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International Journal of Pharmaceutics 288 (2005) 335–348
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Crystal forms of tolbutamide from acetonitrile and 1-octanol: effect of solvent, humidity and compression pressure

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Received 26 April 2004; received in revised form 2 September 2004; accepted 20 October 2004

Abstract

The possibility of obtaining tolbutamide polymorphs was investigated using the solvents acetonitrile and 1-octanol. Tolbutamide is an oral hypoglycemic agent that exists in four polymorphic forms. Characterization of the various polymorphs was carried out by differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), infrared spectroscopy (FTIR), optical microscopy and dissolution studies. Form A, crystallized from acetonitrile, resembled the form I polymorph, while form O, crystallized from 1-octanol, resembled the form III polymorph. Tablets of both form A and form O were produced at compression pressures of 2500 lbs and 5000 lbs using cornstarch and talc and were exposed to 40%, 75% and 95% RH conditions. DSC and PXRD studies did not show any significant drug-excipient interaction. Moreover, the change in the crystalline state of either form upon exposure to humidity was not evident. Dissolution studies showed a significantly lower drug release rate from form O tablets compressed at 5000 lbs pressure and exposed to 95% RH. Pressure and humidity had no significant effect on the dissolution profiles on the form A tablets. It was concluded that form A was the robust choice for further formulation development.

Keywords: Tolbutamide; Solvent; Polymorph; Humidity; Pressure; Drug release

1. Introduction

The existence of a pharmaceutical solid as a polymorph, pseudo-polymorph or a solvate, have been the focus of continuous research because of their influence on the physicochemical properties of the drug (Giron, 2001). Many pharmaceutical solids exhibit "polymorphism", which may be defined as the ability of the same substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice (Haleblian and McCrone, 1969; Haleblian, 1975; Brittain, 1999). Polymorphic changes can be induced by heat, stress, or solvent mediated processes (Byrn, 1982). Different polymorphs of the same substance can have different physical properties such as melting points, chemical

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doi:10.1016/j.ijpharm.2004.10.006

reactivities, dissolution rates and bioavailability (Byrn, 1982; Brittain, 1999), due to differences in molecular packing. Thus, the knowledge of polymorphism is of importance in pharmaceutics since it can impact the dissolution rate, stability and the bioavailability of the formulation (Byrn, 1982).

The solvent plays an important role in the formation of polymorphs, as well as in polymorphic transitions. For example, in desolvation reactions, the product separates into a new crystal form, and the process usually involves (i) molecular loosening, (ii) breaking of host-solvent bonds, (iii) solid solution formation, and (iv) separation of another polymorph as a product phase (Byrn, 1982). Polymorphs can also be obtained by crystallization from a single solvent. Commonly used crystallization methods involve controlled temperature changes such as slow cooling of a hot saturated solution (for compounds more soluble at higher temperatures) or slow warming (for compounds less soluble at higher temperatures). Crystallizing solvents having varying polarities are preferred since molecules in such solutions tend to form different types of hydrogen-bonded aggregates (Byrn et al., 1994). Some solvents favor the crystallization of a particular form because they selectively adsorb to specific faces of the crystal. Hence, they either inhibit their nucleation (cluster formation), or retard their post-nucleation growth. Some of the commonly used crystallizing solvents are water, methanol, propanol, ethanol, isopropanol, acetone, acetonitrile, ethyl acetate, hexane, etc (Brittain, 1999). For example, sulfur crystallizes as orthorhombic crystals (α) from a carbon disulfide solution and as monoclinic crystals (β) from the melt (Byrn, 1982).

Stability of compounds exhibiting polymorphism is one of the primary concerns in the pharmaceutical area. Drug degradation in the solid and the semi-solid states is usually affected by water content, and the polymorphs having different affinity for water often exhibit different chemical reactivities. Moisture catalyzes chemical degradation either by (i) participating in drug degradation as a reactant, or (ii) by adsorbing onto the drug surface and forming a moisture-sorbed layer in which the drug is dissolved and degraded (Yoshioka and Stella, 2000). Other physico-chemical properties of pharmaceutical products that are affected by the presence of water, include flow, compaction and dissolution (Adeyeye et al., 1995).

