

## Effects of environmental factors on the dehydration of diclofenac HEP dihydrate and theophylline monohydrate

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### Abstract

The effects of temperature and humidity on the kinetics of dehydration of diclofenac *N*-(2-hydroxyethyl)pyrrolidine dihydrate (DHEPH) were examined. Dehydration threshold temperature ( $T_d$ ) was shown to be unsuitable for such investigations. Nine solid state reaction models were applied to the dehydration data. In the temperature range 34–40°C, a diffusion model gave the best fit to the data, dehydration rate varied significantly and activation energies of dehydration ( $E_{ad}$ ) were constant (average 240.7 kJ/mol) with respect to change in relative humidity. In the temperature range 42–48°C, best fit to the data was given by a phase boundary model, dehydration rate did not vary with relative humidity change and activation energies of dehydration were constant (average 140.2 kJ/mol). Choice of solid state reaction model within the diffusion or phase boundary types did not significantly affect the derived activation energy values. Previously reported differences in  $E_{ad}$  values for theophylline monohydrate (TH) may be explained in terms of the different experimental temperature ranges used. The use of activation energy of dehydration values in the study of factors affecting dehydration and in comparing hydrate physical stability, requires careful consideration of sample factors, relative humidity and temperature range of experimentation. © 1997 Elsevier Science B.V.

**Keywords:** Hydrate; Physical stability; Humidity and temperature; Dehydration kinetics; Diclofenac *N*-(2-hydroxyethyl)pyrrolidine; Theophylline monohydrate

### 1. Introduction

Solid state changes of pharmaceuticals, such as hydration and dehydration, may occur during processing and storage and can alter product per-

formance (Herman et al., 1989; Otsuka et al., 1991; Khankari and Grant, 1995). Thus, an understanding of the critical factors involved in the dehydration of pharmaceutical hydrates is an important part of preformulation. Several methods have been used for such studies including isothermal vapour pressure/composition studies (Otsuka

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et al., 1991), isothermal microcalorimetry (Duddu et al., 1995), thermomicroscopy (Byrn, 1982) and thermogravimetrically determined dehydration threshold temperatures (Byrn, 1982; Forbes et al., 1992).

A more structured approach to examining solid state stability of pharmaceutical hydrates, in the form of studies on dehydration kinetics, has been used by several workers (Nakagawa et al., 1981; Sekiguchi et al., 1984; Kitamura et al., 1989; Suzuki et al., 1989). Recently, the kinetics of dehydration of theophylline monohydrate were examined (Agbada and York, 1994) and it was concluded that both the mechanism and activation energy of dehydration ( $E_{aD}$ ) of a hydrate could be altered by sample characteristics, such as particle size, sample weight, crystal defects and surface characteristics. It was also suggested that the effects of environmental factors on dehydration could be studied using dehydration kinetics.

Sekiguchi et al. (1984) state that the activation energy of dehydration of sulfaguanidine hydrate is increased by increasing the levels of water vapour in the sample environment. This may suggest that a single  $E_{aD}$  value cannot specifically quantify the effect of temperature on dehydration kinetics. In order for  $E_{aD}$  values to offer a method of quantification of the thermal stability of medicinal hydrates, as proposed by Agbada and York (1994), the relationship between temperature, relative humidity and  $E_{aD}$  values must be clarified.

Diclofenac hydroxyethylpyrrolidine anhydrate (DHEPA) readily forms a crystalline dihydrate (DHEPH) in an aqueous environment (Ledwidge et al., 1996). The present work uses DHEPH as a model for quantitative investigation of the effects of humidity and experimental temperature range on dehydration kinetics. To this end, the usefulness of dehydration threshold temperature and dehydration kinetics is compared. The work investigates the effects of choice of solid state reaction model on  $E_{aD}$  values of DHEPH. The effects of temperature range on  $E_{aD}$  of theophylline monohydrate (TH) are examined in an attempt to clarify apparent discrepancies in  $E_{aD}$  values published for TH (Suzuki et al., 1989; Agbada and York, 1994). The ultimate objective of the work is to further clarify parameters which affect  $E_{aD}$  and

its usefulness as a quantitative indicator of pharmaceutical hydrate physical stability.

