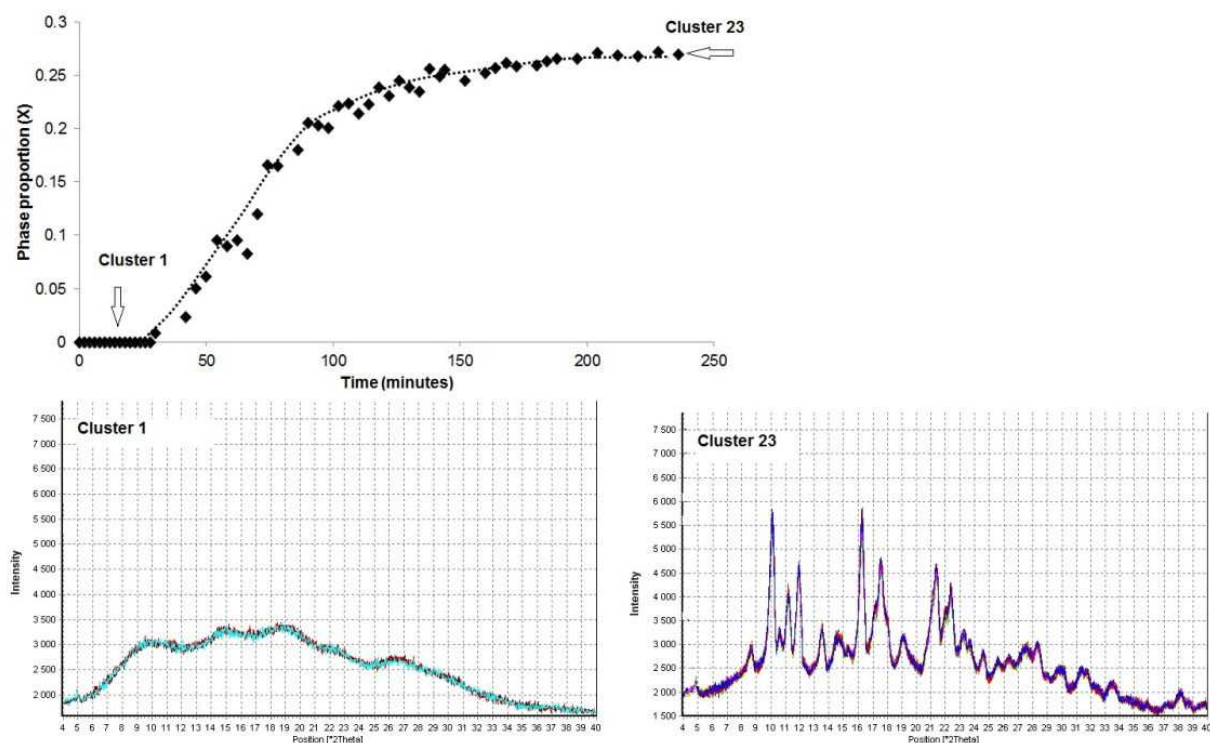
Figure 4. Phase conversion of amorphous roxithromycin at 25°C (± 2°C) determined with XRPD cluster analysis (PCA).
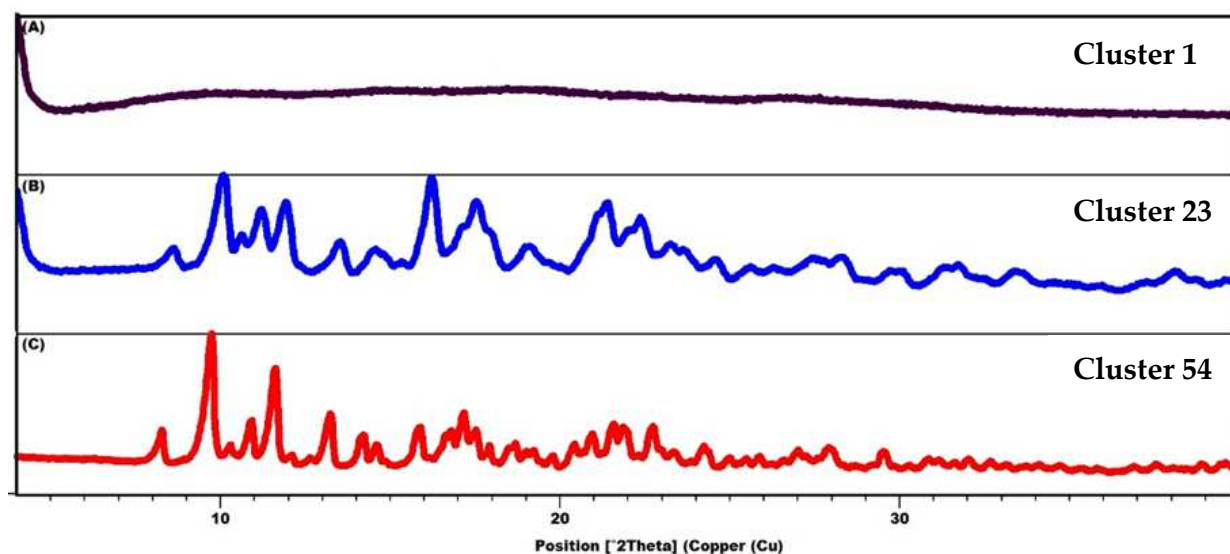

Figure 5. Representative XRPD patterns showing the solid-state transformation of amorphous roxithromycin (A). (B=PCA Cluster 23: partial conversion; C=PCA Cluster 54: complete conversion to Form I).

drug, resulting in a supersaturated solution that can lead to nucleation and crystal growth of the more stable, less soluble drug within the gastro-intestinal tract.

