Drying Pharmaceutical Solids—Hydrates and Enantiotropic Polymorphs

“Pharmaceutical Solids” discusses scientific principles associated with pharmaceutical solids useful to practitioners in validation and compliance. We intend this column to help the understanding of principles associated with pharmaceutical solids and to be a useful resource for daily work applications. Enhanced process understanding is an important objective of the quality-by-design initiative. The key objective for this column: Usefulness.

Readers comments, questions, and suggestions are needed to help us fulfill our objective for this column. Please send your comments and suggestions to column coordinator John Bauer at consultjb@comcast.net or to journal coordinating editor Susan Haigney at shaigney@advanstar.com.

KEY POINTS

The following key points are discussed in this article:

- Hydrate is a broad term used to describe the various ways that water can be incorporated into the crystal of a pharmaceutical solid
- Dehydration of different hydrates requires different amounts of energy
- The most useful analytical methodologies for studying dehydration are thermogravimetric analysis (TGA), differential scanning calorimetry (DSC), hot stage microscopy, and hot stage X-ray diffraction (XRD)
- Pharmaceutical dryers can heat by either convection or conduction
- Changes in dryer types or drying parameters should require validation
- Near-infrared spectroscopy (NIR) is a reliable process analytical technology (PAT) technique for monitoring drying
- Drying temperatures must avoid the transition temperature for enantiotropic systems
- Drying can lead to dehydration of hydrates leading to desired or undesired solid form changes
- Drying can impact other physical properties of solids including particle size and shape
- Drying can lead to surface and interstitial activated sites in pharmaceutical solids
- Validation and compliance practitioners should understand critical material properties that may be affected by process parameters. These should also be considered when evaluating manufacturing equipment and process changes.

INTRODUCTION

As reported in previous columns, this author has been involved in several manufacturing problems. Often when investigating the manufacturing processes, whether bulk drug or dosage form, there are extensive details given about the crystallization, blending, and compressing processes but only a simple report that the “material was dried.” In fact, the drying process can be critical in the case of some pharmaceutical solids. Two examples discussed in this article are hydrates and enantiotropic polymorphic systems. Emphasis on the details and an understanding of the impact of the drying operation are important in controlling and troubleshooting many manufacturing processes.
HYDRATES
Manufacturing processes often refer to drying the pharmaceutical solid when the actual end result is dehydration of the crystalline hydrate. Drying requires only enough energy to evaporate the free water associated with the solid as a result of product isolation. Dehydration of the crystalline material, on the other hand, requires additional energy to overcome whatever forces maintain the water of hydration within the crystal structure.

The term hydrate is generally applied broadly to crystals that have water incorporated into the structure, whether in a specific stoichiometry or not. In actuality, there are distinctly different ways of incorporating water into the solid. Consequently, the ease with which the water is removed can vary greatly.

Figure 1 shows three ways in which water can be incorporated into a crystal. The first (cavity type) involves water molecules isolated from one another by parts of the host molecule as if trapped in small enclosed compartments or cavities within the crystal. The second (channel type) involves water molecules interacting directly with each other and that group of water molecules occupying or filling a channel or tunnel within the crystal. The third (cation-attached type) involves water molecules bound or attracted through the oxygen molecule to some specific positive site in the crystal such as a cation like sodium or calcium. In addition to these reasonably strong hydrate attractions, it is also possible for a solid to have water adsorbed on the surface through relatively weak electrostatic attraction.

ENANTIOTROPIC SYSTEMS
As discussed in a previous installment of this column (1), many crystalline pharmaceutical solids can
exhibit polymorphism, that is, they can exist in a multiple of symmetric arrangements or crystal lattices. At any given combination of temperature, pressure, and humidity, one of the crystal forms will have the lowest energy and be the most stable arrangement and preferred form. Under favorable energetic conditions, the other forms will transform to the most stable form. In some systems, called enantiotropic systems (Figure 2A), one crystal form is more stable at higher temperatures and a different form is more stable at lower temperatures. In a large percentage of cases, one crystal form is most stable regardless of temperature. These systems are referred to as monotropic systems (Figure 2B).

WHY DRY?
Because of the variety of ways water molecules bind in pharmaceutical crystals, saying a solid was dried can be a very misleading statement. Sometimes not enough thought is put into drying during development. The first question to be asked is “why are we drying the solid?” Do we want to dry it to remove the surface water and minimize potential bacterial growth? Do we simply want to produce a non-hygroscopic solid for reliable weighing? Do we want to obtain a stable hydrate or remove the water of hydration also? Do we want to produce a crystalline anhydrate? Selection of the dryer type, drying temperature and time depends greatly on the drying goal. Once the drying parameters have been established, they should not be changed without revalidation.

