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COMMUNICATIONS

DEHYDRATION AND HYDRATION KINETICS, PHASE CHANGE, SOLUBILITY AND DISSOLUTION BEHAVIOR OF FENOPROFEN CALCIUM

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ABSTRACT

The role of water of hydration on the crystal structure, the solubility and the rate of dissolution of fenoprofen calcium dihydrate was examined. The rate of dehydration of fenoprofen calcium dihydrate at 0% relative humidity (R.H.) increased from 0.0400 to 0.7488 fraction dehydrated/hour over a temperature range of 50°C to 80°C and appeared to occur by a combination of diffusion and nucleation processes. The enthalpy of dehydration was 21.897 kcal/mole. Hydration of dehydrated fenoprofen calcium occurred rapidly at 100% R.H. X-ray powder diffraction analysis showed that the upon dehydration fenoprofen calcium dihydrate underwent a change in its crystal structure to form anhydrous fenoprofen calcium. The rate of dissolution of fenoprofen calcium dihydrate tablets at 37°C was not significantly different than that of tablets containing anhydrous fenoprofen. The enthalpies of solution (ΔH_{sol}) of fenoprofen calcium dihydrate and anhydrous fenoprofen calcium were 2.0504 and 3.5583 kcal/mole respectively. The transition temperature at which the dihydrate and anhydrous fenoprofen had equal solubilities was approximately 59.91°C.

INTRODUCTION

The stability of crystalline drug hydrates is of importance because it has been established that the loss of water of hydration or a change in the level of hydration can alter their physical-chemical properties (1-5) such as solubility and dissolution behavior (6-10). In this study we have attempted to evaluate the dehydration and the

subsequent hydration processes and the phase changes to determine whether they correlate to the dissolution behavior. Fenoprofen calcium dihydrate, a non-steroidal anti-inflammatory agent, was chosen as the model drug hydrate.

MATERIALS

Fenoprofen calcium dihydrate was purchased from the Sigma Chemical Company. Dehydrated fenoprofen calcium was obtained by drying fenoprofen calcium hydrate over a desiccant at 80°C. Microcrystalline cellulose, corn starch, magnesium stearate, potassium phosphate monobasic, sodium hydroxide and Drierite® were purchased from the Fisher Chemical Company, the Sigma Chemical Company and other reliable sources.

METHODS

Relative Humidity Environments

The 0% and 100% R.H. environments were created by using a desiccant (Drierite, W.A. Hammond Drierite Co.) and distilled water respectively in tightly closed glass jars with plastic racks (Kontes®).

Dehydration and Hydration Kinetics

The rates of dehydration and hydration were studied at 50°C, 60°C, 70°C and 80°C. For the dehydration study approximately 0.1 g of fenoprofen calcium dihydrate was accurately weighed out on 1 inch diameter polyethylene snap caps. These were placed on racks in glass jars containing the desiccant. The glass jars were tightly shut and placed in a Precision Scientific® constant temperature oven preset at the required temperature. The samples were removed periodically and weighed on a Sartorius Basic® electronic balance until a constant weight was reached. Moisture uptake by the dehydrated fenoprofen calcium was similarly studied except that the samples were now placed in a 100% relative humidity environment.

X-Ray Powder Diffraction (XPD) Analysis

Fenoprofen calcium dihydrate and dehydrated fenoprofen calcium were studied using X-ray powder diffraction analysis on a Siemens D500 diffractometer. The source of radiation was Cu-K (λ = 1.5406 Å). A step-scan mode was employed with 0.04 degrees per step and 0.1 seconds per degree. The samples were placed on a quartz sample holder and scanned between 2θ values of 2 and 52 degrees.

Dissolution and Solubility of Hydrated and Anhydrous Fenoprofen Calcium

Tablets of anhydrous and dihydrate fenoprofen calcium were prepared by direct compression. 0.1g of fenoprofen calcium was lightly ground in a mortar with microcrystalline cellulose, corn starch and magnesium stearate and compressed at approximately 1.5 metric tons of pressure on a Carver tablet press to form tablets weighing about 0.46g.

The dissolution test was carried out in a Vankel 6100® dissolution tester equipped with a Vankel 650 circulating pump. The dissolution medium was 0.1M aqueous phosphate buffer at pH 7 maintained at 37°C (± 0.1°C). The tablets were placed in a wire mesh chamber (USP Apparatus I) and rotated at 100 rpm. Approximately 5 ml of the samples were withdrawn, filtered and analyzed for UV absorbance at 271 nm on a Beckman-DU64® spectrophotometer. A 1 ml quartz cell was used for this purpose. The concentrations were determined from a standard calibration curve of known concentrations of fenoprofen calcium.