Another theoretical possibility is that, during dissolution testing, the undissolved portion of a metastable solid could undergo solvent-mediated and/or solvent-catalysed transformation

parallel to the solution-mediated process in which the dissolved portion is participating. To investigate the possibility of parallel solvent-interactive transformations occurring during the dissolution testing of metastable roxithromycin forms, vapour-sorption studies were performed. The vapour sorption isotherm given in Figure 6 shows no recrystallisation due to solvent-interactive transformation. Had solvent-interactive crystallisation taken place, it would have been evident from a step increase or-decrease in the weight of the sample [18] as opposed to the observed gradual increase and decrease corresponding to relative humidity. A step increase in the weight during crystallisation can be explained by the incorporation of solvent molecules in the new crystal structure to form a solvate/hydrate by solvent-mediated transformation. When a step increase is observed during sorption analysis, care should be taken to rule out the possibility of deliquescence however, this will likely manifest as a more drawn-out process of weight gain and the sample will become visibly wet. Deliquescence of a sample due to the exposure to vapour might lead to a solution-mediated transformation. A step decrease in sample weight associated with solvent-interactive transformation can be ascribed to the fact that a form results which has a denser crystal structure, more efficient molecular packing arrangement and fewer voids which may accommodate solvent molecules. The transformation to a denser form therefore leads to the displacement of solvent molecules from the solid and a resultant decrease in sample weight. A step decrease may be observed if an anhydrous crystalline form is obtained *via* solvent-catalysed transformation OR if the hydrate/solvate, produced *via* solvent-mediated transformation, incorporates less solvent than the starting material can accommodate at the same humidity level.

Evaporative recrystallisation (at 25°C ± 2°C) of roxithromycin monohydrate (Form I) from dichloromethane (DCM) results in a roxithromycin DCM solvate *via* solution-mediated transformation. Drying of the DCM solvate in an oven at 50°C for 24 hours, results in desolvation to roxithromycin anhydrate (Form III) by means of a non solvent-interactive solid-solid transformation. The XRPD patterns of Form I, Form III and the DCM solvate are given in Figure 7.

Roxithromycin is also capable of a solid-state transformation through a solvent-mediated process by means of solvent exchange. Mallet *et al.* [19] reported the transformation of a 1:1 roxithromycin acetonitrile (ACN) solvate to roxithromycin Form I *via* a solid-solid transformation in the presence of water vapour. During this study, well-defined single crystals of the roxithromycin ACN solvate were removed from the crystallisation medium and maintained at 100% relative humidity (RH) and ambient temperature. The investigators observed that the initially clear crystals became opaque after 48 hours however, the shape of the crystals remained unchanged. Subsequent analysis of the opaque crystals showed that the acetonitrile molecules had been replaced by water, resulting in a stoichiometry of 1:1 (roxithromycin : water). One might argue that the transition could also have been due to a solution-mediated process since an environment of 100% RH could have led to deliquescence of the crystals and resultant dissolution and recrystallisation. Further studies by Aucamp [20] however, showed that the same transformation will occur at ambient conditions. The study showed that, upon storage of the acetonitrile solvate crystals