## 2. Experimental

### 2.1. Preparation and characterisation of DHEPH and TH

DHEPH was prepared by dissolving the anhydrate in distilled water at 40°C and recrystallising the hydrous form (Ledwidge et al., 1996). TH was prepared by dissolving the anhydrate (Sigma) in hot water (70°C), cooling the solution and filtering the precipitated solid. Both hydrates were exposed to ambient conditions for 48 h to allow loss of excess moisture. The resulting solids were lightly ground and sieved to between 90 and 125  $\mu\text{m}$  and were stored in closed glass flasks. Final solids were characterised by differential scanning calorimetry (DSC), scanning thermogravimetric analysis (TGA), X-ray diffraction (XRD), Karl Fischer titration analysis and elemental analysis by experimental methods described previously (Ledwidge et al., 1996). Water contents of DHEPH and TH were  $7.97 \pm 0.06\%$  w/w (dihydrate) and  $8.84 \pm 0.07\%$  w/w (monohydrate), respectively. Reproducible XRD intensities were obtained for different batches of sieved DHEPH powders.

### 2.2. Vapour pressure/composition study

Relative-humidity/composition data was obtained for DHEPA and DHEPH at 25°C by equilibrating 500 mg powdered samples with vapour from appropriate constant humidity slurries in sealed containers (The Pharmaceutical Handbook, 1980). The saturated salt solutions used were sodium phosphate ( $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$ ), sodium chloride (NaCl), magnesium nitrate ( $\text{Mg}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ ), magnesium chloride ( $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$ ) and potassium hydroxide (KOH). Weight changes were monitored over a period of 14 days and the solid forms were then characterised as described above.

### 2.3. Dehydration threshold temperature ( $T_d$ ) determination

The  $T_d$  (temperature at which 2% dehydration has occurred) for DHEPH was determined by scanning TGA on 6 mg powdered samples using the Mettler TA3000 Thermal Analysis System. This is comprised of a TC10A processor with a TG 50 measuring cell. Data was processed using Mettler GraphWare TA72 software package on a conventional PC. TG temperature calibration was carried out using the ferromagnetic properties of standards supplied by Mettler. The effects of different relative humidity levels, obtained using constant humidity slurries linked to the Mettler TG 50 measuring cell and different scanning rates (2°C/min and 6°C/min) were examined. Each measurement was carried out in triplicate and the results were tested for significant difference using the MINITAB (ver. 9.1) statistical computer package, ©Minitab, 1992.

### 2.4. Isothermal dehydration

The dehydration kinetics of DHEPH and TH were studied using isothermal TGA performed on powdered samples using the Mettler TA3000 Thermal Analysis System, as described above. In the analysis of DHEPH a range of temperatures was used (34–48°C) at three relative humidity levels (8, 33 and 76%). The weight loss of 6-mg samples was monitored over specified periods of time.

### 2.5. Determination of activation energy of dehydration ( $E_{aD}$ )

The results obtained were fitted to each of the solid state reaction Eqs. 1–9 (listed in Table 1) using a modification of the method of Agbada and York (1994). Conformity to the kinetic models was quantified using the correlation coefficient,  $r$  and standard deviation of the slope of the regression line. The  $E_{aD}$  values were calculated using the appropriate dehydration rate constants in an Arrhenius plot generated from Eq. (10) (Haines, 1995), where  $k$  is the reaction rate constant,  $A$  is the pre-exponential factor,  $E_{aD}$  is the

activation energy of dehydration,  $R$  is the molar gas constant and  $T$  is the absolute temperature.

$$k = Ae^{(-E_{aD}/RT)} \quad (10)$$

## 3. Results and discussion

### 3.1. Vapour-pressure/composition (VPC) study on DHEPH

The results of the VPC study on DHEPH are presented graphically in Fig. 1. At and above 76% RH (25°C) the anhydrate forms the dihydrate. This ease of hydration agrees with a previous report (Ledwidge et al., 1996) and the observation that in all samples of DHEP studied by Holgado et al. (1995) endotherms corresponding to the hydrate were present. The VPC method is useful for studying the solid state forms before and after hydration/dehydration and for detecting any intermediate hydrate forms. In the case of DHEPH no such intermediate hydrates were observed.