The equilibrium solubilities of fenoprofen calcium dihydrate and dehydrated fenoprofen calcium were also measured at 40°C, 50°C and 60°C. Approximately 200 ml of saturated fenoprofen calcium solution was agitated at a constant speed with a Caframo® overhead stirrer. The temperatures were maintained in a water bath (± 0.1°C). 5 ml samples were drawn after allowing the solution to equilibrate, filtered through Whatman No.2 Qualitative® filter paper and analyzed for absorbance (λ = 271nm).

RESULTS

Kinetics of Fenoprofen Dehydration and Hydration

The kinetic profiles for the dehydration of fenoprofen calcium dihydrate at 0% R.H. and its subsequent hydration at 100% R.H. are shown in Figures 1 and 2 respectively. The percent weight change is plotted as a function of time. The rate of dehydration increased from 0.0400 to 0.7488 fraction dehydrated.hr^{-1} as the temperature was increased from 50°C to 80°C. The values are tabulated in Table 1. Figure 3 shows an Arrhenius type plot of ln(K), where K is the rate of dehydration, on the Y-axis versus the reciprocal of absolute temperature (1/T) on the X-axis. From the slope the energy of activation was determined to be 21.897 kcal.mol^{-1}.

The hydration of dehydrated fenoprofen calcium occurred rapidly in about 15 minutes at all temperatures. At the 100% R.H. humidity to which the samples were exposed, a correlation between the temperature and the rate of hydration was not evident (Fig. 2). The percent weight increase was greater than 6.45% in some instances because the calculations were based on a theoretical value of 2 moles of water equalling 6.45% w/w and did not account for the weight of the moisture that would be adsorbed on the powder surface.

Phase Change and Powder Diffraction Analysis.

Figures 4 and 5 show the X-ray powder diffractograms for fenoprofen calcium dihydrate and dehydrated fenoprofen calcium respectively. Upon dehydration fenoprofen calcium changed to a stable anhydrous form having a different crystal structure which was apparent from the absence of prominent peaks between 2θ values of 12 to 35 degrees. Instead there was the appearance of an "amorphous hump" indicating some loss of crystalline order upon dehydration.

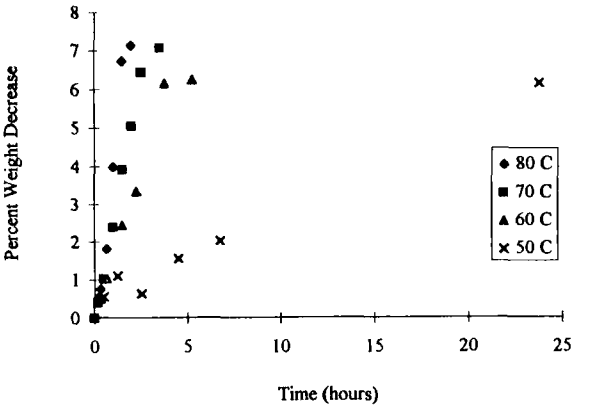

FIGURE 1
Dehydration of Fenoprofen Calcium Dihydrate at 0% Relative Humidity

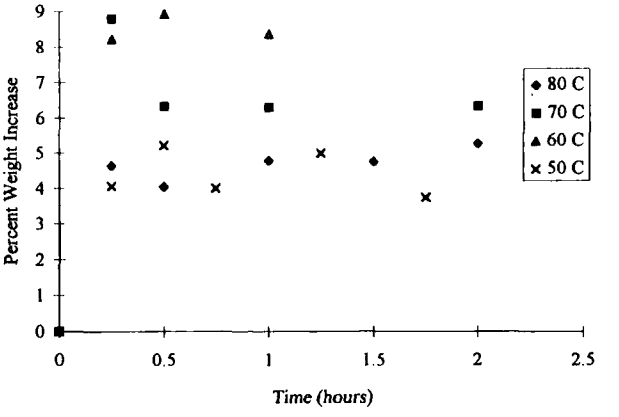

FIGURE 2
Hydration of Dehydrated Fenoprofen Calcium at 100% Relative Humidity

TABLE 1

Temperature (°C)	Rate of Dehydration (fraction dehydrated/hour^{-1})
50	0.0400
60	0.2030
70	0.4207
80	0.7488

