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An Etoricoxib Phase Diagram: Hemihydrate and Anhydrate

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Abstract:

Anhydrate and hemihydrate phases of etoricoxib (5-chloro-6′-methyl-3-[4-(methylsulfonyl)phenyl]-2,3′-bipyridine) are described. The ternary phase diagram of etoricoxib, isopropyl acetate, and water at 10 °C is reported. The critical water/isopropyl acetate ratio at this temperature, below which etoricoxib will exist as anhydrate at equilibrium, is 0.21 ± 0.04 wt % water, as determined from measurements made on the ternary solution in simultaneous equilibrium with anhydrate and hemihydrate solids.

Introduction

The existence and properties of crystalline hydrates must be taken into consideration in the development of the processing and isolation conditions of pharmaceutical substances.[1] Solid hydrates incorporate water into their crystal structure, and the water molecules frequently, but not always, occupy regular, repeating positions within the crystal lattice.[2] Researchers working in this area may draw upon a vast literature of carefully determined phase diagrams[3,4] and studies of the interactions of water with pharmaceutical materials.[5−8]

The conditions of solvent composition and temperature under which anhydrous and solvated forms of a desired product are stable can be determined by measurement of equilibrium properties of the system. In this example, the properties of the hemihydrate and anhydrate forms of etoricoxib, (**1**, Figure 1) a selective cyclooxygenase-II inhibitor, have been examined, with the goal of developing a robust process for the isolation of the anhydrate form from isopropyl acetate. The heterogeneous equilibria involving the anhydrate, hemihydrate, and solutions of etoricoxib in isopropyl acetate and water were investigated at 0, 10, and 25 °C. The goal of the research was to determine the compositions of the system at which hemihydrate could be avoided, and thereby ensure that a single, well characterized phase, rather than a mixture of phases, was present in the drug substance. All portions of the phase diagram of the system, including those removed from the potential processing conditions, were investigated at 10 °C.

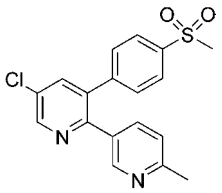

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Figure 1. **Structure of etoricoxib (1).**

Experimental Section

Materials. Anhydrous etoricoxib was isolated from isopropyl acetate by cooling followed by filtration and drying under nitrogen. Etoricoxib hemihydrate was obtained by cooling a water-saturated toluene solution of etoricoxib, followed by filtration and drying. Isopropyl acetate (Aldrich, 99%) was used as received. Water used in the experiments was distilled and then passed through a deionization and purification system.

Solubility Measurements. Liquids and solids (or only liquids in the case of the ^{i}PrOAc/water equilibrium measurements) were added to glass ampoules which were chilled and sealed with a flame. The ampoules were agitated in a thermostat for periods of from 1 to 3 days, and then centrifuged, opened, and rapidly filtered through cotton. When two liquid phases were present, they were carefully separated and filtered separately. Aliquots of the solutions were weighed immediately for quantitative liquid chromatographic analysis and were retained in sealed vials for subsequent gas chromatographic analysis or Karl Fischer titration. Wet solids were retained in closed containers for subsequent X-ray powder diffraction analysis.

Quantitative Liquid Chromatographic Analysis. Following quantitative dilution first with acetonitrile and finally with 1/1 (v/v) water/acetonitrile, solutions were analyzed with an Agilent HP1100 series liquid chromatographic system with UV detection at a wavelength of 220 nm. A reverse-phase YMC-ODS-AQ column with gradient elution (A = aqueous phosphate (pH 3.1), B = acetonitrile; A:B (v:v) 72:28 (0 min), 72:28 (11 min), 30:70 (30 min)) at 35 °C was used. Peak areas were used to quantify the instrument response, which had been standardized with solutions made from weighed quantities of etoricoxib standard material of established purity. The concentration range of the diluted solutions was within the range of linearity of the method. Two injections of each sample were performed and the results averaged.