at ambient conditions (25°C / 65% RH), the same transformation occurs, resulting in roxithromycin : water (1:1) stoichiometry.
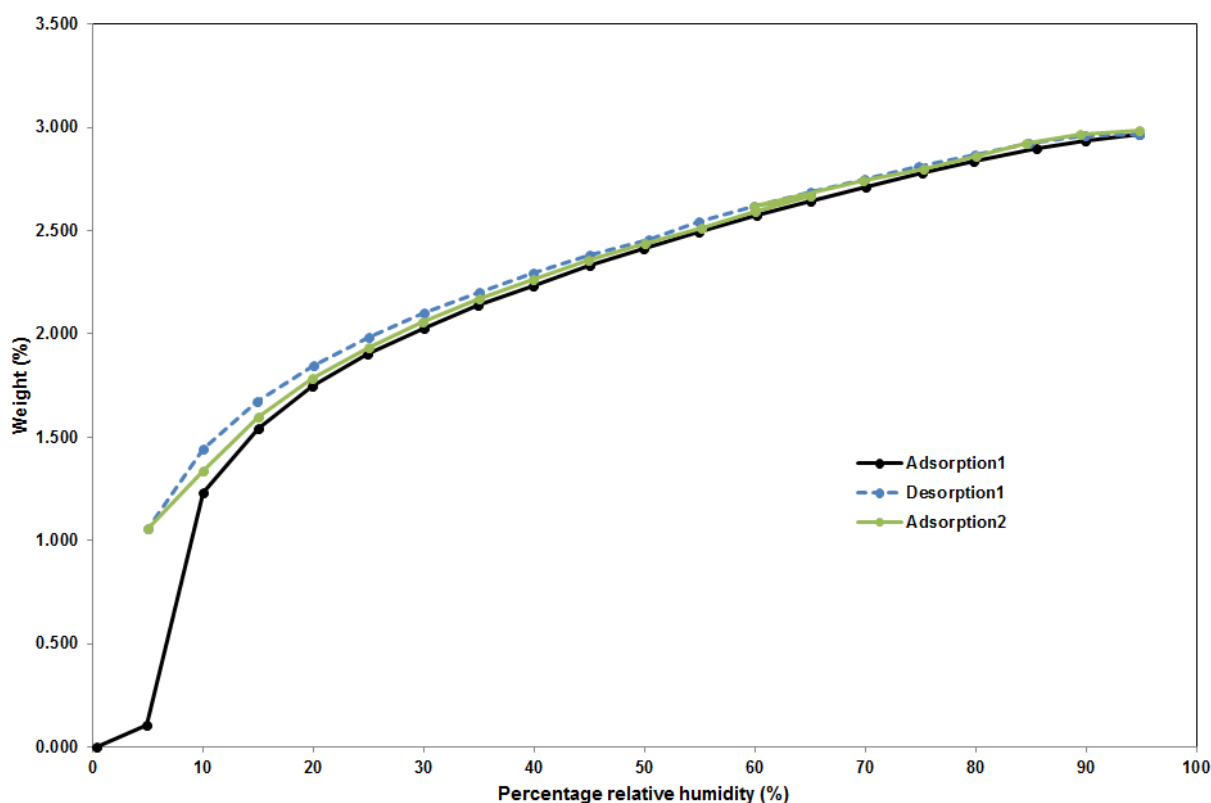

Figure 6. Moisture sorption isotherms of amorphous roxithromycin. Adapted, with permission, from [16].

Considering the fact that it can be challenging to determine whether any given solvent-interactive transformation is occurring in isolation, in parallel with others, or even as part of a number of transformation steps, care should be taken when interpreting experimental observations and, where possible, multiple techniques should be used to verify results.

5. Solid-state transformations and pharmaceutical manufacturing

The previous sections focused on neat APIs and transformations that occur during pre-formulation steps. However, it should be mentioned that the combination of drugs with excipients might also lead to significant phase changes. Tablets and capsules contain drugs and excipients and are formulated in such a manner that enhanced performance and physical appearance will be obtained. Even if the physico-chemical properties of the drug are taken into
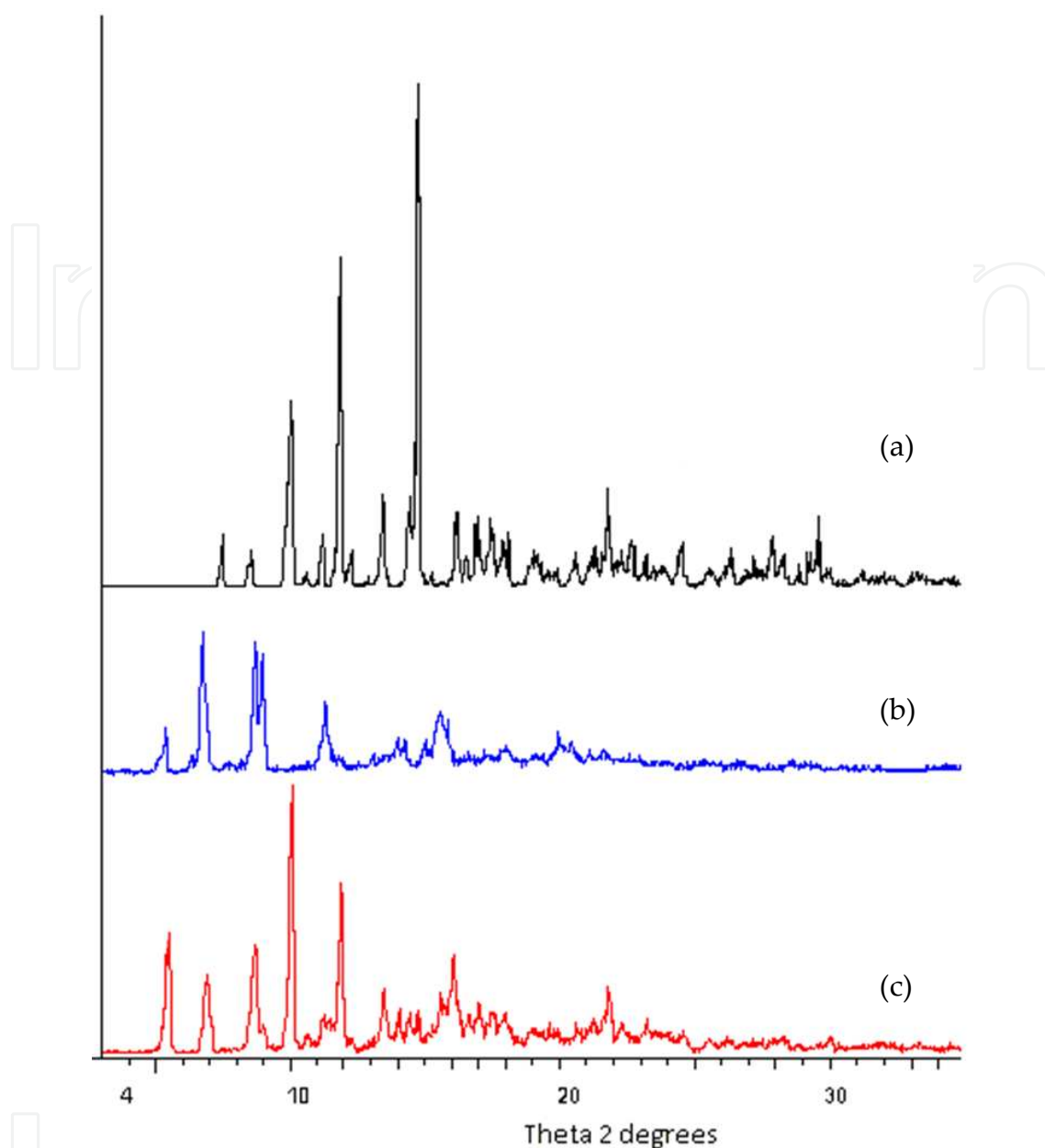
Figure 7. XRPD patterns of (a) roxithromycin monohydrate (Form I), (b) a roxithromycin DCM solvate and (c) roxithromycin anhydrate (Form III). Single crystal structural data of roxithromycin Form I (monohydrate) is available from the Cambridge Structural Database (reference code: FMPROA) [19].

