Polymorphism in Pharmaceutical Solids

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Preface

Since the middle of the last century, it has been noted that organic molecules can be obtained in more than one distinct crystal form, a property that became known as polymorphism. Once experimental methods based on the diffraction of x-rays were developed to determine the structures of crystalline substances, it was quickly learned that an extremely large number of molecules were capable of exhibiting the phenomenon. In addition, numerous compounds were shown to form other nonequivalent crystalline structures through the inclusion of solvent molecules in the lattice.

It was also established that the structure adopted by a given compound upon crystallization would exert a profound effect on the solid-state properties of that system. For a given material, the heat capacity, conductivity, volume, density, viscosity, surface tension, diffusivity, crystal hardness, crystal shape and color, refractive index, electrolytic conductivity, melting or sublimation properties, latent heat of fusion, heat of solution, solubility, dissolution rate, enthalpy of transitions, phase diagrams, stability, hygroscopicity, and rates of reactions are all determined primarily by the nature of the crystal structure.

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Structural Aspects of Hydrates and Solvates

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HARMACEUTICAL IMPORTANCE OF RYSTALLINE HYDRATES

otential pharmaceutical impact of changes in hydration state of lline drug substances and excipients exists throughout the devel- nt process. The behavior of pharmaceutical hydrates has become)ject of increasing attention over the last decade, primarily due tly or indirectly) to the potential impact of hydrates on the devel- nt process and dosage form performance. Substances may te/dehydrate in response to changes in environmental condi- processing, or over time if in a metastable thermodynamic state

t may not be practical or possible to maintain the same hydrate d at the discovery bench scale synthesis during scale-up activities ydrated compound. The choice of counterions to produce a more e salt form may also be dictated by the extent and type of hydra- bserved for a given salt and/or by the moisture level that may ely accommodated by the dosage form [2].

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

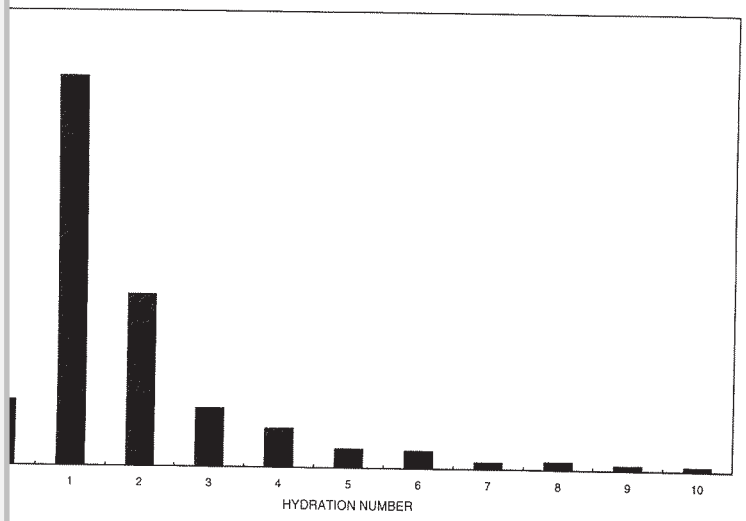
forms with lower solubility. In any case, the resulting ''new'' forms would represent unique entities that, depending on the dosage form, might have to be maintained throughout the manufacturing process and in the clinic and would impact on the regulatory status of the compound. Most often this demands 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.

e arguments just provided detail the potential issues around
s in the development process. The other consideration is the
cy with which hydrates are encountered in real life. Focusing
e drug substances, it is estimated that approximately one-third
harmaceutical actives are capable of forming crystalline hy-
3]. A search of the Cambridge Structural Database (CSD) shows
roximately 11% of all the reported crystal structures contain
ar water [4]. This represents over 16,000 compounds. If organ-
c compounds are excluded, this number drops to approximately
.8%), and the breakdown of these according to hydration num-
own in Fig. 1. This shows the expected trend in which monohy-
re most frequently encountered, and where the frequency de-
almost exponentially as the hydration number increases. The
lrate stoichiometry occurs approximately as frequently as the
te, which should serve as a caution to explore fully the occur-
fractional hydration. That is, an apparent stoichiometry of 0.6
olecules could be a partially dehydrated monohydrate, or it



Occurrence of various crystalline hydrate stoichiometries.

could be a hemihydrate with additional sorption due to defects or amorphous material.

The symmetry of these hydrate crystals follows fairly closely with that reported for organic structures overall [5]. Table 1 shows the breakdown for space groups, organized by crystal system, accounting for the top approximately 90% of the structures. $P2_1/c$ (number 14) is the most common space group here as with the general population of organic molecules contained in the CSD. It has been reported for inorganic species that hydrated structures are generally of lower symmetry than are their anhydrous counterparts [6]. This is attributed to the fact that the highest symmetry associated with the water molecule is C_{2v} and most inorganic structures are of higher symmetry. This is not obviously the case for organic structures. Regardless of the solvation state, organic molecules generally exhibit lower symmetry than do inorganic compounds, so the impact of the symmetry constraints imposed by water does not appear to be the controlling element. Further comparisons would be required to explore the phenomena fully.

Table 1 Space Groups for the Top 90% of Organic Crystalline Hydrates in the Cambridge Structural Database

Space group	Crystal system	Percent occurrence
P_{-1}	Triclinic	15.5
P_1	Triclinic	2.6
$P_{21/c}$	Monoclinic	23.2
P_{21}	Monoclinic	13.4
$C_{2/c1}$	Monoclinic	5.8
C_2	Monoclinic	2.8
P_{212121}	Orthorhombic	17.8
P_{bca}	Orthorhombic	2.3
P_{21212}	Orthorhombic	1.8
P_{na21}	Orthorhombic	1.8
P_{nma}	Orthorhombic	1.3
Unknown		1.2