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Solid Phase transformation considerations during process development and manufacture of solid oral dosage forms – A Review

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Abstract : Solid phase transformations (SPTs) during pharmaceutical manufacturing processes are well known but difficult to predict and often difficult to control. The quality and performance of a solid oral dosage form depends on the choice of the solid phase, the formulation design, and the manufacturing process. The potential for process-induced solid phase transformations must be evaluated during design and development of formulations and manufacturing processes. This article briefly reviews the basic principles of polymorphism, defines the classes of phase transformation and the underlying transformation mechanisms, and discusses respective kinetic factors. The potential phase transformations associated with common unit operations employed in manufacturing solid oral dosage forms are highlighted. Specific examples are given to illustrate the importance of solid phases, and process-induced phase transitions in formulation and process development.
Keywords: Phase transformation; Pharmaceutical processing; Solid oral dosage forms; Polymorph; Mechanism.

Introduction

Solid oral dosage forms offer convenience, physical and chemical stability, ease of product handling, high through put, and low manufacturing costs. The active pharmaceutical ingredient (API) and the excipients in a solid oral dosage form may exist in different crystalline forms or may be amorphous. Common crystal forms are polymorphs and solvates. Polymorphs have different internal crystal structure and therefore possess different physicochemical properties. Solvates are crystalline adducts containing solvent molecule within the crystal structure and if the entrapped solvent is water, it is termed as hydrate. When a pre-defined solid phase of a drug substance or crystalline excipient in a solid formulation is subjected to a variety of processing conditions during dosage form manufacturing, many phase transitions may take place including interconversion among polymorphs, solvates/hydrates, and the amorphous form.[1-2] Different Crystal form may influence the physical, chemical, and mechanical properties of solids. Therefore, the solid state properties of the API and the excipients must be understood in order to ensure consistent product performance.[3]

Even if the identification and characterization of crystal forms are performed thoroughly and the appropriate crystal form is selected for development, it is important to ensure that the crystal form in the final product remains unchanged. During production, certain unit operations such as heating, milling, and exposure to solvent may present favourable conditions for a change in crystal form.[4] Therefore, the possibility of crystal form alteration during formulation and process development must be considered. The potential phase transformations that can occur during common pharmaceutical processing operations, the underlying mechanisms, anticipation/ prevention, and impact on product quality are important to be considered during manufacturing of dosage forms.[5]

Phase transition:

A phase transition is the transformation of a thermodynamic system from one phase or state of matter to another. During a phase transition of a given medium certain properties of the medium change, often discontinuously, as a result of some external condition, such as temperature, pressure, and processing conditions.

Mechanisms phase transformations:

Knowledge of the mechanism of phase transitions is very helpful in identifying the potential for such transitions and the factors affecting their kinetics. Such a mechanistic understanding facilitates rational formulation design and the selection of robust processes to ensure consistent product manufacturing and performance. Ensure consistent product manufacturing and performance.[6-7]

[1] Solid State:

Some phase transitions occur in the solid-state without passing through intervening transient liquid or vapour phases. The kinetics of phase transition via a solid-state mechanism is influenced by the environment like temperature, pressure, relative humidity the presence of crystalline defects, particle size and distribution, and impurities.

[2] Melt:

When a compound is heated above its melting point, and is subsequently cooled back to the ambient temperatures, the original solid phase may not be regenerated. Therefore, through this heating/cooling cycle, a phase transition may occur. Among the factors determining the final solid phase are the relative rates of nucleation, crystal growth, and cooling. Impurities or excipients are also likely to affect the course of crystallization.

[3] Solution:

Very often the drug will be dissolved, or partially dissolved, in a solvent (typically water) during processing. If subsequent solvent removal induces a transformation, this transformation mechanism is considered a solution mechanism. For instance, the drug may partially dissolve in water during wet granulation, or it may completely dissolve in water during freeze-drying or spray drying. Once the solvent is removed, the solid drug will be regenerated from the solution. The regenerated solid may not be the same crystal form as the original phase and it may consist of a mixture of phases. Thus, through solvent removal, a phase transition may occur.

[4] Solution-mediated:

The solution- mediated mechanism only allows the transition from a metastable phase to the stable phase. This type of transformation is driven by the difference in solubility between the two phases. In contrast to the solution mechanism where transformation occurs during drying, the solution-mediated mechanism operates when the metastable phase is in contact with the saturated solution. Three consecutive steps are involved in a solution mediated transformation:

- Initial dissolution of the metastable phase into the solution to reach and exceed the solubility of the stable phase.
- Nucleation of the stable phase.
- Crystal growth of the stable phase coupled with the continuous dissolution of the metastable phase.