Table 1  
Kinetic equations used to describe solid state processes (taken from Haines, 1995)

Equation number	Details	Description
1	$\alpha^2 = kt$	1d-diffusion
2	$(1-\alpha) \ln(1-\alpha) + \alpha = kt$	2d-diffusion
3	$1 - (2/3)\alpha - (1-\alpha)^{2/3} = kt$	3d-diffusion (Ginstling-Brounshstein)
4	$1 - (1-\alpha)^{1/2} = kt$	2d-phase boundary (contracting surface)
5	$1 - (1-\alpha)^{1/3} = kt$	3d-phase boundary (contracting volume)
6	$[-\ln(1-\alpha)]^{1/n} = kt$	Avrami-Erofe'ev ( $n = 2, 3, 4$ ) (nucleation)
7	$\ln(\alpha/(1-\alpha)) + C = kt$	Prout-Tompkins (nucleation)
8	$-\ln(1-\alpha) = kt$	First order
9	$1/(1-\alpha) = kt$	Second order

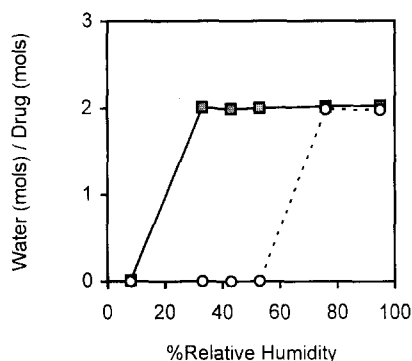


Fig. 1. Vapour-pressure/composition diagram for DHEPH (squares) and DHEPA (circles) at 25°C carried out over 14 days.

### 3.2. Dehydration threshold temperature ( $T_d$ ) determination

The  $T_d$  values for DHEPH at three %RH levels and two scanning rates are presented in Table 2. The values obtained at the higher heating rate (6°C/min) show no difference between the results obtained at different relative humidities (ANOVA, one way,  $P = 0.21$ ). A two sample  $t$ -test on the smallest and largest means (33%RH and 76%RH) showed no significant difference ( $P = 0.12$ ). The results demonstrate that either, (1) changes in environmental humidity do not affect the dehydration of DHEPH, or that (2) the  $T_d$  value is not sensitive enough, at this heating rate, to demonstrate the effects of different %RH values.

At the lower heating rate (2°C/min), the  $T_d$  values obtained were consistently lower than those obtained at 6°C/min. Also there was significant difference between the variances of the samples obtained at the three relative humidities

Table 2  
Dehydration threshold temperatures for DHEPH at two different heating rates and three different relative humidities

%RH	$T_d$ value at 6°C/min heating rate (°C, $n = 3$ )	$T_d$ value at 2°C/min heating rate (°C, $n = 3$ )
8	$35.0 \pm 0.3$	$33.3 \pm 0.2$
33	$35.0 \pm 0.2$	$33.6 \pm 0.1$
76	$35.2 \pm 0.1$	$34.0 \pm 0.1$

(ANOVA, one way,  $P = 0.005$ ) implying that environmental humidity can affect the dehydration threshold temperature of DHEPH. However, significant differences ( $P < 0.05$ , two sample  $t$ -test) only existed between the results at 76%RH and either 8%RH or 33%RH. Furthermore, the  $T_d$  value is significantly lower than any of the values quoted for the xanthine hydrates (Byrn, 1982).

Although convenient for classification of the physical stability of pharmaceutical hydrates, these results indicate that the use of  $T_d$  values must involve standardisation of environmental factors such as heating rate and relative humidity. However, it is not a suitable method for quantitatively examining the possible effects of relative humidity on the dehydration of DHEPH.

### 3.3. Effect of model choice on $E_{ad}$

The dehydration of DHEPH was determined below the hydrate melting point (60°C) (Ledwidge et al., 1996). To avoid any errors due to the occurrence of phase changes, especially at higher temperatures, initial rate data was used (Monkhouse and Van Campen, 1984). Sample dehydration data (fraction dehydrated versus time) and best fit data for DHEPH at 8% RH in the temperature ranges 34–40°C and 42–48°C are presented graphically in Figs. 2 and 3, respectively, and Arrhenius plots are presented in Fig. 4.