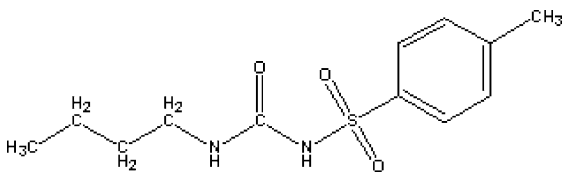

Fig. 1. Chemical structure of tolbutamide.

Compression pressure is an important parameter that needs to be monitored while investigating drug and excipients in tablet dosage forms. Several properties of tablets are influenced by compression pressure, namely (i) density and porosity, (ii) hardness and tensile strength, (iii) disintegration, and (iv) dissolution properties (Lieberman and Lachman, 1982). Compression pressures may also alter the crystal form of the drug leading to a polymorphic transformation (Brittain, 1999), which may also affect the tablet properties. For example, piroxicam showed phase transformation during compression when the needle like α-phase was converted to the cubic β-phase upon compression (Ghan and Lalla, 1992).

Tolbutamide (Fig. 1) (Chu et al., 1977) belongs to the aryl sulfonylurea group of compounds. Four polymorphic forms (I, II, III and IV) have been reported and characterized earlier (Simmons et al., 1972; Burger, 1975; Leary et al. 1981; Kimura et al., 1999), and these studies cite the use of benzene, hexane and ethanol as the crystallizing solvents for obtaining polymorphs. There are conflicting reports regarding the stability data of form I and III (Rowe and Anderson, 1984; Kimura et al., 1999). We investigated the possibility of crystallization of tolbutamide from two solvents acetonitrile and 1-octanol, and have compared them with the results in the literature. The effect of other factors such as compression pressure and humidity on crystalline properties has also been reported. In all cases, the dissolution profile of the drug has been investigated to note the effect of these factors on drug release from tablets.

2. Materials and methods

2.1. Materials

Tolbutamide (Sigma–Aldrich Co.), acetonitrile (Mallinckrodt Baker Inc.), 1-octanol (Fisher Scientific), cornstarch U.S.P. and talc U.S.P., sodium hy-

droxide (Fisher Scientific) and potassium phosphate (monobasic) (Fisher Scientific) were used "as is".

2.2. Methods

2.2.1. Sample preparation

One gram of the drug was accurately weighed and dissolved in 2 mL of acetonitrile, previously heated to 60 °C on a hot plate. The resulting solution was cooled overnight at room temperature. It was then filtered and vacuum dried for a week to obtain a completely dry residue. The same procedure was observed for crystallization from 1-octanol. The samples obtained from them were evaluated using DSC and PXRD studies.

2.2.2. Evaluation of untreated single components and physical mixtures

Tolbutamide samples obtained by crystallization from acetonitrile and 1-octanol were characterized by DSC and PXRD studies. IR and optical microscopy studies were carried out to further investigate the properties of the forms obtained. The DSC and PXRD traces of the individual excipients, cornstarch and talc were also analyzed. A physical mixture of drug, cornstarch and talc in the ratio of 1:1:1 was prepared to allow for maximum drug-excipient interaction. Solubility studies were carried out by dissolving known concentrations of each of the two drug samples in a known volume of dissolution medium (phosphate buffer, pH 7.4). The standard curve was obtained by plotting the concentration values as a function of the absorbance data.

2.2.3. Differential scanning calorimetry (DSC)

MDSC 2910 (TA Instruments), New Castle, DE, with Thermal Advantage® Universal Analysis® 2000 software for data analysis were used. Samples (5–7 mg) were weighed using a Mettler MT 5 microbalance, placed in a 40 μL crimped aluminum pan (closed lid-without pinhole) and placed in the DSC module, using an empty aluminum crimped pan as the reference. The sample was heated at a rate of 10 °C/min from 25 °C to 150 °C (or 160 °C for drug-excipient mixtures). Nitrogen flow was maintained at 50 mL/min and ice was used as the coolant. The DSC was calibrated by the melting points of indium (156.6 ± 0.2 °C) and zinc (419.5 ± 0.3 °C) standards.