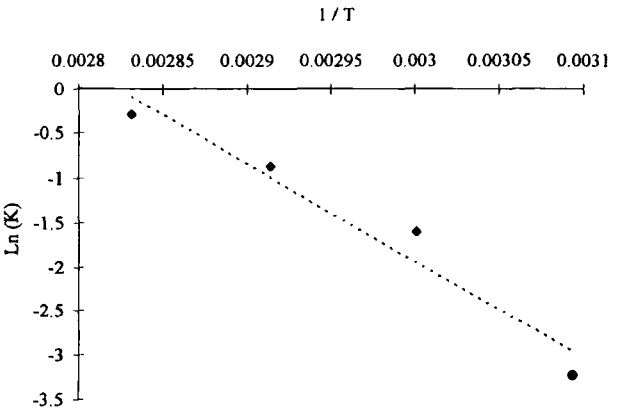

FIGURE 3
Energy of Dehydration of Fenprofen Calcium Dihydrate

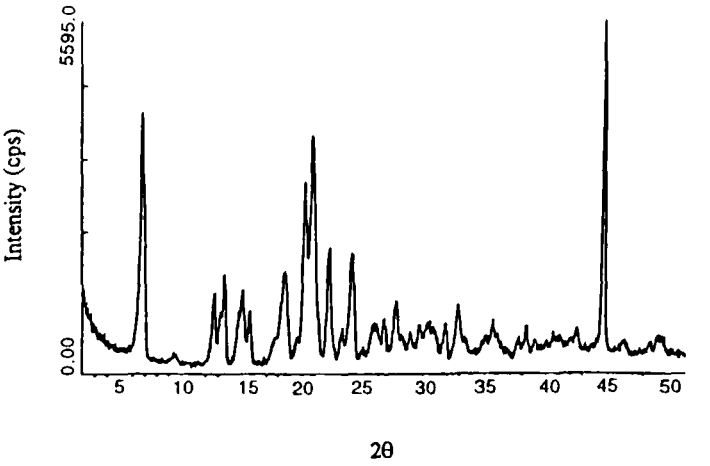

FIGURE 4
X-Ray Powder Diffractogram of Fenoprofen Calcium Dihydrate

Dissolution and Solubility of Fenoprofen Calcium.

The dissolution profiles for tablets containing about 0.1g of fenoprofen calcium dihydrate and dehydrated fenoprofen calcium each are shown in Figure 6. Dehydrated fenoprofen calcium did not have a significantly different rate of dissolution profile as compared to the hydrate. In Figure 7, the natural logarithm of the solubility of the hydrated and the dehydrated forms of fenoprofen are plotted as a function of the reciprocal of the absolute temperature. Linear relationships were

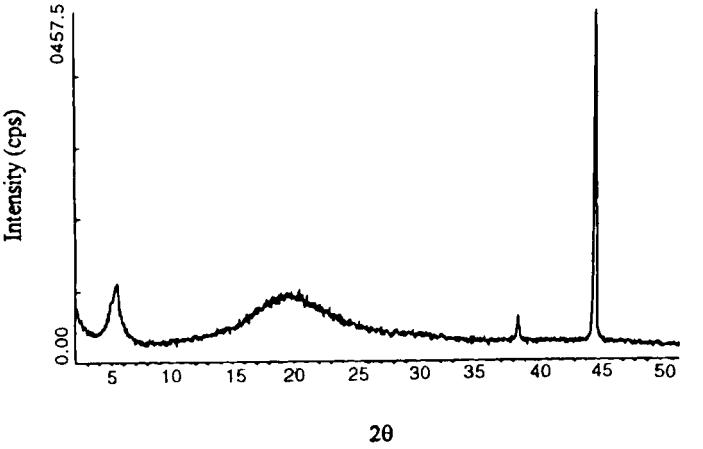

FIGURE 5
X-Ray Powder Diffractogram of Anhydrous Fenoprofen Calcium

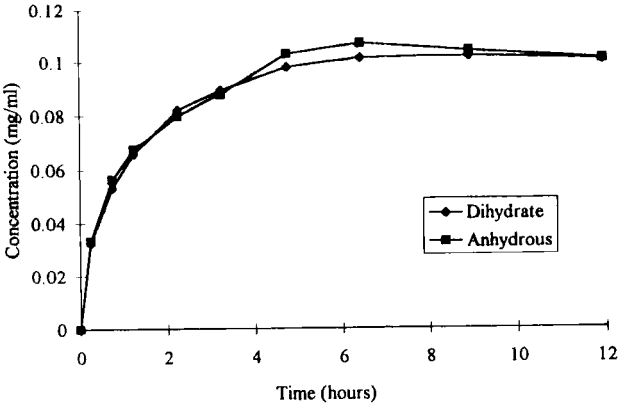

FIGURE 6
Dissolution of Fenoprofen Calcium Tablets at 37°C in a pH 7.0 Phosphate Buffer Solution