It was found that in the temperature range 34–40°C the best fits were obtained using the one-dimensional (1d) diffusion model (Eq. 1, Table 1). It is important to note that good fits ( $r > 0.99$ ) were also obtained with all three diffusion models presented in Table 1. Although each diffusion model yields different rate constant values, we found that the  $E_{ad}$  values were identical, within the determined standard deviations. For example, the  $E_{ad}$  values determined at 33%RH (34–40°C) were  $234.4 \pm 8.2$ ,  $238.7 \pm 8.3$  and  $240.0 \pm 8.4$  kJ/mol using the 1d, 2d and 3d diffusion models respectively.

Similarly, in the temperature range 42–48°C although the best fit was obtained with the three-dimensional (3d) phase boundary model, good fits ( $r > 0.99$ ) were obtained with the two dimensional (2d) phase boundary model. The resulting  $E_{ad}$  values were also equivalent.

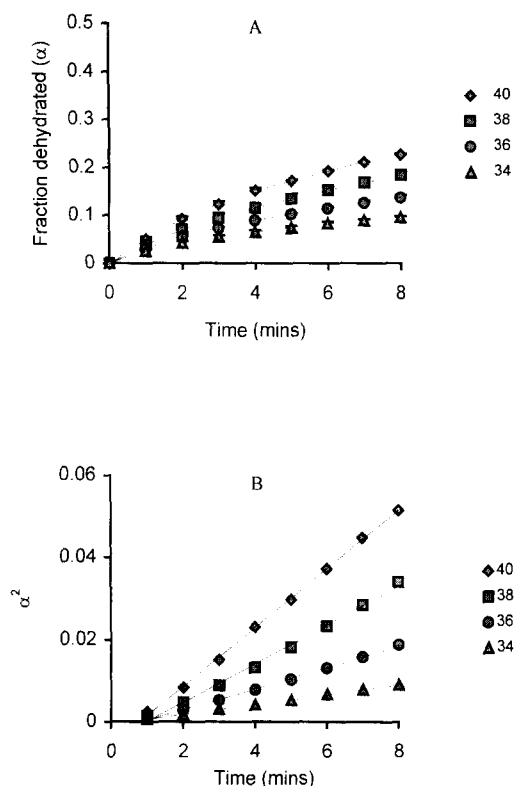


Fig. 2. (A) Fraction dehydrated ( $\alpha$ ) versus time for DHEPH at 8%RH, 34–40°C ( $n = 3$ ). (B) Dehydration data obtained at 8%RH, 34–40°C, fitted to Eq. 1 (1d-diffusion) in Table 1.

Good fits to the data (42–48°C) were also obtained using the first order model. However, the theoretical basis for this model is not well defined for solid state reactions (Byrn, 1982) and it is frequently only used for analytical convenience (Sharp et al., 1966). The mathematical applicability of the first order equation to solid state decompositions may be accounted for by its similarity to the phase boundary models (Carstensen, 1974). It is, nonetheless, interesting to note that the derived  $E_{aD}$  values are similar to those obtained from the phase boundary models. For example, the average result (all relative humidities) using the 3d phase boundary model was  $140.2 \pm 3.8$  kJ/mol and that using the first order model was  $148.0 \pm 3.6$  kJ/mol.

It has been shown that, in relation to solid state kinetic equations, there are three main groups of solid state reaction: (1) diffusion controlled; (2)

phase boundary controlled; and (3) nucleation controlled (Sharp et al., 1966). This work by Sharp et al. (1966) demonstrated that for  $\alpha < 0.7$  it would be difficult to distinguish fits to the reaction models within the above groups. The results presented here indicate that, when the initial rate data is being used ( $\alpha < 0.5$ ), for diffusion and phase boundary controlled reactions, it is not necessary to discriminate between the models within a group for reproducible  $E_{aD}$  values.

Since several models give good fits to the data, the kinetic treatment outlined here cannot be used to establish which particular reaction mechanism, within a category, is applicable. However, it may be possible to draw conclusions as to the general mechanism (i.e. diffusion or phase boundary).