Looking at Figure 1, we might propose a generalization that the surface water would be easiest to remove, the water from channels (Figure 1-2) next easiest because they have a natural exit, and the cation-attached (Figure 1-3) and cavity (Figure 1-1) water would require the most energy. In the case of cavity water, it does not appear that it can be removed without seriously disrupting the crystal and would, therefore, likely result in a change in solid form.

ANALYTICAL TOOLS
Thermogravimetric analysis (TGA) in conjunction with differential scanning calorimetry (DSC), hot stage microscopy, and hot stage X-ray diffraction (XRD) with or without vacuum applied, are the best techniques to investigate the impact of drying on pharmaceutical solids. TGA (see Figure 3A) uses a microbalance to record changes in sample weight under a programmed heating cycle. The y-axis registers the sample weight (as % of original) and the x-axis registers the temperature.

DSC (see Figure 3B) uses a similar programmed heating cycle but plots temperature against the heat flow in the sample. Changes in heat capacity reflect changes in state such as melting and recrystallization or dehydration.

Figure 4 shows an overlay of TGA and DSC scans of the fluoroquinolone broad spectrum antibiotic saraflaxin (2). The stable hydrate of this drug contains approximately 11% water. As can be seen in Figure 4, the water is released in three portions at different temperatures, indicating that these water molecules are bound in different ways within the crystal.

The DSC scan indicates three endothermic (downward) peaks reflecting three energy consuming dehydrations followed by an exothermic (upward) peak indicating the energy emitting decomposition of the

Figure 2: Enantiotropic (2A) and monotropic (2B) polymorph systems.
drug. These data clearly indicate that drying sarafloxacin at 60°C or 110°C would result in weight loss but would not completely dehydrate the solid.

Referring to Figure 1, it is easy to understand that water would have an easy exit from the channel type hydrate where the water can simply exit through the tunnel or channel it occupies. In fact, if a crystal of this type is suspended in mineral oil and heated on a hot stage microscope, droplets of water can be observed streaming from specific sites on the crystal. This type of hydrate can be dehydrated with a relatively small amount of energy. The water can be removed with low heat, with vacuum, or even with a strong desiccant. Therefore, using excessive temperature is unnecessary and can possibly lead to degradation or produce free mobile water that can facilitate changes in physical states of drug and excipients. Again, it is important to understand the purpose of the drying process. The water in this type of hydrate can be very labile and non-stoichiometric. The amount of water in the channels may vary, equilibrating with environmental humidity. This could lead to weighing or dispensing errors if the humidity is not controlled.

Over drying, on the other hand, can lead to more serious problems. At least part of the water of hydration in erythromycin dihydrate is located in channels. Bauer, et al. (3) reported an example of over drying affecting the performance of erythromycin tablets. When the water is removed from a channel hydrate, it generally does not affect the crystal form of the drug but leaves behind an activated cavity that can rapidly reabsorb water or a similar hydrogen bonding solvent, or small molecule. In the situation described in the erythromycin paper, the activated erythromycin interacted with the excipient magnesium hydroxide, which significantly slowed the dissolution rate of the tablets.

Dehydration of cation-attached hydrates requires enough energy to overcome the interaction between the water oxygen and the positive site on the molecule. This would be expected to require a higher temperature and lower vacuum to vaporize the water and remove it from the crystal. Removal of this water may or may not affect the crystal form and/or conformation of the drug, depending on whether the water is necessary to maintain a given conformation as in some proteins. Hot stage XRD can be used to monitor crystal form changes with increasing temperature. This technique records the X-ray crystal pattern at varying temperatures and can be used to investigate the possibility of form changes during drying.

In dehydrating both of these types of hydrates, it is necessary to remove the water from the environment around the drug, or re-absorption of the water is probable. Dehydration of cavity-type hydrates requires enough energy to not only mobilize the water in either the liquid or gaseous state but also to break through the portion of the crystal enclosing the water molecules. This often will result in destruction of the crystal lattice and creation of disordered or amorphous regions. These amorphous regions will be more prone to degradation and to re-absorption of water. In some cases, the disordered crystal will rearrange to a stable anhydrous crystal form. This is the case with the antihypertensive compound terazosin. Terazosin exists as a stable dihydrate but can be dried to produce a stable anhydrous form.

