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A Comparison of Trehalose Dihydrate and Mannitol as Stabilizing Agents for Dicalcium Phosphate Dihydrate Based Tablets

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ABSTRACT This study investigated the possible utility of trehalose dihydrate (TD) as a tablet stabilizing agent. Acetylsalicylic acid was used as the model hydrolyzable drug and dicalcium phosphate dihydrate (DCPD) as the base excipient, because it is well documented that ASA/DCPD tablets are unstable during storage at low temperature and high relative humidity; DCPD is usually combined with mannitol in order to improve tablet stability.

Tablets comprising DCPD, 10% ASA, and 0%, 10%, or 20% w/w of TD were prepared by direct compression and stored at 35°C and 82.9% relative humidity for 6 months. Additionally, control tablets with DCPD and ASA, only, or with DCPD, ASA and 20% mannitol, were also evaluated. At predetermined time intervals, formulations were tested for drug content, mechanical, microstructural, and drug dissolution properties. Additionally, thermal analyses and ASA solution stability studies were carried out. Results reveal that both TD and mannitol significantly reduce degradation of ASA included in DCPD-based tablets, but neither effectively protects against the marked decline in tablet mechanical properties on aging. The ASA stabilization effects of TD and mannitol were also observed in solution, indicating an interaction between these sugars and ASA.

KEYWORDS Trehalose dihydrate, Stability, Dicalcium phosphate dihydrate, Tablets, Aspirin

INTRODUCTION

Trehalose (α-D-glucopyranosil α-D-glucopyranoside) is a disaccharide present in diverse organisms, consisting of two hexose rings linked by a very low energy (1 kcal.mol^{-1}) oxygen bond. Yeast cells such *Saccharomyces cerevisiae* accumulate trehalose under stress conditions, high temperatures, or dehydration, favoring survival. It is one of the most chemically unreactive and stable sugars in nature. A very wide range of potential applications have been

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proposed for this sugar, including use as a sweetener, a humectant, a stabilizer of fatty acids, and as a protector of proteins, viruses, and antibodies during drying, as well as of cells and organs for surgical transplants (Paiva & Panek, 1996; Richards et al., 2002). The properties of trehalose are of great interest in pharmaceutical technology. It is 45% as sweet as sucrose but is not cariogenic. It has high thermostability and a wide pH-stability range. Because it is a nonreducing sugar, it does not undergo a Maillard reaction with amino compounds. Its interactions with water show important differences from those of other sugars with higher glass transition temperature (Higashiyama, 2002).

While the use of trehalose dihydrate as a biomolecule preservative has been receiving considerable attention, little attention has been paid to its possible use as an excipient in solid dosage forms (Armstrong et al., 1998; Delgado & Remers, 1998; Gribbon et al., 1996), probably because of its initially high cost. However, the production cost of trehalose has recently been substantially reduced. It is thus necessary to re-evaluate the usefulness of this product for the pharmaceutical industry (Richards et al., 2002).

The present study investigates the possible utility of trehalose as a pharmaceutical stabilizing agent. Specifically, we investigated the utility of trehalose dihydrate (TD) as stabilizing agent in acetylsalicylic acid (ASA) tablets with dicalcium phosphate dihydrate (DCPD) as base excipient. ASA is a hydrolyzable drug often used as a model to study the effects of excipients on the stability of solid dosage forms (Landín et al., 1994a; Mitrevej and Hollenbeck, 1983; Nicolic et al., 1995). In DCPD-based tablets, ASA is expected to be chemically unstable, because the DCPD-ASA mixtures microenvironment have pH of about 5, markedly higher than pH 2.5 at which the stability of ASA is maximal (James et al., 1999). Moreover, DCPD-based tablets are known to show decreases in weight and deterioration in their mechanical properties during storage at low temperature and high relative humidity, that have been attributed to the dehydration of DCPD under these conditions (De Haan et al., 1990; Lausier et al., 1977). In the present study we compared TD with mannitol, a sugar that is widely used to improve the stability of DCPD-based tablets (Shiromani & Bavitz, 1988).