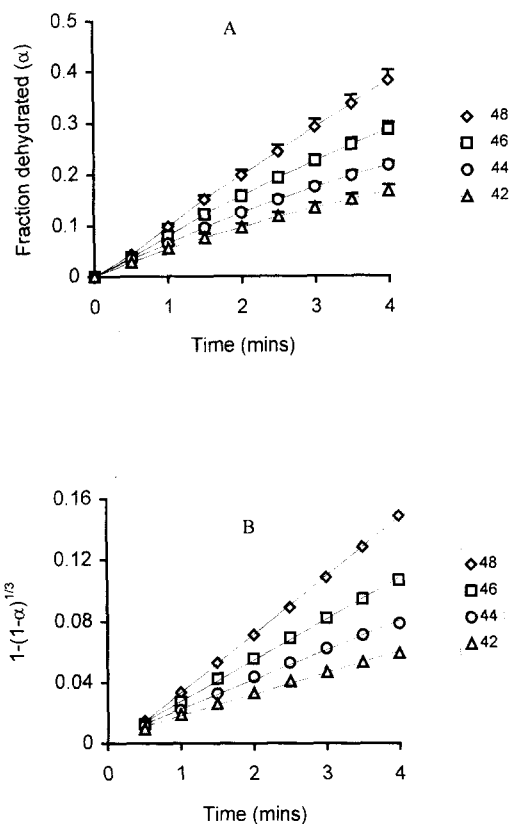


Fig. 3. (A) Fraction dehydrated ( $\alpha$ ) versus time for DHEPH at 8%RH, 42–48°C ( $n = 3$ ). (B) Dehydration data obtained at 8%RH, 42–48°C, fitted to Eq. 5 (3d-phase boundary) in Table 1.

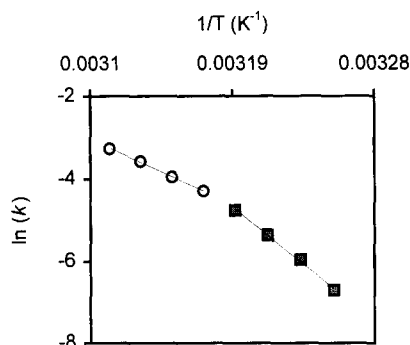


Fig. 4. Arrhenius plot for dehydration of DHEPH using rate data obtained at 8%RH and 34–40°C (squares), 42–48°C (circles).

### 3.4. Effect of temperature range on $E_{aD}$

Monkhouse and Van Campen, 1984, point out that the Arrhenius relation must be very carefully applied to solid state reactions due to underlying assumptions including the following: (1) that the  $E_{aD}$  is temperature independent; (2) that the reaction mechanism remains the same at all temperatures; (3) that the reacting system does not undergo phase changes (such as melting). The last stipulation is relevant to DHEPH and many pharmaceutical hydrates, which melt at relatively low temperatures.

In all solid state reactions the activation energy will vary depending on the partial heat capacity of all the components (Monkhouse and Van Campen, 1984). Consequently narrow temperature ranges should be used. The temperature ranges in this work (6°C) yielded good linearity in the Arrhenius plots ( $r > 0.99$ ).

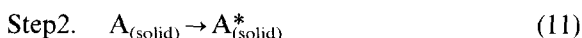
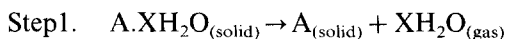
Furthermore, the mechanism of reaction may not remain the same over a large temperature range. This is demonstrated by the data presented here (see Tables 3 and 4). While recognising the specific mechanistic limitations of the kinetic approach, the best fit model changes from diffusion to phase boundary, and is accompanied by a significantly different activation energy  $\leq 40^\circ\text{C}$  compared to  $\geq 42^\circ\text{C}$ . This is consistent with a change in the mechanism of initial dehydration over this temperature range.