account and compensated for, the excipients included in the formulation, as well as, the manufacturing steps taken, can still cause unforeseen solid-state transformations of the drug. It cannot be emphasised enough that, after an in-depth physico-chemical study of the drug, the next step should be to investigate the effects that excipients and processing of the drug in combination with excipients will have on the solid-state properties of the drug. Excipients may facilitate conversion of an amorphous form to a crystalline form or *vice versa*. Hydration or dehydration of a drug might be triggered by an excipient, which might lead to the formation of metastable or stable forms or mixtures of various crystalline forms of a given drug. All of

these solid-state changes can have detrimental effects on the product stability and ultimately the treatment of patients.

A multitude of processes are employed during the manufacturing of solid dosage forms (Figure 8). Although some of these methods do not involve the use of solvents, it should be realised that these methods can alter the solid-state of the drug and this altered state might be prone to solvent-interactive transformations at a later stage.

Generally, the first step during the manufacturing of a solid dosage form is size reduction of the drug particles. Size reduction is necessary to improve morphological characteristics, powder flow properties and uniformity. Size reduction is usually achieved through milling [4]. Milling or grinding imparts mechanical stress and often generates heat that might cause dehydration or complete/partial vitrification of the drug. If the intactness of the preferred solid-state is not confirmed at this stage, any undetected solid-state transformation will be problematic during ensuing stages of manufacturing or during after-production quality testing. Therefore, because milling can cause solid-solid transformations it is imperative to understand that incorporation of a drug, with an already altered state, into a product will most probably lead to solvent-interactive transformations during other stages of the production cycle.

Granulation is often the next processing step to which a drug is subjected. During this step, the combination of the drug with some or other excipients come into play. Granulation is a processing step that is employed to improve flowability, cohesiveness, compressibility and/or lubrication of the bulk material. There are very few APIs that do not need improvement in terms of flowability or compressibility and therefore a substantial percentage of drugs are granulated before further formulation steps towards tablet/capsule production. Two types of granulation are commonly used in industry, namely: wet granulation and dry granulation. Wet granulation is the most widely used due to its versatility and superior results in terms of bulk properties. Even though wet granulation is usually the preferred method for granulation it is also the most likely to induce solid-state transformations. The liquid used during the granulation process, drying parameters, drug loading, solubility of the drug in the granulation fluid and the procedure for including the drug into the granules are all factors that may affect the solid-state form of the drug. Wet granulation creates favourable conditions for solvent-interactive transformations to occur, often resulting in hydration/solvation, polymorphic conversions, vitrification or crystallisation [4].

In solid dosage form manufacturing, the use of dry granulation is reserved for drugs that are sensitive to moisture and/or elevated temperatures, because it requires neither solvents for granulation nor heat for drying. The mechanical stresses imparted on the drug through the dry granulation process can lead to solid-solid transformations that ultimately might lead to solvent-interactive transformation further along the manufacturing process. For both wet-and dry granulation, mixing with excipients might also induce solid-state transformations due to incompatibility reactions that might occur.