MATERIALS AND METHODS

Materials

Enzymatically produced trehalose dihydrate was kindly supplied by British Sugar, Inc. Acetylsalicylic acid (lot 81110003), salicylic acid (lot K15841535), and dicalcium phosphate dihydrate (lot 133K16409646) were supplied by Merck. Sodium stearyl fumarate (PRUV) (lot 142-01) was supplied by Juliá-Parrera S.A. Mannitol (lot 9605182) was a gift from ZENECA Farma S.A (now AstraZeneca S.A).

Methods

Tablet Manufacture

Tablets were made from the mixtures shown in Table 1. Sodium stearyl fumarate (PRUV) 1% was included as the tablet lubricant because it has been reported not to show the disadvantages of magnesium stearate with regard to tablet strength, disintegration, dissolution, and compatibility with aspirin (Mroso et al., 1982). The mixtures were blended in a Turbula T2C mixer for 15 min at 30 rpm. Tablets (350 mg) were compressed using a maximum compaction force of 220 MPa in an instrumentalized Korsch EK-O eccentric press fitted with 9-mm-diameter flat punches.

Tablet Storage

Tablet formulations were stored at 35°C in hermetically sealed containers containing saturated solutions

TABLE 1 **Tablet Compositions**

	Percentage				
Formulation	ASA	PRUV	DCPD	TD	Mannitol
Control	10	1	89	0	0
Trehalose 10	10	1	79	10	0
Trehalose 20	10	1	69	20	0
Mannitol 20	10	1	69	0	20

of KCl providing a relative humidity of 82.9%. These storage conditions were selected on the basis of a previous study (Landín et al., 1994a). Samples were taken and characterized after 0,1.5, 3, and 6 months.

Characterization of Tablets

Samples of tablets of each formulation were subjected to the following tests before storage and after 1.5, 3, or 6 months of storage.

Acetylsalicylic acid content. ASA content was determined on the basis of salicylic acid (SA) content, determined spectrophotometrically by a method described previously (Landín et al., 1994b). Briefly, samples of milled tablets were mixed with boric acid-KCl-NaOH buffer (pH 7.4) by vigorous shaking for 3 min at 0°C. Immediately after membrane filtration (Millipore, 0.22 μm) to obtain the supernatant, absorbance at 298 nm was determined against a blank obtained by identical treatment of the corresponding DCPD/sugar mixture without drug.

ASA and SA calibration curves were constructed using standard solutions containing TD or mannitol. Analytical methods were validated using the criteria of Castro et al. (1989).

Tablet dimensions. Tablet thickness and diameter ($n = 6$ per formulation) were determined with a digital calibrator (Mitutoyo 0–25 mm range; 0.001 mm sensitivity).

Weight. The weights of 20 tablets per formulation were determined individually, and the mean weight and coefficient of variation were then calculated.

Tensile strength. This was calculated for each of the six tablets per formulation from the equation:

$$TS = 2CS/\pi.D.E$$

where CS is crushing strength determined in an Erweka TB24 apparatus, D is tablet diameter, and E tablet thickness.

Friability. Weight loss through friability was determined for 10 tablets per formulation after 15 min in an Erweka TAP apparatus at 25 rpm.

Disintegration time. The disintegration times of six tablets were measured individually in acetate buffer ($pH = 4.5 \pm 0.5$) in a Turu Grau DT-1 apparatus fulfilling the USP specifications.

Dissolution rate. ASA dissolution rates in acetate buffer ($pH = 4.5 \pm 0.5$) were determined for six tablets in a Turu Grau apparatus following the procedure established in the USP. Dissolved ASA was determined spectrophotometrically at 265 nm, and dissolution rate was characterized as dissolution efficiency over the first 210 min (Khan & Rhodes, 1972).

Microstructural characterization. Micropore structure was investigated by mercury intrusion porosimetry with a Micromeritics 9305 Pore Sizer equipped with a 5-mL penetrometer for solids. Working pressures covered the range 0.6–25000 psi. Total porosity and mean pore diameter were determined twice for each formulation.