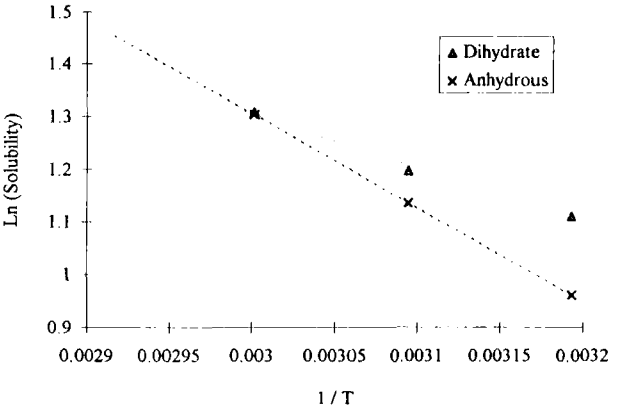

FIGURE 7
Enthalpy of Solution and Transition Temperature of Fenoprofen Calcium

obtained and the enthalpies of solution (ΔH_{sol}) were determined from the slopes. ΔH_{sol} for fenoprofen calcium dihydrate and dehydrated fenoprofen calcium were calculated to be 2.0504 kcal/mol and 3.5583 kcal/mol respectively. The transition temperature, where the solubility of the dihydrate and dehydrated forms were equal, was determined to be approximately 59.91 °C.

DISCUSSION

The rate of dehydration of fenoprofen calcium dihydrate was proportional to the temperature. This was expected because the dehydration most likely occurred by the diffusion of the H_2O molecules out of the crystals and therefore was a function of the temperature. The dehydration process was probably also accompanied by a three-dimensional growth of nuclei of dehydrated fenoprofen as suggested by the Avrami equation (11). In Figure 8, $(-\ln(1-x))^{1/3}$, where x is the fraction dehydrated, is plotted as a function of time. The resulting linear relationship was indicative of a 'good fit' of the data to the Avrami Equation. This in itself was not conclusive proof but it at least gave a possible mechanism for the process of dehydration. XPD analysis showed that upon dehydration there was a change in crystal structure to a stable anhydrous form with a distinctly different crystal structure due to the reorganization of the fenoprofen calcium molecules upon losing the water of hydration. Hydration of dehydrated fenoprofen calcium was very rapid and probably occurred by a combination of nucleation, recrystallization and diffusion processes. The effect of humidity on fenoprofen calcium dihydrate was significant. After equilibration, on a w/w basis, the samples had 2 to 4 moles of H_2O. This was either due to the formation of higher hydrates and/or a non-stoichiometric uptake of H_2O molecules, especially at the higher temperatures.

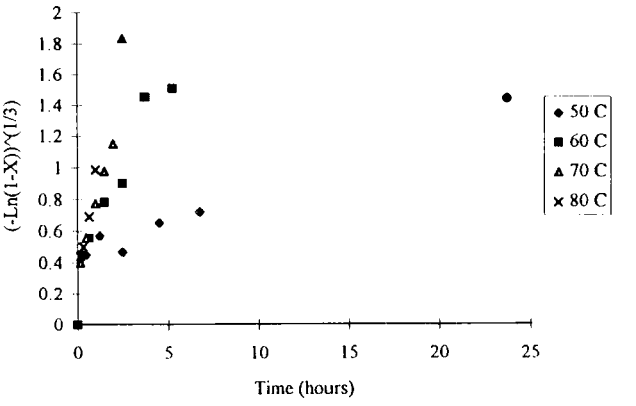

FIGURE 8
Mechanism of Dehydration of Fenoprofen Calcium Dihydrate - Avrami Equation

The rate of dissolution of the anhydrous form was not significantly different than that of the dihydrate form. Anhydrous fenoprofen calcium had a lower solubility at 40°C and 50°C than fenoprofen calcium dihydrate however the solubilities overlapped and crossed over at about 59.91°C. Dehydrated fenoprofen calcium also had a larger enthalpy of solution than the dihydrate. This data would suggest that the loss of water of hydration results in a more compact reorganization of the fenoprofen molecules which need a larger energy input for its breakdown as it dissolves. The significantly large energy of dehydration (21.897 kcal/mol) is reflective of the stability of the dihydrate form.

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