Spray-drying is a technique that produces homogenous particles of uniform shape and size. This process requires the complete or partial dissolution of the drug in a solvent and therefore increases the probability of solid-state changes due to solvent-interactive transformation.
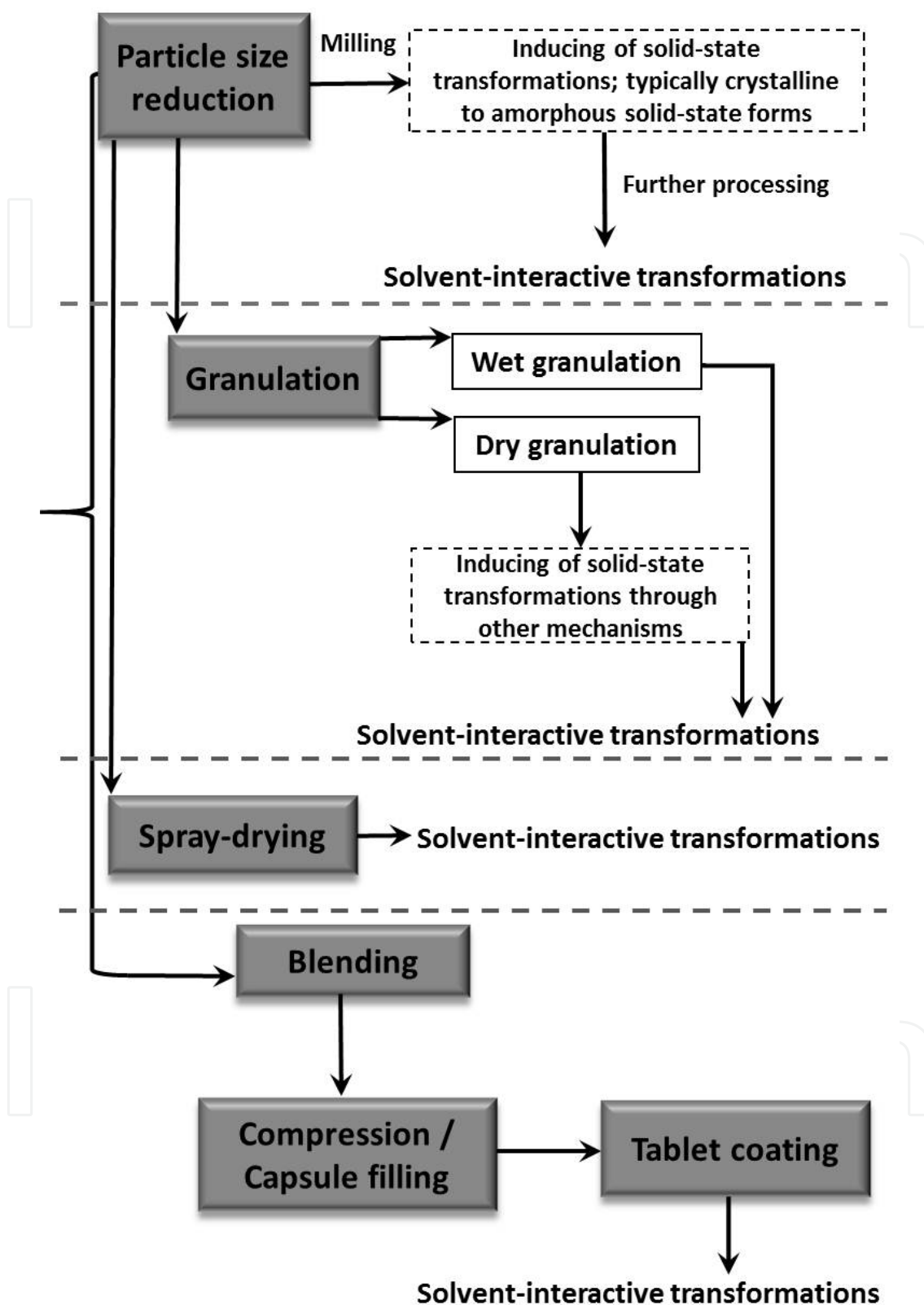
Figure 8. Flow diagram illustrating the processing steps for a pharmaceutical product, to obtain a solid dosage form, indicating where solvent-interactive transformations can occur.

Solvent removal from the spray of droplets is a rapid process that may lead to crystallisation of a metastable form or even another polymorphic form [4, 21].

After powder characteristics have been improved, a second granulation or blending step usually follows. This processing step is generally considered a low energy and- intensity step and is unlikely to induce solid-state changes, although it should not be completely excluded as a possibility. Also, the fact that the drug is now being mixed with lubricants, glidants and disintegrants makes the detection of phase changes more difficult. Tablet compression is another high energy process that can induce solid-solid transformations to metastable forms. Following compression of the drug-excipient blends, a coating process may be required or desired. In most cases it is unlikely that a solid-state change will occur during film-coating due to the fact that process parameters have been optimised to such an extent that the period of time for which the tablet is subjected to the coating solution is minimal. Drying of the coating by means of an efficient air exchange method also ensures a short exposure time of the tablet to the coating solution [4]. On the other hand, coating procedures used in the manufacture of modified release products may cause problems. Generally, in the case of modified release products, a portion of the total dose may be applied as a drug coating layer. This coat is essential in providing immediate release for fast onset of action. Typically, the drug layer is applied by spraying a drug-excipient solution or suspension onto the tablet surface. Dissolving or suspending the drug in a liquid significantly increases the probability of solvent-interactive transformations occurring. Furthermore, the rapid solvent removal after the coating process could lead to the precipitation of an altered solid-state form in the coating layer [4].