Thermal Analysis

Differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) were performed on raw materials and tablets before and after 6 months storage, using a Shimadzu DSC-50 and TGA-50 apparatus, respectively. DSC and TGA thermograms of 2- to 3-mg samples were recorded at a heating rate of 5°C/min in an open aluminium pan over the range 25–230°C.

Studies of ASA Stability in Solution

Solutions of ASA and the ASA/sugar mixtures in the same ratios as in the solid formulations were prepared. The ASA hydrolysis at 25°, 30°, 35° and 40°C was continuously followed with time using a Shimadzu UV-1603 spectrophotometer. Percentages of SA in borate buffer were determined at 298 nm according to the method used before (Landín et al., 1994b). The temperature of the reaction mixture was controlled by a Grant Y6 ± 0.2°C water bath. Apparent first-order rate constants and energies of activation from Arrhenius plot were calculated.

RESULTS AND DISCUSSION

Tablet Characteristics Before Storage

Tablets made from all four mixtures showed acceptable mechanical properties before storage (Table 2) despite the fact that none of the components is a direct compression material. However, tablets with TD had lowest tensile strength. Together with the lower percentage of porosity in these tablets, this suggests that trehalose leads to the reduction of DCPD

TABLE 2 Mean Prestorage Values of Tensile Strength (TS), Friability, Porosity, Mean Pore Diameter (Dm), Disintegration Time (DT), and 210 min Dissolution Efficiency in 210 min (DE) for the Four Tablet Formulations Studied (Standard Deviations in Parentheses)

Formulation	TS (MPa)	Friability (%)	Porosity (%)	Dm (μm)	DT (min)	DE (%)
Control	1.65 (0.16)	0.94	18.33 (0.67)	0.082 (0.005)	168 (34)	48.91 (1.44)
Trehalose 10	1.25 (0.22)	0.99	18.14 (0.26)	0.088 (0.015)	56 (18)	55.38 (4.14)
Trehalose 20	0.99 (0.26)	0.97	15.85 (0.45)	0.081 (0.001)	47 (20)	56.38 (2.31)
Mannitol 20	1.44 (0.47)	0.90	13.63 (0.01)	0.062 (0.002)	49 (19)	63.93 (6.21)

particle-particle bonds. The decrease in tensile strength for the mannitol formulation is lower, probably because it is a more plastic material (Roberts & Rowe, 1985).

Tablets containing TD or mannitol showed shorter disintegration times than the control tablets because they are soluble materials, though in both cases longer than 30 min. These reductions in disintegration time led to an increase in drug dissolution rate, as is reflected in 210 min dissolution efficiencies (Table 2).

Tablet Characteristics After Storage

Storage for 1.5–6 months at 35°C and 82.9% relative humidity led to significant changes in the values of all parameters considered. It has been previously shown by Glombitza & Schmidt (1995) that the degradation of ASA in solid dosage forms mainly occurs in the water layer at the surface of the solids. Marked ASA degradation was observed in all of our formulations (Fig. 1), as expected given that the pH of DCPD-ASA mixtures (around five) differed considerably from the optimum for ASA stability (pH 2.5). Similar results have been obtained previously (Landín et al., 1994b; Patel et al., 1988). At high relative humidity, the degradation of aspirin can be studied using the Leeson-Mattocks model, which considers that in the cases where the number of moles of (free) water in a solid dosage form exceeds that of the drug, the moisture can be considered present as bulk phase saturated in drug. The decomposition is mainly accounted for by the (pseudo-zero order) decomposition of this quasi suspension system (Carstensen et al., 1985; Kelly, 1970). In line with this, degradation curves were best fitted by zero order kinetics ($r>0.99$), with the rate constants (k) calculated (Fig. 1). Rate constant values agreed previous reports (Kelly, 1970). This analysis indicates that both sugars decrease the value of ASA degradation rate constant in tablets.