In some cases of hydrates, regardless of the type, heating to a higher temperature than necessary can cause the dehydrated hydrate to recrystallize to a stable anhydrous form. Figure 5 shows the DSC curve for erythromycin dihydrate (4) that contains
an endothermic peak for dehydration [1] and a small endothermic peak for either melt of the dehydrated hydrate and/or liquification of the amorphous material [2]. This is followed by exothermic crystallization of the monohydrate form [3] and subsequent dehydration and melt of the monohydrate form [4]. The TGA shows a weight loss of approximately 4.5% at temperatures below 80°C, corresponding to a dihydrate. This hydration is of the channel type. This is confirmed by the fact that this water can also be removed using a desiccant like P₂O₅ without change in X-ray pattern. A second weight loss appears around 180°C corresponding to water from the monohydrate that crystallized after the dehydrate melt at 135°C. This example illustrates how complicated the simple drying of a pharmaceutical solid can be.

DRYERS
Drying in general requires the simultaneous transfer of heat, mass, and momentum whereby heat penetrates into the solid or mixture and moisture is removed by evaporation into an unsaturated gas phase. In some instances heat is not required and water can be removed based on a moisture concentration or affinity gradient between the solid and the atmosphere surrounding it, such as a desiccated chamber. Most dryers can be divided into those that dry by convection and those that dry by conduction. Convection dryers work indirectly by exposing the material to be dried to heated or very low moisture air that flows across or through the solid or mixture and removes the water from the solid. Conduction dryers use direct contact of the solid with a heated surface. Some of the most commonly used pharmaceutical dryers are as follows:

- **Belt dryer.** Belt dryers pass a conveyer belt with the drug or mixture to be dried spread in a thin layer through a chamber where hot air is passed up and down through the material to dry it evenly.
- **Fluid bed dryer.** A fluid bed dryer passes dried air through a fluidized layer of solid particles.
- **Spray dryer.** A spray dryer sprays wet material as a fine mist into a hot air chamber collecting the dried solid on the bottom.
- **Rotary dryer.** A rotary dryer tumbles and rotates the material in a drum that has several heated surfaces and/or is fed with heated air.
- **Vacuum tray dryer.** A vacuum tray dryer is the most commonly used batch dryer in which the material to be dried is spread out on trays that are then placed on heated plates mounted like shelves in the box-shaped dryer. These are operated under vacuum or with a heated medium flowing through the chamber.

Figure 4: Overlay of TGA and DSC curves for sarafloxacin.
• **Lyophilizer.** A lyophilization process comprises freezing of a solution of the pharmaceutical solid, followed by sublimation of frozen water under reduced (micron levels) chamber pressure.

Unvalidated use of any of these dryers or dryer settings can have a dramatic impact on the resulting dried solid. Again it is very important to understand the goal of the drying process when choosing and programming the dryer. Any of the above dryers would remove surface water and water of hydration in channel type hydrates. However, those using only heated air to dry may not remove water of hydration from cavity and cation-attached hydrates. Overheating a channel hydrate using a direct contact dryer may lead to increased degradation and/or loss of crystallinity. Removing all the water from a solid cake can reduce compactability and compromise compressibility.

Overheating of mixtures can cause undesirable dehydration of excipients like lactose hydrates or unexpected competition between excipient and drug for any available water. For example, when terazosin dihydrate was over dried in the presence of polyethylene glycol (PEG), the disordered terazosin solid could not compete successfully with PEG for any available water and recrystallized into a previously unknown anhydrate form. The anhydrate form had significantly different aqueous solubility characteristics that impacted the formulation pharmacokinetics (5).

**PROCESS ANALYTIC TECHNOLOGY**

During process development, it is important to understand and model to the best extent possible the drying process using TGA, DSC, hot stage microscopy, and when available, controlled temperature and humidity X-ray. Initial and final water content can be quantitatively determined using Karl Fischer titration or gas chromatography. These techniques, although very accurate and useful, require offline testing and numerous samplings. They also supply only average water content values.

In some dryers, it is possible that the contact between heated air or heated surface and the solid is not uniform, resulting in an unevenly dried batch similar to a poorly-baked cake with an overly moist center and over-dried edges.

Near infrared spectroscopy (NIR) has been used successfully as both an online and in-line water content monitor for following the extent and uniformity of the drying process. NIR is a somewhat unique technique in that it shows distinct bands corresponding to water in a sample (see Figure 6). Note the differences in respective peaks of lot 1 and lot 2 at approximately 2.0 micrometers. The differences in the peak splitting and shape indicate water incorporated into different sites in the two lots. Quantitation can be achieved based on peak area or height, validated against Karl Fisher or gas chromatography measurements. In some cases (6), it is possible to use the techniques to examine the actual movement of water within a crystal.

**TRANSITION TEMPERATURE**

Because most pharmaceutical solids and/or mixtures are isolated from aqueous media, they are usually dried whether or not they are hydrates. In the case of non-hydrates, the most critical aspect of the drying operation is the extended time at elevated temperature.