Nucleation is rate-determining any factor that affects nucleation will influence the overall transformation. These factors include solubility and solubility difference between the phases, processing temperature, contact surfaces, agitation, and soluble excipients/ impurities. When crystal growth is the rate-controlling step, the kinetics of the conversion is determined by solubility difference, solid/solvent ratio, agitation, processing temperature, particle size of the original phase, and soluble excipients/impurities.[8-9]

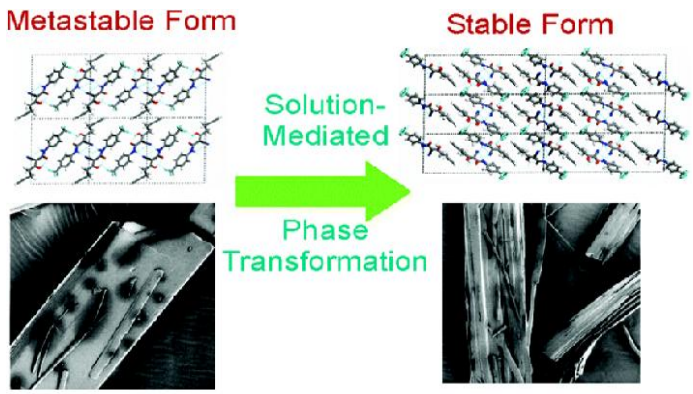

Figure 1: Solution mediated transformation

Analytical techniques used to characterize phase transitions:

The prediction and control of possible processing-induced phase transformations (PITs) may be complicated. To adequately control the process, changes in solid state need to be examined and mechanisms of conversions understood. Several guidelines and strategies have been developed which list the analytical methods and tests that can be used to help the characterization of solid state systems of API .Proposed techniques allow the full characterization of hydrates in situ after preliminary crystallization which is needed for scientific and regulatory purposes. However, methods are also needed for further steps in drug development and manufacturing providing information about the behavior of APIs under processing conditions. Final product testing and a process validation alone, do not guarantee a sufficient quality, efficacy and control. The in-line, on-line and at-line monitoring with process analytical technology (PAT) tools allow deeper insight into process understanding and can reveal the potential phase transformations during manufacturing. Thus, the stability of final product upon storage can be assured.[10]

1. Molecular level properties characterized by:

- Fourier transform infrared absorption spectroscopy.
- Solid state nuclear magnetic resonance spectroscopy.
- Raman spectroscopy.

2. Particle level properties characterized by:

- X-Ray diffraction analysis.
- Optical microscopy.
- Hot stage microscopy.
- Scanning electron microscopy.
- Differential scanning calorimetry.
- Thermogravimetric analysis.

Unit processes for preparing solid dosage forms:

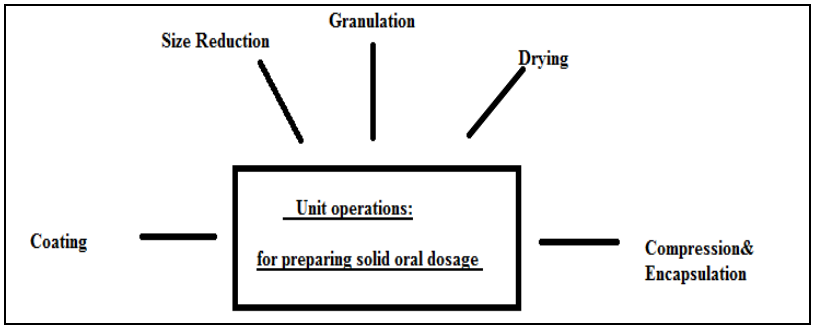

Figure 3: Unit Processes for preparing solid dosage forms

Commonly used methods and associated unit operations for preparation of solid dosage form are size reduction, granulation and drying as shown in Figure 3 summarized above. This processes impact on solid phase transformations. [11-13]

1. Size Reduction:

The first step during solid product processing often involves size reduction. Size reduction facilitates subsequent processing and may enhance product performance (e.g. through improved morphology/ flow properties, minimized segregation, enhanced uniformity, increased surface area, etc). The principal means for accomplishing size reduction is by milling, which involves shearing/cutting, compressing, impacting or attrition of drug particles. Impact mills (e.g. hammer mills) and fluid-energy mills (e.g. jet mills) are widely utilized in the pharmaceutical industry. Since impact milling typically imparts mechanical stress and often generates heat, it may induce phase transitions, such as polymorphic transitions, dehydration, or vitrification via solid-state or melt mechanisms. The rate and extent of these phase transitions will depend on characteristics of the original solid phase, the type of mill and the milling conditions. Digoxin, spironolactone and estradiol are reported to undergo polymorphic transformations during the combination process.