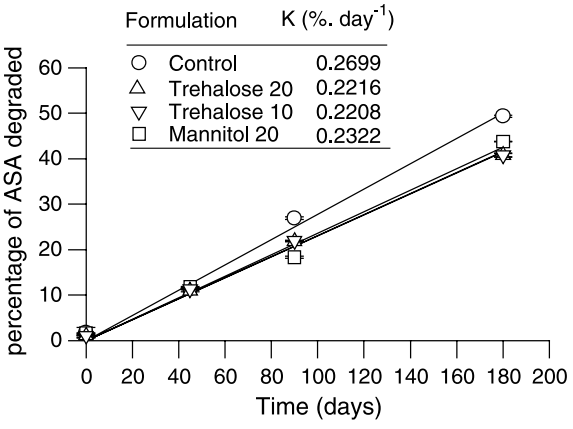

FIGURE 1 Plots of Percentage ASA (n=6) Degraded Against Storage Time for the Four Tablet Formulations Studied. All Data were Well-fitted by Pseudo-order Models Allowing Estimation of Degradation Rate Constants (K).

The ANOVA for the parameter percentage of ASA degraded at 6-month storage showed statistically differences between formulations. In order to isolate exactly where the significant differences lie, posthoc tests were performed. Least significant difference test showed the three following subsets: Control≠mannitol 20≠(trehalose 10 = trehalose 20), having the formulations containing trehalose the highest stability.

At 6 months, ASA content in the TD formulations (regardless of TD content) was about 10% higher than in the control formulation. ASA content in the mannitol formulation after 6 months was only about 5% higher than in the control formulation, despite the fact that the mannitol/ASA molar ratio was about twice as high as TD/ASA molar ratio.

Figure 2 summarizes tablet changes during storage in mechanical, microstructural, and disintegration properties of tablets.

Loss of weight as a result of DCPD dehydration was expected (Fig. 2), but the comparison between weight before and after 6 months storage by the ANOVAs has just shown statistically significant differences for the

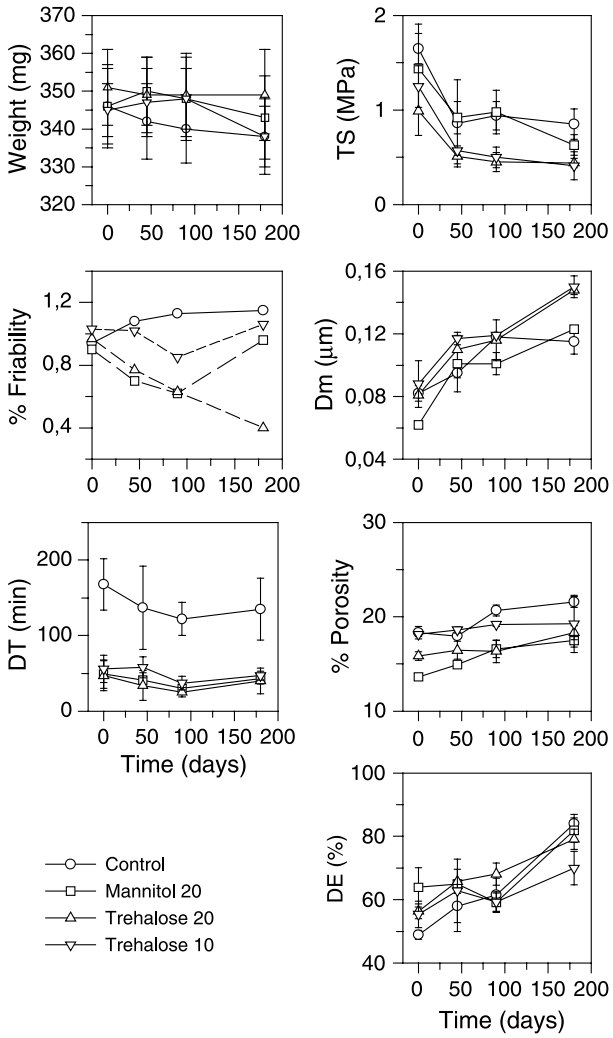

FIGURE 2 **Variations in Weight (mg), Friability (%), Tensile Strength (TS; MPa), Disintegration Time (DT; min), Mean Pore Diameter (Dm; μm), Porosity (%) and 210 min Dissolution Efficiency (DE) over the 6 Months' of Storage for the Four Tablet Formulations Studied.**