Referring again to Figure 2A, there is a temperature \(T_0\) in the enantiotropic system where both forms have equal energy and are equally stable. Drying a solid at or near this temperature can result in a mixture of crystal forms, while drying significantly above or below this transition temperature would yield only one form which may not be the form desired. Therefore, good control of the temperature in validated equipment during drying can be critical when dealing with enantiotropic systems. The labile range around the \(T_0\) is dependent on the specific system and should be carefully evaluated by hot stage XRD during development.

**OTHER PHYSICAL CHANGES**

This discussion has focused on changes in crystal form of a material during the drying process. There also may be changes in physical characteristics such as particle size, surface area, and particle shape. These properties were discussed in a previous column (7). Dried solids will have different particle characteristics after being

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**Figure 5:** DSC of erythromycin dihydrate with vent for moisture.

[Diagram showing DSC with peaks labeled 1 to 4, indicating temperature ranges from 50 to 250°C.]
Lyophilized compared to being oven dried on trays or to being dried in a fluidized bed dryer. Lyophilized solids will likely be fragile amorphous solids (depending on concentration of the original solution); oven-dried solids will likely be lumps of varying sizes; solids dried in a fluidized bed dryer will likely be uniform, generally spherical particles of relatively smaller particle size. Subsequent pharmaceutical processing will need to consider the varying particle size impact of the drying process.

**PRACTICAL CONSIDERATIONS—IMPLICATIONS FOR COMPLIANCE AND VALIDATION**

This discussion has described technical considerations involved in drying pharmaceutical solids, specifically for drying of hydrates and enantiotropic polymorphic systems. These considerations are critical in manufacturing process control, preventing manufacturing problems, and troubleshooting problem occurrences. Validation and compliance practitioners should be wary of the following areas.

**Understanding Solid-State Physical Properties And Potential Processing Effects**

It is a standard requirement for pharmaceutical companies to perform polymorph studies on the new chemical entities (NCE) in development. These studies usually involve solvent-mediated processes and simple heating. For the most part, they look at crystal form transitions and desolvation including dehydration. They include some stability studies at normal storage temperatures and perhaps an elevated temperature. These data are very useful for understanding some of the potential problems that may be involved in drying. They do not, however, consider such factors as vacuum and continuing humidity changes in the atmosphere around the drug due to air flow. Development scientists generally determine dehydration temperatures by TGA but are not concerned with the impact of temperature and pressure combinations. The author would recommend that these studies be expanded to include some typical manufacturing drying conditions such as vacuum drying at 50°C or conventional oven drying at 85°C.

**Considerations During Product And Process Development**

In this era of accelerated development, formulation development occurs concurrently with NCE synthesis, and consequently, development lots of active ingredient may have been dried differently especially as lot size increases. Early lots may be dried by lyophilization or solvent stripping, then drying could change to tray drying or rotary drying as the lot sizes increase.
Ideally these data would be combined to define a design space in the process justification report, within which the compound and or formulations of the compound can be safely dried.

Without good understanding of material properties and the effects of drying temperature, critical and expensive development programs may be at risk. Instances of polymorphic changes that unknowingly occurred during development with disastrous consequences are known.

**Change Control**

All aspects of drying processes must be considered when changes to the drying process are being considered. For example, a change from a tray drying process to a fluidized bed dryer may be required to increase the process throughput. Drying temperature changes and their effects on the material must obviously be considered. If, for example, no drying temperature changes were necessary, one could safely conclude that there would be no effects on the stability or the polymorphic form of the solid. However, significant particle size changes are likely because of the process change. These particle size effects may affect subsequent downstream processing including blending, tableting, encapsulation, and so on. Often the most simple change will result in unexpected effects on solid physical properties with very significant ramifications.

**CONCLUSION**

Drying is a highly energetic operation, and it is important to understand the impact of that energy input on the pharmaceutical solid that is being dried. Sometimes there will be no effect of the heat except to remove any residual volatile solvents including water from the surface of the solid. There are other cases in which chemical decomposition could be the result of excess heat. This paper has discussed an additional situation in hydrates and enantiotropic systems where the heat of drying can cause changes in the crystalline lattice of the solid and consequently effect its properties. This phenomenon can be difficult to detect if there is uneven drying occurring and, therefore, a non-uniformity created within the batch. This can lead to a quality concern in the finished dosage form.

It is very important that the drying operation and its impact be well understood and validated when designing a manufacturing process and that a comprehensive process justification be performed. Any deviations or changes to the manufacturing equipment and process should be carefully evaluated and may require validation.

**REFERENCES**


**ARTICLE ACRONYM LISTING**

| DSC | Differential Scanning Calorimetry |
| NCE | New Chemical Entity |
| NIR | Near Infrared Spectroscopy |
| PAT | Process Analytical Technology |
| TGA | Thermogravimetric Analysis |
| XRD | X-Ray Diffraction |