2. Granulation/Size Enlargement:

Granulation methods are used to impart the required characteristics like, physical characteristics including flowability, cohesiveness, compressibility and lubrication.

There are two commonly used methods of preparing granulations for tablet compression or capsule manufacture:

- Wet granulation.
- Dry granulation.
- Melt granulation.

Other granulation processes include spray drying and melt granulation, such as high shear melt pelletization, spray-congealing, and melt-extrusion.

A) Wet Granulation:

Wet granulation is most widely used due to its versatility, and the greater probability that the resulting granules will meet the physical requirements for further processing.[26] The potential for phase transition of a substance will depend not only on its properties, but also on the conditions and the methods used for granulation and drying. Conditions such as the amount of liquid used for granulation, the exposure time of the solid to the liquid, air flow, drying temperature, etc. vary with granulation and drying methods the method used for granulation and drying may influence the phase formed in the dried granules. Thus, in addition to the properties of the API, the granulating and drying conditions and methods will determine whether solution or solution-mediated phase transformations, such as polymorphic conversion, hydration/dehydration or vitrification/crystallization will occur. When poorly soluble drugs are suspended in the granulating fluid the anhydrous phase will tend to convert to a hydrate via a solution mediated transformation.

B) Dry granulation*:*

Dry granulation is typically used when the formulation ingredients are sensitive to moisture or when they are unable to with stand an elevated drying temperature. It is also used when the formulation ingredients have sufficient inherent binding or cohesive properties. Slugging and roller compaction are the two most commonly used dry granulation methods. However, the applied mechanical stresses during processing may lead to phase transformation via the solid-state or melt mechanisms.

C) Melt granulation:

The melt granulation process consists of partially or completely melting solid excipients, then granulating with the API and other excipients, followed by reducing the mixture to granules by chilling and congealing. During this process, the API is subjected to heat, and may be partially or completely dissolved in the molten excipient. If the melting point is relatively low or the heating temperature is sufficiently high, the API may melt during processing. Partially or completely melted API may also serve as a binder or congealing carrier. Subsequent cooling could induce phase transitions through the solid-state or melt mechanisms. In a

spray-congealing process, a low melting point carrier is employed to provide the fluidity necessary for spraying. At high temperature, all or a fraction of the drug may be solubilized in the molten carrier. During spray-congealing, the hot droplets cool rapidly and solidify. Since rapid cooling/congealing is required for the formation of small particles with a narrow size distribution, it is possible that the drug may precipitate as an amorphous phase or as a metastable crystal form, following Ostwald's rule of stages likely to initiate phase transition.

3. Drying:

Spray drying produces powder particles that are homogenous, porous, uniform in size and shape. The technique may also be used for encapsulating or coating drugs, to provide protection or release rate control. This process requires complete or partial dissolution of the drug in a solvent, thus increases the likelihood for phase transitions involving solution mechanism. While the conditions for freeze-drying can have a major influence on the solid phase of the drug in the product.

4. Compression and Encapsulation:

Lubricated granules are either compressed into tablets or filled into hard gelatin capsules. During tableting, granulations may be subject to compression forces as high as 40 kN with dwell times on the order of a few milliseconds. An energy impact of this magnitude may cause solid phase changes in either the API or the excipients via the solid-state mechanism. For example, caffeine, sulfabenzamide, and maprotiline hydrochloride have been reported to undergo polymorphic transformations during compression.

5. Coating:

When manufacturing finished tablet dosage forms, a film coating is often applied as an aqueous or solvent-based polymer system in coating pans or in a fluid-bed. The film coating process involves the application of a thin polymer based coating to an appropriate substrate (tablets, granules, or crystals) using a spray-atomization technique and thus the interaction between the core material and the coating liquid is generally minimal during film coating. In most cases it is unlikely that a phase transition will occur via the solution mechanism during film coating. When necessary, prior to application of the film coat, a polymer based seal coat may be applied to the surfaces of the tablet cores. This will prevent a solid–liquid interaction from occurring during the film coating process. For modified release products, a portion of the total dose may be applied as a drug coating layer. Dissolving or suspending the drug in a liquid increases the potential for phase transitions to occur through the solution or solution-mediated mechanism.