control and for trehalose 10 formulations. Formulations containing 20% sugar, mannitol or trehalose, do not show statistically significant differences in weight. In addition, it should be noted that the weight loss of the sugar-free control formulation, after 6 months storage was only 2.3%, far less than the 18.6% expected if all the hydration water of the DCPD were lost (being DCPD 89% in the formulation), as suggested by some authors (Lausier et al., 1977; Rabach & Mielck, 1981).

Tablet tensile strength (TS) initially decreased markedly (>50%), but with increased storage time reached a plateau (Fig. 2). Analysis of variance indicated that the maximum decline in TS did not vary significantly among the four formulations, suggesting that neither TD nor mannitol protect DCPD tablets against the deterioration in mechanical properties at the conditions of the study. During storage at high relative humidity, water condenses in the tablet pores, reducing intermolecular bonding. In line with this, dissolution of soluble components can be expected to lead changes in tablet microstructure (Fig. 2). One such expected change is increased porosity and mean pore diameter, as observed in the present study (Table 2), and probably partially responsible for the decline in tensile strength with storage (Alderborn & Ahlneck, 1991).

Similar tensile strength variations of DCPD tablets have been described by other authors (Lausier et al., 1977), and have been explained in terms of dehydration of DCPD (Shiromani & Bavitz, 1988). As noted, however, there is no evidence of any such dehydration.

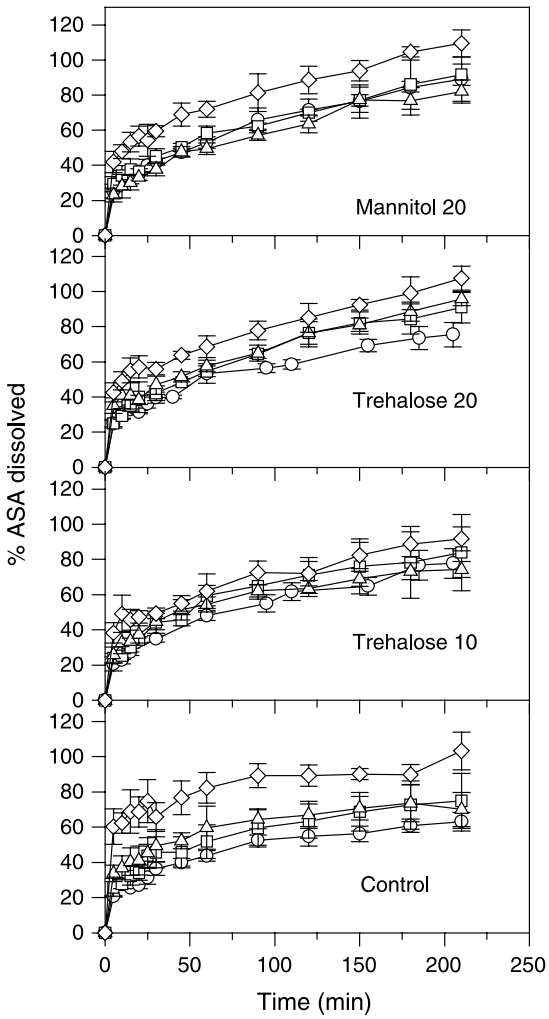

FIGURE 3 **Mean ASA Dissolution Curves for Each of the Four Tablet Formulations Studied, Before and After 1.5, 3, and 6 Months' Storage at 35°C and 82.9% RH. (○ Before Storage, □ 1.5 Months, △ 3 Months, ◇ 6 Months).**