Table 3

Sample dehydration rate constant ( $k$ ) data and activation energies of dehydration ( $E_{aD}$ ) obtained for DHEPH in the temperature range 34–40°C and at three relative humidities

%RH	$k$ Values at 40°C ( $\text{min}^{-1}$ ) [1d diffusion model]	$E_{aD}$ values at temperatures 34–40°C (kJ/mol)
8	$7.098 \times 10^{-3}$	$235.7 \pm 18.6$
33	$3.644 \times 10^{-3}$	$234.4 \pm 8.2$
76	$1.319 \times 10^{-3}$	$251.9 \pm 15.6$

The dehydration of a polymorphic hydrate (i.e. one that dehydrates into a different crystalline form), such as DHEPH, may be considered a two step reacting system of the type described as follows,



where  $A_{(\text{solid})}$  and  $A^*_{(\text{solid})}$  represent the hydrated and dehydrated crystalline forms of the drug A, respectively. According to Byrn (1982), Step 1 describes the breaking of hydrogen bonds involving the water molecules and Step 2 the collapse of the hydrate crystal structure into that of an anhydrate.

An explanation for the observed change in dehydration, in terms of the two step dehydration reaction described above (Eq. (11)), could be that at higher temperatures ( $\geq 42^\circ\text{C}$  in the case of DHEPH) the rate-limiting step is collapse of the hydrate crystal structure into that of the anhydrate, i.e. there is sufficient thermal energy in the system to overcome all hydrogen bonds associated with the water molecules.

Table 4

Sample dehydration rate constant ( $k$ ) data and activation energies of dehydration ( $E_{aD}$ ) obtained for DHEPH in the temperature range 42–48°C and at three relative humidities

%RH	$k$ Values at 48°C ( $\text{min}^{-1}$ ) [3d-phase boundary model]	$E_{aD}$ values at temperatures 42–48°C (kJ/mol)
8	$37.94 \times 10^{-3}$	$143.1 \pm 2.4$
33	$37.25 \times 10^{-3}$	$135.9 \pm 5.8$
76	$35.61 \times 10^{-3}$	$141.5 \pm 10.9$

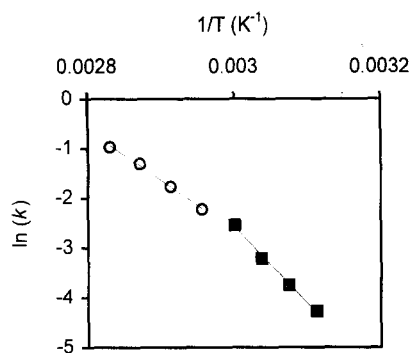


Fig. 5. Arrhenius plot for dehydration of TH using rate data obtained at 8%RH and 48–60°C (squares), 65–80°C (circles).

Agbada and York (1994) reported the  $E_{aD}$  of theophylline monohydrate as 70–90 kJ/mol and pointed out that the  $E_{aD}$  value for theophylline monohydrate quoted by Suzuki et al. (1989) appears to be high (120 kJ/mol) in view of the stability properties of xanthine hydrates. Different best fit Avrami-Erofe'ev models were obtained. They state that the mechanisms and activation energies of dehydration could be technique dependent. While recognising the validity of this argument it is important to note that the two studies were carried out over significantly different temperature ranges: 60–80°C (Agbada and York, 1994) and 47–53°C (Suzuki et al., 1989). In the context of the work presented above on DHEPH, higher  $E_{aD}$  values might be expected for the dehydration process at lower temperatures. With this in mind, isothermal dehydration experiments were carried out on TH at 8% RH which demonstrates that from 48–60°C the best fit mechanism is the Avrami-Erofe'ev equation with  $n = 1/2$  and  $E_{aD} = 125 \pm 10$  kJ/mol. From 65–80°C, the best fit model is the Avrami-Erofe'ev equation with  $n = 1/4$  and  $E_{aD} = 84 \pm 4$  kJ/mol. The Arrhenius plot for these data is presented in Fig. 5.

As in the case of DHEPH these results demonstrate the significant effects of temperature range on  $E_{aD}$ . They agree with the reports of both groups and imply that there is no inconsistency between differences in  $E_{aD}$  values reported for dehydration of TH. The importance of using similar temperature ranges for the purposes of comparing  $E_{aD}$  values is demonstrated.