Considering all the pitfalls and challenges mentioned above, it becomes clear that solid-state transformations and the prevention thereof are of critical importance to the pharmaceutical industry. Not only must the pharmaceutical scientist keep a watchful eye out for solvent-interactive transformations occurring during the manufacturing of neat drugs, but attention must also be paid to solid-solid transformations arising during final product manufacturing.

6. Regulatory requirements: Solid-state characterisation and monitoring

According to the Food and Drug Administration's (FDA's) guideline on drug substances it is a regulatory requirement that the solid-state form of a drug be controlled throughout all processing and manufacturing steps. It is also required that the solid-state form of a drug must be known at any given time during the product manufacturing process, as well as during storage and distribution. Guidelines established by the International Conference for Harmonization (ICH) require a complete polymorphic study of a new drug prior to the product development stage [1, 4, 22].

Nearly a decade ago, a regulatory framework, namely Process Analytical Technology (PAT), was established. This FDA initiative encompasses the following:

1.   To ensure product quality and performance through the design of effective and efficient manufacturing processes;

2. Specifications of products and processes are based on a mechanistic understanding of how processing steps and formulation can affect product performance;

3. Continuous and real-time quality assurance of the pharmaceutical compound;

4. Risk-based regulatory approaches to understand how formulation and manufacturing processes can affect the quality and performance of the end-product; and

5. The establishment of process control strategies to prevent or mitigate the risk of having a poor quality product at the end of a manufacturing process.

PAT was developed to ultimately build quality into pharmaceutical products. The guide highlights the necessity for understanding processes that could detrimentally affect pharmaceutical products [22, 23]. It is not only thorough initial characterisation (and the reporting of knowledge gained) that is essential, but also the continuous monitoring of pharmaceutical ingredients during the manufacturing of medicines. In essence, this guide states that the solid-state form used to produce a dosage form must be known, as well the effects of solid-state changes on the performance or stability of the drug product. The influence that solvent-interactive transformations can have on the solid-state properties of a drug was discussed in detail in the previous sections of this chapter.

Numerous analytical techniques are available for the rigorous characterisation and monitoring of solid-state forms of APIs. To avoid oversights and inconclusive results, it is always advisable to use multiple complimentary techniques. Advances made in the refinement of techniques, and the improvement of equipment sensitivity, allow for better characterisation of not only new chemical entities (NCEs), but also older ones for which comprehensive data was not previously available. The "re-discovery" of older drugs is important and opens up many opportunities for the development of optimised products with improved patient treatment outcomes.

7. Characterisation techniques

Many analytical techniques are used to study and characterise the solid-state forms of APIs. The following paragraphs will elaborate on the techniques and the valuable information that can be obtained from the resulting data. Rather than defining the techniques or explaining in detail the underlying principles on which they are based – information that is widely available – we will focus on their application within the context of solid-state transformations.

7.1. X-Ray Powder Diffraction (XRPD)

XRPD is used to generate X-ray diffraction patterns that are unique to a specific crystalline arrangement of a particular drug. This may serve as an identification method for specific polymorphs. Any change in crystal structure will result in changes in the peak positions of the diffraction pattern. XRPD may also be used to quantify the relative proportions of two forms during a transformation process by monitoring changes in relative peak intensity, of peaks unique to each of the two forms, over time. If an X-ray diffractometer is equipped with a

controlled temperature-and humidity-chamber, transformations due to temperature or moisture changes can be studied [24].

An amorphous material gives a diffraction "pattern" that lacks peaks, but instead features broad humps, referred to as an amorphous halo [23]. Crystallisation of an amorphous material can be confirmed if peaks appear on the diffraction pattern. The amorphous halo is not meaningless or devoid of information, but is the result of the short-range order within the material. If an amorphous halo is recorded with a high-energy X-ray source, and pair-distribution-function analyses are performed, the extent of short-range order can be determined and sometimes even "matched" to the most similar crystalline polymorph [25].

7.2. Differential Scanning Calorimetry (DSC)

This thermal method measures the amount of energy taken up or released by a sample during a heating and/or cooling program. Thermal events such as melting, glass transition, desolvation and crystallisation are recorded on a thermogram showing heat flow against temperature or time. Any given solid-state form of a drug will have thermal events that are characteristic for that particular form. Changes in the number or nature of thermal events are indicative of changes in the solid-state, as are changes in the temperature at which melting of crystalline materials occur. Integration of the area under the heat flow curve yields the enthalpy change associated with that particular thermal event. Although DSC analysis is not a direct method for quantifying solid-state changes due to solvent-interactive transformations, it is still a helpful tool to identify whether changes did occur and to what extent solid-state characteristics were affected [4, 23].

7.3. Thermogravimetric Analysis (TGA)

TGA is a thermal technique that measures sample mass change under either isothermal conditions or ramped heating at a set rate [26, 27]. Weight loss at temperatures lower than the melting point of the drug is usually due to the loss of solvent. Adsorbed/absorbed moisture or solvent vapour is usually lost gradually, whilst solvent included in the crystal structure is typically lost in a characteristic step-wise manner. Weight loss profiles can be analysed to determine the amount or percentage of weight lost at any given temperature [26]. By factoring in the respective molecular weights of the drug and the lost solvent, one can also determine the stoichiometric relationship.