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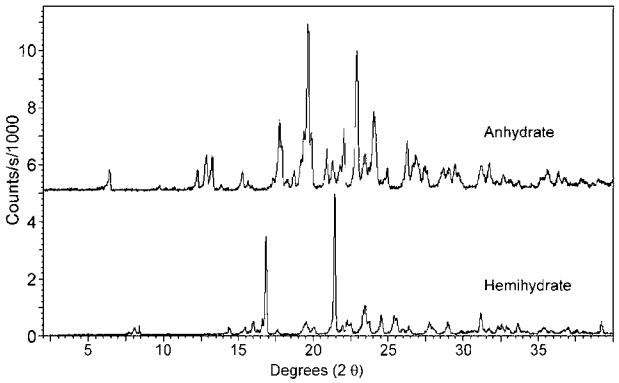

Figure 2. **X-ray powder diffraction patterns of etoricoxib anhydrate and hemihydrate.**

Gas Chromatographic Analysis. Weighed aliquots of the filtered aqueous solutions were diluted quantitatively in DMSO. The samples were analyzed on a Hewlett-Packard HP6890 gas chromatographic system with a flame ionization detector. The injector temperature was 200 °C. The injected samples were eluted with a helium flow of 10 mL/min through a Stabilwax 0.53 mm × 60 m column. The column was maintained at 50 °C for 3 min followed by a heating ramp of 20 °C/min to 220 °C. Gravimetrically prepared standard solutions of isopropyl acetate in DMSO were used to standardize and demonstrate the linearity of the instrument. Peak areas were used to quantify the instrument response and were within the demonstrated linearity range of the method. Two injections of each sample were performed and the results averaged.

Karl Fischer Titration. Weighed aliquots of the filtered organic solutions, or weighed quantities of solids, were added directly to the titration vessel of a Metrohm 701 KF Titrino volumetric titrator. Methanol was used as solvent. The titrant, Riedel-deHaen Hydranal Composite 2, was dispensed automatically and the endpoint determined potentiometrically. The response of the instrument was calibrated by injecting weighed quantities of water.

X-ray Powder Diffraction. Samples were analyzed using a Philips APD 3710 diffractometer with copper Kα radiation generated at an accelerating potential of 45 kV and a current of 40 mA. Residual solids from solubility experiments were ground briefly in a mortar if necessary and analyzed rapidly with precaution to avoid changes in the phases due to reaction with the atmosphere.

Thermogravimetric Analysis. Solid samples were analyzed using a Perkin-Elmer thermogravimetric analyzer (TGA7) which had been calibrated using a standard weight and Curie-point temperature standards. The samples were heated at a rate of 10 °C/min under nitrogen.

Results and Discussion

The X-ray powder diffraction patterns of etoricoxib anhydrate and hemihydrate phases are shown in Figure 2. These patterns are distinct from one another, indicating different crystal structures. The differences are sufficient to permit the detection of mixtures of the two phases.

The solid anhydrate and hemihydrate were further characterized by thermogravimetric analysis and Karl Fischer titration. No significant weight loss (<0.05%) was observed for the anhydrate sample until the melting point (approximately 134 °C) was reached, and the titration results indicated less than 0.05 wt % water. The hemihydrate solid exhibited a weight-loss step of 2.5% from approximately 75 to 125 °C during heating, and Karl Fischer titration resulted in a water content of 2.51 ± 0.03 wt % (n = 3). The stoichiometric water content of etoricoxib hemihydrate is 2.45 wt %, in agreement with the thermogravimetric analysis and titration results.

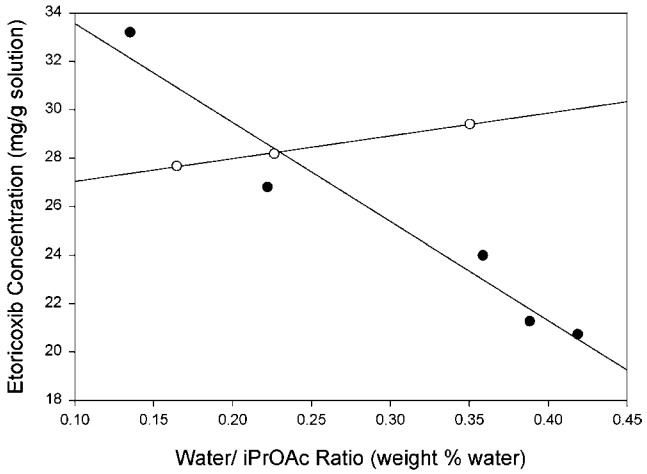

Figure 3. **Solubilities of etoricoxib hemihydrate and anhydrate as a function of the water:isopropyl acetate ratio in solution at 10 °C. (●): Hemihydrate. (○): Anhydrate.**