Influence of solid phase and process-induced phase change in product quality:

The important quality attributes of a solid product include stability, dissolution, bioavailability, appearance, manufacturability, density, hardness, etc., all of which may be influenced by phase transformations. In general, the influence of phase transitions on dissolution/bioavailability is of major concern for insoluble drugs because such transitions often can lead to changes in solubility as well as other characteristics of the API in the dosage form e.g. particle size. Phase transitions may impact stability or processing characteristics of both soluble and insoluble molecules. Solid-state physical stability is highly dependent on the environmental conditions, during processing, the API is often exposed to temperature, pressure and humidity changes, and process-induced phase transformations can potentially occur. Commonly encountered process-induced phase transitions include partial or complete formation of metastable polymorphs, an amorphous phase, and hydrates/solvates or desolvated forms depending on the API and processing conditions.

Metastable polymorphs with different solubilities and stabilities may be slowly converted to other metastable polymorphs or to the thermodynamically stable form over time, resulting in variations in the stability and dissolution performance of a dosage form on storage. The amorphous form typically has poorer physical stability, higher solubility, and increased chemical reactivity even if it is physically stabilized in certain cases. Recrystallization of the amorphous phase of either drug or excipient over time may also affect other properties of a tablet (e.g. hardness, disintegration, and dissolution). Excipients may facilitate conversion to the amorphous drug, which may subsequently compromise chemical stability (example in the following section given below).

Hydration–dehydration cycles of a solid API may lead to formation of a (1) metastable or stable form, (2) an amorphous form, or (3) mixtures of various crystalline forms including other hydrates or solvates. All of these solid phase changes can have detrimental effects on product quality.[14]

Anticipation and prevention of phase transformations:

To anticipate and prevent solid phase transitions during manufacturing it is critical to have a thorough understanding of crystal forms and the amorphous phase of the API and excipients, as well as the interconversion mechanisms and processing options. This integrated knowledge is essential for the rational selection of the physical form of the API, the excipients, the manufacturing process, and for the selection of appropriate handling and storage conditions. In certain cases even after the solid form and the preferred process are defined, it is advisable to monitor the crystal form of all incoming raw materials and the physical forms present in the final dosage unit.

This monitoring is especially important in cases where dissolution or stability of the product is very sensitive to solid phase changes. The rigor used in monitoring will depend on the API, formulation, process, and analytical method. For a highly soluble, stable and bioavailable molecule, the risk of process-induced phase change on stability and bioavailability may be relatively low. However, process-induced phase changes in excipients and/or the API may impact manufacturability or disintegration of the dosage form.

Following ways to anticipate phase transformations:

In selecting the crystal form of an API for development, the physicochemical, biopharmaceutical, and processing properties must all be taken into consideration. In some cases, it may be necessary to select an alternate crystal form in order to eliminate stability issues, dissolution rate differences or process-induced phase transitions. It is desirable to choose the crystal form that is least susceptible to phase transformations induced by heat, moisture, and mechanical stresses provided the API's biopharmaceutical and processing characteristics are acceptable.

Sometimes an alternate salt having fewer crystal forms may be chosen to minimize process-induced transitions. Phase transitions in crystalline excipients and their impact on product performance also cannot be ignored. For example, process-induced age-hardening in tablets may lead to a decrease in dissolution rates during storage of formulations containing a high level of crystalline excipients such as mannitol. If process induced hardening is anticipated, variable product dissolution can be minimized through the use of intra and extra-granular super disintegrants, or by selecting alternative excipients. Excipients are considered to be inert in therapeutic or biological actions; they may prevent unwanted phase transitions and ensure the required stability of the drug in the formulation during the manufacturing process and storage. In designing manufacturing processes for solid dosage forms, process-induced phase transformations can be anticipated based on preformulation studies. These transformations can be controlled and circumvented by selecting the appropriate process. If a solid phase is sensitive to moisture or to solvent, a dry or melt granulation may be used. If a drug substance undergoes an undesirable transition during milling or compression, melt granulation through melt-extrusion may be more desirable provided the drug is thermally stable. It may be possible to avoid milling the drug substance if particle size and shape can be controlled during crystallization.[15]

Conclusion

The quality and performance of solid oral dosage forms depend on choice of solid phase, formulation design, as well as on the manufacturing process. An important aspect of the relationship of dosage form processing to product quality is the potential for process-induced solid phase changes of the API during manufacturing processes. Therefore, rational formulation and process designs require an integrated knowledge of solid state properties drugs, API and its polymorphism, interconversion mechanisms and available processing options. In order to insure consistent product quality performance, it is essential to anticipate, control or prevent phase transformation in process design and development.

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