7.4. Hot Stage Microscopy (HSM)

This is one of the simplest and oldest thermal analysis methods. It is used to study solid-state transformations by observing a sample as it is heated and cooled. HSM is used to visually confirm DSC findings and to identify thermal events that cannot be conclusively identified from DSC thermograms. Possible observations include morphology, birefringence (polarising filter required), solid-solid transformations, interaction between different compounds, dissolution of one compound in another, sublimation and/or evaporation, vapour deposition, melting/liquefaction, crystallisation/solidification, charring/decomposition, crystal growth

and rate thereof. Gas evolution during desolvation can be observed if a sample is covered in a drop of mineral oil [28].

7.5. Vibrational spectroscopy and microscopy

The most prominent vibrational spectroscopic methods for solid-state form identification are infrared-(IR) and Raman spectroscopy. These two techniques can be used as qualitative and quantitative analytical methods. Although these techniques are generally used as complimentary methods they are still important, especially for investigating differences in hydrogen-bonding patterns that often differ with solid-state forms [8, 29]. An IR or Raman spectrum consists of several absorption bands, each band is related to a specific vibrational or rotational frequency. These frequencies are dependent on the intermolecular interactions and bond strength. Therefore, the obtained 'pattern' due to the vibrational frequencies is highly characteristic of a given drug. Any changes in the spectra due to solid-state transformations will be identifiable through changes in the relative intensities, frequencies, number and contours of the absorbance bands [24]. Confocal Raman microscopy can be used for the identification of a particular solid-state form of a drug in solid dosage forms. Not only is this a useful application for determining drug homogeneity in the dosage form, but the identification of solid-state transformations is also possible. Raman microscopy furthermore allows the investigation of amorphous-to-crystalline transformation at the dissolving interface of a solid dosage form [30].

7.6. Dissolution studies

In vitro dissolution studies are extremely useful for the identification and even quantification of solvent-interactive transformations. As mentioned earlier, the incorporation of metastable solid-state forms in solid dosage forms, especially amorphous forms, has become increasingly prevalent over the last decade. However, it has been demonstrated that general methods for testing dissolution and equilibrium solubility are not optimised for determining the true solubility advantage that these metastable forms offer [31].

Solution-mediated transformation, occurring during dissolution, involves three stages: (1) a pre-transformation stage, during which the metastable phase dissolves at a constant rate; (2) the transformation stage that begins after the solution has become supersaturated with respect to the stable form. During this stage the nucleation and crystal growth of the stable form, as well as dissolution of both forms occur. The relative amount of the stable form increases and as a result thereof the overall dissolution rate decreases until no metastable form is left. After the transformation stage, a steady-state stage (3) is reached (Figure 9) [32]. Aaltonen *et al.* [32] reported a Raman spectroscopy method that is ideal for accurately determining drug concentration in solution as well as the concomitant analysis of the solid phase within the dissolution environment.

7.7. Microcalorimetry

Microcalorimetry is a technique that has a variety of applications in the pharmaceutical research environment. This technique involves the real-time monitoring of chemical and
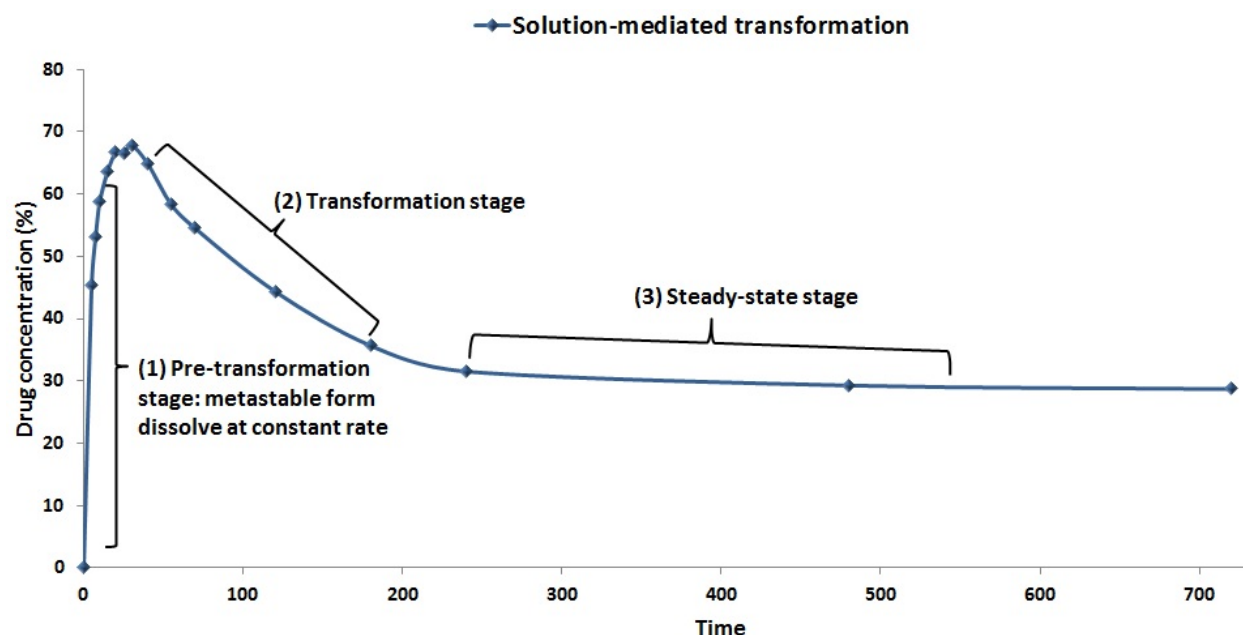
Figure 9. Typical dissolution graph showing the effect on concentration of solution-mediated solid-state transformation of a metastable drug to a stable form of the drug.