### 3.5. Effect of humidity on $E_{aD}$

The effects of the change in %RH on the  $E_{aD}$  values of DHEPH are presented in Tables 3 and 4. As long as the relative humidity is maintained constant,  $E_{aD}$  value estimates are identical within their standard deviations. This confirms the ability of the  $E_{aD}$  value to consistently quantify the effect of temperature on dehydration of DHEPH as long as sample factors and %RH are controlled. Unlike those presented by Sekiguchi et al. (1984) using sulphaguanidine, the data here suggest that  $E_{aD}$  values are not altered by changes in relative humidity.

Dehydration rate values at lower temperatures are significantly altered by relative humidity changes (Table 3). The progressive decrease in reaction rate, as %RH is increased, is graphically demonstrated in the Arrhenius plot for data in the temperature range 34–40°C presented in Fig. 6. In view of the magnitude of the differences in the rate constants obtained for the range 34–40°C, if the %RH were not controlled errors in the resulting  $E_{aD}$  values could result. At higher temperatures, dehydration rates appear to be independent of relative humidity change (Table 4).

These results are consistent with the proposal that the change in reaction mechanism is due to a change in the rate limiting step as per Eq. (11) described above. At temperatures  $\leq 40^\circ\text{C}$  the rate-limiting step may involve the breaking of the hydrogen bonds with the water molecules (Step 1). This view is supported by the fact that the data

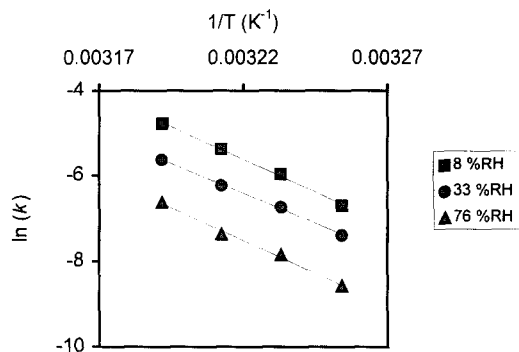


Fig. 6. Arrhenius plot for dehydration of DHEPH using rate data obtained at 34–40°C at three relative humidity levels.

fit a diffusion model and hence apply to a reaction that involves gas molecules (in this case water vapour) (Monkhouse and Van Campen, 1984) and also by the significant effects of relative humidity on the extent of dehydration. At higher temperatures ( $\geq 42^\circ\text{C}$ ) the rate limiting step may be the collapse of the hydrate crystal structure into that of the anhydrate (Step 2). The experimental data support this view because water molecules are not involved in step 2 and large changes in relative humidity have no effect on the reaction rate.

#### 4. Conclusions

It is shown that, in the case of DHEPH, although relative humidity can have an effect on the dehydration threshold temperature it is not a suitable method to quantify such effects.

The dehydration data obtained, using isothermal TGA, suggest that once good fits have been obtained for either diffusion type or phase boundary type reaction models, the choice of solid state equation within the model type does not have a significant effect on the derived  $E_{\text{aD}}$  value.

The importance of relative humidity control is demonstrated by the magnitude of the effect of relative humidity on the rate of dehydration of DHEPH at temperatures  $\leq 40^\circ\text{C}$ . Furthermore, the data obtained for DHEPH at temperatures  $\geq 42^\circ\text{C}$  shows that dehydration reactions are not always affected by changes in humidity. That different temperature ranges have significant effects on the dehydration mechanism and derived  $E_{\text{aD}}$  values is clearly shown for DHEPH.

Apparent inconsistencies in the  $E_{\text{aD}}$  values obtained for theophylline monohydrate Agbada and York, 1994; Suzuki et al., 1989) may be explained by changes in the mechanism and activation energy of dehydration which occur because of the different experimental temperature ranges used.

The changes in mechanism of dehydration with temperature and the effects of humidity thereon, are consistent with the two-step dehydration mechanism (Eq. (11)) proposed by Byrn (1982).

In addition to providing useful, quantitative information on the variables that affect dehydration kinetics it may be possible to use  $E_{\text{aD}}$  values to compare the thermal stability of pharmaceutical hydrates, as proposed by Agbada and York (1994).

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