TABLE 3 Raw Material Characteristics Obtained from TGA and DSC Curves

	DSC				TGA (25–300°C) Weight loss (%)
ASA	Peak Temp (°C)	142	183		64.05
	Enthalpy (J/g)	−176.62	−28.78		
SA	Peak Temp (°C)	161	181		99.77
	Enthalpy (J/g)	−292.77	−116.68		
DCPD	Peak Temp (°C)	136.7	190		19.05
	Enthalpy (J/g)	−72.22	−408.43		
Mannitol	Peak Temp (°C)	168			
	Enthalpy (J/g)	−298			–
Trehalose	Peak Temp (°C)	100	119	196	12.24
Dihydrate	Enthalpy (J/g)	−192.01	−37.59	−133.60	

No major changes were observed in disintegration times as a result of storage (Fig. 2). The observed variations in 210 min dissolution efficiency and in ASA dissolution profiles (Fig. 3) can be explained by the above-mentioned reduction in tensile strength and increase in porosity during tablet storage.

DSC and TGA data of the raw materials included in the tablets and SA (Table 3) should be useful to understand the DSC and TGA thermograms of formulations studied before and after 6 months storage (Fig. 4).

DCPD DSC thermogram shows the occurrence of two dehydration stages (at 136.7°C and 190°C. Loss of weight calculated from TGA data follow two steps at the same temperatures with a total weight lost of 19.05%, less than the stoichiometric value of 20.9% (Landín et al., 1994b).

The trehalose thermal profile is characterized by two sharp endotherms with peaks at 100°C and 196°C, with a third, less well-defined endothermic region at 119°C. The weight loss profile between 90–125°C under the same experimental conditions was close to

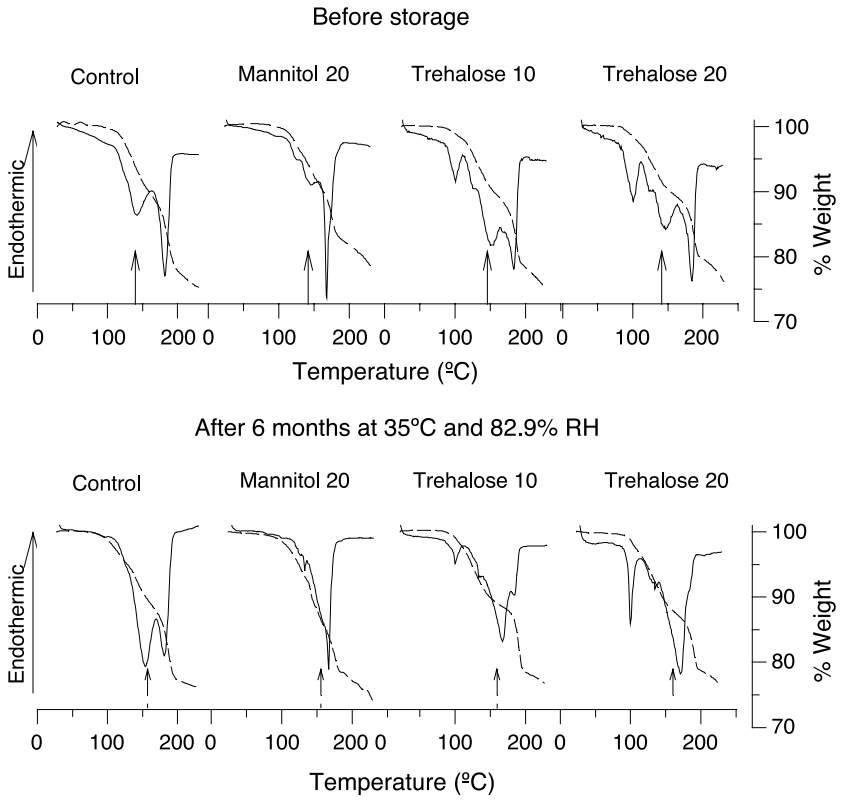

FIGURE 4 DSC (——) and TGA (– – –) Thermograms for Each of the Four Tablet Formulations Studied, Before and After 6 Months' Storage at 35°C and 82.9% RH. (⟶ ASA Peak; – – > SA Peak).