In a process developed for manufacture of anhydrous etoricoxib, the solid was isolated from isopropyl acetate at 10 °C. The conditions under which hemihydrate could form in this system were desired, and therefore, a study of the solubilities of the anhydrate and hemihydrate in isopropyl acetate at 10 °C with different water contents was conducted. Hemihydrate solids or anhydrate solids were equilibrated with isopropyl acetate to which different amounts of water had been added. The equilibrated systems appeared to contain a single liquid phase at each condition. Residual solids were analyzed by X-ray powder diffraction after the solubility experiments, and the results showed that the patterns of the starting materials were unchanged after the equilibration.

The results of these studies are illustrated in Figure 3. They indicate that over the range of solution water contents studied, the solution concentration of etoricoxib increases with increasing water content for the anhydrate and decreases with increasing water concentration for the hemihydrate. The solubility curves cross at an intermediate water content, which is 0.23 wt % water, expressed as the ratio of solution water content to isopropyl acetate content. The crossing point was determined by simultaneous solution of the best-fit lines for each data set. The calculated etoricoxib concentration at the crossing point is 28.3 mg/g solution.

At the crossing-point water content in Figure 3, hemihydrate and anhydrate can coexist in equilibrium with solution. The water content and the etoricoxib concentration of the solution in simultaneous equilibrium with these solids is fixed, as shown by application of the Phase Rule.[3] Therefore, the equilibrium conditions were also found by a second

Table 1. **Equilibrium liquid compositions for the etoricoxib−water−isopropyl acetate system**

			organic liquid phase[b]		aqueous liquid phase[b]	
labels[a]	solid phase(s)	liquid phase(s)	etoricoxib (mg/g soln)	water:^{i}PrOAc (wt % water)	etoricoxib (mg/g soln)	^{i}PrOAc (mg/g soln)
A; a, b, c	anhydrate and hemihydrate	organic	0 °C: 22.1 ± 0.2 10 °C: 28.4 ± 1.0 25 °C: 43.4 ± 0.2	0 °C: 0.13 ± 0.01 10 °C: 0.21 ± 0.04 25 °C: 0.30 ± 0.01	−	−
f, g	−	organic and aqueous	−	1.54 ± 0.01	−	32 ± 1
E; c, e, h	hemihydrate	organic and aqueous	16.8 ± 0.2	1.60 ± 0.05	0.11 ± 0.03	46 ± 4
i	hemihydrate	aqueous	−	−	0.048 ± 0.003	−

[a] Labels refer to Figure 4 and the text. Temperature 10 °C, or as indicated. [b] Values are averages of triplicate determinations. Imprecisions are the calculated standard deviations.

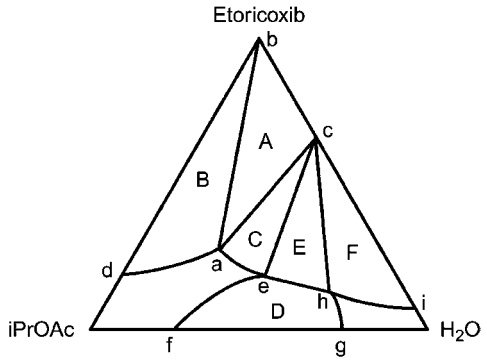

Figure 4. **Ternary phase diagram for etoricoxib−water−isopropyl acetate at 10 °C. Labels are explained in the text and in Table 1.**