physical processes occurring when a compound is subjected to certain conditions (temperature, humidity, solvent vapour or in combination with another compound). The monitoring process can extend over a period of hours or days and it measures the onset, rate, extent and energetics of reactions or transformations. During microcalorimetric analysis, the heat flow of a sample is measured and recorded *versus* elapsed time. This analytical tool was developed around the basic principle that all chemical and physical processes are either exothermic or endothermic. Microcalorimetry is such a sensitive method that it can detect very slow processes. It will also detect physical or chemical reactions that generate minuscule amounts of heat. To study solid-state transformations due to solvent vapour exposure, a small amount of drug will be added to an inert ampoule and a micro hygrostat filled with the solvent will be inserted into the ampoule [33]. A specific humidity environment can also be created within the sealed ampoule by using a micro hygrostat containing saturated salt solutions and maintaining the calorimeter at a specific temperature. Any solid-state transformation will be seen as either an increase or decrease in the measured heat flow. The heat flow data can be applied to calculate the kinetics of a transformation process.

7.8. Vapour sorption analysis

Vapour sorption analysis, also known as dynamic vapour sorption (DVS), is a gravimetric technique that measures the amount and rate of solvent absorption/adsorption by a sample. Typically, water sorption-desorption isotherms are obtained by exposing a sample to a relative humidity (RH) cycle ranging from 0 – 98% and plotting the corresponding weight change. During typical vapour sorption studies the temperature is kept constant at 25°C ± 0.5°C, however some sorption analysers have the ability to apply a temperature ramp as well.

Sorption analyses usually involves 3 steps, namely a first up-ramping of the RH (0 to 98%), secondly a downwards ramp of the RH (98 to 0%) and thirdly and finally another upward ramping (0 to 98%). These RH ramping steps are usually applied when one wants to study the effect that water has on a drug during high % RH conditions. The resulting moisture sorption and desorption isotherms will indicate any change in the sample weight during the humidity ramps. Differences in the adsorption and desorption isotherms is referred to as hysteresis.

The solid-state change of an amorphous drug can be detected through sorption analysis. The glass transition is the point where an amorphous material becomes less stable and rearrangement to the more stable crystalline structure occurs. Typically the glass transition is affected by temperature and humidity. Hence, it can be determined using either ramped temperature experiments at constant humidity or using ramped humidity experiments at constant temperature. The amorphous material gains weight until the glass transition is reached. Then, as the amorphous drug rearranges to the crystalline form, there is a step increase or decrease in weight [18]. Another occurrence that can easily be identified from vapour sorption studies is that of deliquescence. Drugs that are susceptible to deliquescence will absorb very little moisture during a humidity ramp until the % RH reaches a "critical" level. At that point the drug will absorb any available moisture. This will result in a rapid increase of the monitored sample weight [34]. It should be noted that, if possible, vapour sorption studies should be performed in conjunction with XRPD, DSC and/or TG analyses. This will assist in the definitive identification of solid-state changes due to exposure of the drug to vapour.

8. Conclusion

Pharmaceutical compounds have the ability to exist in different solid-state forms. The rearrangement of molecules, that allows a single drug to present itself in various solid-state forms, presents an array of challenges to scientists working in the pharmaceutical industry. Different solid-state forms of the same API differ in terms of physical, chemical and mechanical properties. The understanding of the solid-state properties of APIs is imperative and even more so the factors that can induce changes in the solid-state of a given drug.

This chapter focussed on the solid-state form changes that may occur due to solvent-interactive transformations. There is much confusion and contradiction in current literature when it comes to differentiating the types of solvent-interactive transformations. We have concluded that solvent-interactive transformations may be either indirect and mediated or direct and non-mediated. The latter is a solvent-catalysed solid-solid transformation, whilst the former can be either a solvent-mediated solid-solid transformation or a solution-mediated solid-solution-solid transformation.

Solvent-interactive transformations can affect not only drugs but also excipients used in the formulation of a drug into a dosage form. It is essential to identify possible pitfalls, caused by solvent-interactive transformations, during the complete drug processing and dosage form manufacturing cycle. It is important to know that solvent-interactive transformations can change the solid-state form of a drug at any point between the very start of manufacturing

right up to the time when the drug is absorbed *in vivo* after having been administered to a patient.

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