9.5%, linking DSC results to the dehydration of the dihydrate crystal (Taylor & York, 1998). Mannitol DSC thermogram has a single peak at 168°C corresponding to melting. ASA and SA can be characterized by main peaks at 142°C and 161°C, respectively.

DSC and TGA thermograms of tablets before and after 6 months storage proved very interesting, not withstanding the difficulty of interpreting DSC and TGA results for complex systems (in the present case up to five components).

The main transition seen in the thermograms can be attributed to hydrolysis of ASA (the peak at 160°C corresponding to SA was detectable after 6 months storage in all formulations). Moreover, TGA curves show that for all formulations, with or without sugar, the loss of weight in the range 25–230°C occurred in two main stages, at temperatures beyond 130°C, giving a total percentage weight close to 20%, thus indicating that DCPD (the majority component) does not dehydrate under at the storage conditions used in this study (Landín et al., 1994a).

Studies of ASA stability in solution

In order to investigate possible explanations for the observed effects of the sugars on the degradation of aspirin, ASA stability in solution was studied at 25°, 30°, 35°, and 40°C, in the presence or absence of TD or mannitol. The results show that both sugars significantly reduced the ASA degradation rate constant (Fig. 5).

The effect of sugars on the degradation rate of drugs in solution has been demonstrated for different authors. Mannitol or sucrose contribute to the stability of diltiazem in solution (Suleiman et al., 1988). Sucrose tends to inhibit the hydrolysis of aspirin and sorbitol exerts a pronounced stabilizing effect in solution (Delgado & Remers, 1998).

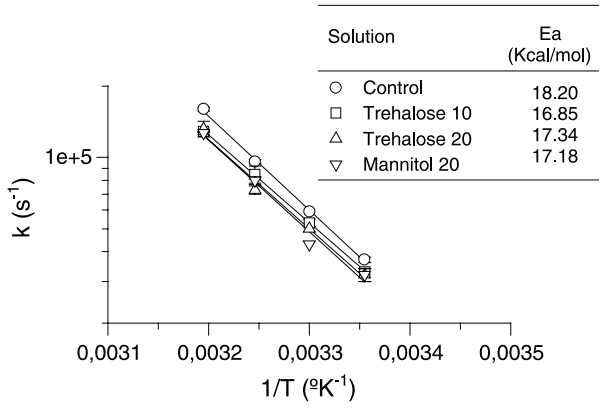

FIGURE 5 **ASA Degradation Rates in Solution Plotted Against Temperature (1/T; $°K^{-1}$) for Each of the Four Mixtures Studied. Activation Energy (Ea) was Calculated from Arrhenius Plots.**

The effect observed on the ASA hydrolysis rate can be related to the reduction in the dielectric constant of the water when sugars dissolution takes place. As a consequence, its capacity to isolate charged ions from the ionized ASA during the hydrolysis reaction should be reduced and the process becomes slower (Kelly, 1970).

Taking into account that the TD/ASA molar ratios studied were lower than the mannitol/ASA molar ratio, we can conclude that trehalose dihydrate has a stronger effect on ASA stability in solution than mannitol, in agreement with our solid state results.

It is not possible to quantitatively compare the solution and solid-state stability data precisely, because different kinetic models were used in each case; however, the effects of sugars in each state are clearly similar, as expected if ASA hydrolysis in solid-state occurs in the liquid interface at high relive humidity. Finally, the similar activation energies observed for all formulations suggest that neither TD nor mannitol substantially modifies the mechanisms involved in the degradation of aspirin.

CONCLUSIONS

The results of this study confirm that trehalose dihydrate, and less effectively mannitol significantly reduce the degradation of ASA in DCPD-based tablets stored at 35°C under high humidity, but do not protect against the decline in tablet mechanical properties observed under these conditions. The observed changes in mechanical, microstructural, and dissolution properties cannot be explained by dehydration of DCPD, and required further investigation. The ASA stabilization effects of trehalose dihydrate and mannitol were also observed in solution, indicating the existence of an interaction between these sugars and ASA.

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