method. Isopropyl acetate was combined with varying amounts of water and sufficient quantities of both hemihydrate and anhydrate at 10 °C so that both solid phases were in equilibrium with the solution. Triplicate determinations were performed with different starting ratios of hemihydrate and anhydrate and different initial water/isopropyl acetate ratios in the solvent. X-ray powder diffraction was used to determine that in each experiment, both hemihydrate and anhydrate were present at the end of the equilibration period. After filtration the solution concentration of etoricoxib was 28.4 ± 1.0 mg/g solution and the water/isopropyl acetate ratio was 0.21 ± 0.04 wt % water, both in satisfactory agreement with the results obtained using the interpolative technique. This result provides the critical water content, below which hemihydrate will not be present at equilibrium. Therefore, this water content was of use in the design and execution of the process to produce etoricoxib anhydrate, including testing of raw materials and in the implementation of precautions taken to minimize adventitious water entry.

A graphical representation of the results are presented in Figure 4. Frankforter and Frary classified different types of ternary diagrams.[4] The present system as represented by Figure 4 corresponds to the third class of diagram according to their classification. The properties of triangular diagrams are described by them and by others.[3] At system compositions within field **A**, the equilibrium compositions will be a mixture of solution (**a**), anhydrate (**b**), and hemihydrate (**c**). The water/isopropyl acetate ratio at point **a** is equal to 0.21 ± 0.04 wt % as measured above. The curves **a**−**d** and **a**−**e** correspond to the solubility curves for anhydrate and hemihydrate, respectively, shown in Figure 3. For saturated solutions with water/isopropyl acetate ratios less than the value at point **a**, that is, within field **B**, all of the water in the system will exist in solution and the solid phase at equilibrium will be the anhydrate. Higher total water/isopropyl acetate ratios may move the system to region **C** where hemihydrate alone is in equilibrium with solutions of variable composition (curve **a**−**e**).

Isopropyl acetate and water are not infinitely miscible at 10 °C, and this is reflected in the two phases **f** and **g**, the organic and aqueous phases, respectively, of a two-phase mixture of isopropyl acetate and water. The addition of etoricoxib to the system also results in two liquid phases anywhere within field **D**. At higher etoricoxib concentrations, field **E** is reached. Field **E** is another ternary field, with a single solid phase (hemihydrate, (**c**)) and two liquid phases of fixed concentration (**e** and **h**). In field **F**, hemihydrate is again in equilibrium with a single liquid phase of variable composition. The solubility of hemihydrate in water in the absence of isopropyl acetate is given by point **i**.

Note that although phase diagrams such as Figure 4 can be drawn to scale, with the positions of the points reflecting the true compositions of the phases in equilibrium, this drawing has been distorted to improve its readability (if drawn to scale, several of the points would be located very close to the isopropyl acetate or water vertices). However, one feature has been accurately represented: point **a** is below a straight line from the isopropyl acetate vertex to point **c**. This indicates that hemihydrate (point **c**) is an incongruently saturating compound: addition of isopropyl acetate to hemihydrate solid will immediately result in the formation of some anhydrate.

Phase diagrams similar to that of Figure 4 have been reported. For example, the nickel (II) nitrate/water/*n*-hexanol system is similar, although the portions analogous to fields **A** and **B** in Figure 4 were not determined.[9] Other ternary systems of this type have been described, such as the potassium fluoride/alcohol/water and the potassium carbonate/alcohol/water systems.[4,10] These systems differ from the present one because of the miscibility of alcohol and water, which are "salted out" or made immiscible by the addition of salt.

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The data used to construct Figure 4 are contained in Table 1. The water contents of the organic liquid phases are expressed as the ratio of water to isopropyl acetate to emphasize that it is this ratio, and not the water content of the solution per se, which is the critical value in determining whether hemihydrate, anhydrate, or both may be present at equilibrium. Also included in Table 1 are data for the ternary point **a** determined at 0 °C and at 25 °C. As expected, the equilibrium composition at the ternary point is a function of the temperature. Satisfactory reproducibility is demonstrated at all three temperatures, indicating that equilibrium was reached in each case.

Although the data presented are specific to the solvent system and temperature investigated, analogous relationships between the phases would be expected in other solvent systems and at other temperatures. The understanding of the phase relationships in this system, embodied in the graphical presentation, is an important contribution to a rational design of an isolation of either the anhydrate or hemihydrate phases of etoricoxib.

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