Polymorphism in Pharmaceutical Solids

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Structural Aspects of Hydrates and Solvates

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I. PHARMACEUTICAL IMPORTANCE OF CRYSTALLINE HYDRATES

The potential pharmaceutical impact of changes in hydration state of crystalline drug substances and excipients exists throughout the development process. The behavior of pharmaceutical hydrates has become the object of increasing attention over the last decade, primarily due (directly or indirectly) to the potential impact of hydrates on the development process and dosage form performance. Substances may hydrate/dehydrate in response to changes in environmental conditions, processing, or over time if in a metastable thermodynamic state [1].

It may not be practical or possible to maintain the same hydrate isolated at the discovery bench scale synthesis during scale-up activities for a hydrated compound. The choice of counterions to produce a more soluble salt form may also be dictated by the extent and type of hydration observed for a given salt and/or by the moisture level that may be safely accommodated by the dosage form [2].

The physicochemical stability of the compound may raise issues during preformulation. Some hydrated compounds may convert to an amorphous form upon dehydration and some may become chemically labile. This is true of cephradine dihydrate that dehydrates to become amorphous and undergoes subsequent oxidation. Other compounds may convert from a lower to a higher state of hydration yielding

forms with lower solubility. In any case, the resulting "new" forms would represent unique entities that, depending on the dosage form, might have to be maintained throughout the manufacturing process and in the clinic and would impact on the regulatory status of the compound. Most often this demands that the form (usually crystalline) be identified and characterized with respect to handling conditions during the early pre-IND stage of the development process.

As dosage form development proceeds, changes in hydration state can result in variable potencies depending on handling conditions during weighing steps, the kinetics of the hydration/dehydration process, and the environmental conditions during processing. Differences in powder flow can result from changes in crystal form and/or morphology that may accompany the hydration/dehydration process. This can affect content uniformity in solid processing either in the mixing process or during transfer to other processing equipment such as tablet presses. Aqueous granulation, particle size reduction, film coating, and tablet compression all provide opportunities to "trap" a compound in a metastable form that may "relax" to a more stable form at some unpredicted point in the life of a dosage form. Alternately, a kinetically favored but thermodynamically unstable form may be converted during these processes to a more stable and less soluble form.

During and after manufacturing, moisture from the environment or that sealed in the package may redistribute throughout the dosage form and change the hydration state(s). These changes can, in turn, visit the negative consequences discussed above for the bulk drug on the dosage form. These can be manifest as changes in tablet/capsule dissolution rates (and perhaps bioavailability), changes in lyophile reconstitution times, tablet capping, chemical instability, discoloration, and more. Of course, the potential for changes in hydration state also exists for many pharmaceutical excipients (such as lactose or magnesium stearate).

Such problems are typically magnified as both synthetic and dosage form production is scaled up. This may be caused by solvent limitations, heat transfer differences in production equipment, changes in raw materials and/or raw material suppliers, changes in processing times, and time and control constraints on product storage, to name a few.

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