2.2.4. Powder X-ray diffraction (PXRD)

XDS 2000 Unit (Scintag Inc.) was used (Cu Kα radiation, $(= 1.54$ Å), with a scan rate of 1°/min, step size of 0.02, and a 2θ range of 5–40°. The sample was powdered finely and placed in a plastic sample holder (1 in.^{2}).

2.2.5. Infrared spectroscopy (IR)

IR studies were carried out using Nicolet 60 SX FTIR model, by diluting the drug into KBr pellets. The results were analyzed using GRAMS/32 software. Nitrogen was used as the purge gas and the sample was purged for about a minute.

2.2.6. Optical microscopy

Crystal images were taken using an Optical Microscope (Nikon SMZ 1500) with Nikon Coolpix 990 (3.34 MPixel) digital camera. The sample was mounted on a glass slide and examined under both normal and polarized light.

2.2.7. Manufacture of tablets

A Carver Laboratory Press (Model C, FREDS Carver Inc.) was used for the manufacture of tablets. A 0.9 cm diameter concave punch and die were used, and the pressures applied were 2500 lbs and 5000 lbs, with a 1-min residence time. Physical mixtures of drug and excipients (cornstarch and talc) were prepared by thorough mixing using a glass mortar with a pestle. Each 300 mg portion of the physical mixture contained 250 mg drug, 45 mg cornstarch and 5 mg talc. The two drug samples (crystallized from the two different solvents) were used. Two batches of 24 tablets each were compressed at each of the two pressures and stored in airtight amber colored bottles. Six tablets from each batch (three each for 2500 lbs and 5000 lbs pressures) were used as control for dissolution studies. Physical mixtures containing the same proportion of drug, cornstarch and talc were prepared for the humidity studies.

2.2.8. Humidity studies

The tablets and physical mixtures of drug and excipients were placed on small plastic boats within glass humidity chambers. Hundred milliliters aqueous solutions containing appropriate concentrations of sodium hydroxide were employed to obtain the desired relative humidity conditions inside each of the chambers. The samples were subjected to humidity conditions of

45%, 75% and 95% for 7 days. The chambers were well sealed with Parafilm® and a layer of petroleum jelly for proper sealing and prevention of water entry or escape. After 7 days of exposure, the tablets and physical mixtures were removed from the humidity chambers and characterized by DSC and PXRD studies to assess any possible effects of water sorption. The drug release rates from the tablets (both in hydrated as well as in control) were analyzed by the dissolution study. The same was repeated for the second batch of tablets.

2.2.9. Dissolution test

The dissolution studies were carried using a Vanderkamp 600, six-spindle apparatus and Cary 5 UV–vis–NIR Spectrophotometer to measure the absorbance at a λ_{max} of 226 nm. Nine hundred milliliters of dissolution medium (phosphate buffer of pH 7.4 in accordance with U.S.P. 25, N.F. 20, 2002) was used. The temperature was maintained at $37 \pm 1^{\circ}C$ and the number of paddle rotations was adjusted to 75 rpm. At regular time intervals, 5 mL of the dissolution medium was pipetted out and assayed spectrophotometrically. Sodium hydroxide and potassium phosphate were used for the preparation of the buffer, and the pH was adjusted using a pH-meter (pH 211, Hanna Instruments). A calibration curve was prepared for tolbutamide prior to the dissolution studies to obtain a reference for determination of drug release rates. Dissolution studies were conducted for a period of 90 min. All studies were carried out in triplicates.

2.2.10. Statistical analysis

The SAS (version 8) software was used as the statistical analysis program to analyze the results obtained from the dissolution studies. The concentration of drug released (mg/5 mL) over different time intervals constituted the sample pool with pressure and humidity as variables (repeated measures ANOVA). The results were interpreted at the significance level of $\alpha = 0.05$.

3. Results and discussions

3.1. Evaluation of samples crystallized from different solvents

Fig. 2 shows the DSC overlay of drug samples crystallized from 1-octanol and acetonitrile along with that of the commercial drug. It can be observed that the sample crystallized from acetonitrile (form A) is identical to that of the commercial form of tolbutamide. A small melting endotherm is observed ~40 °C, followed by a

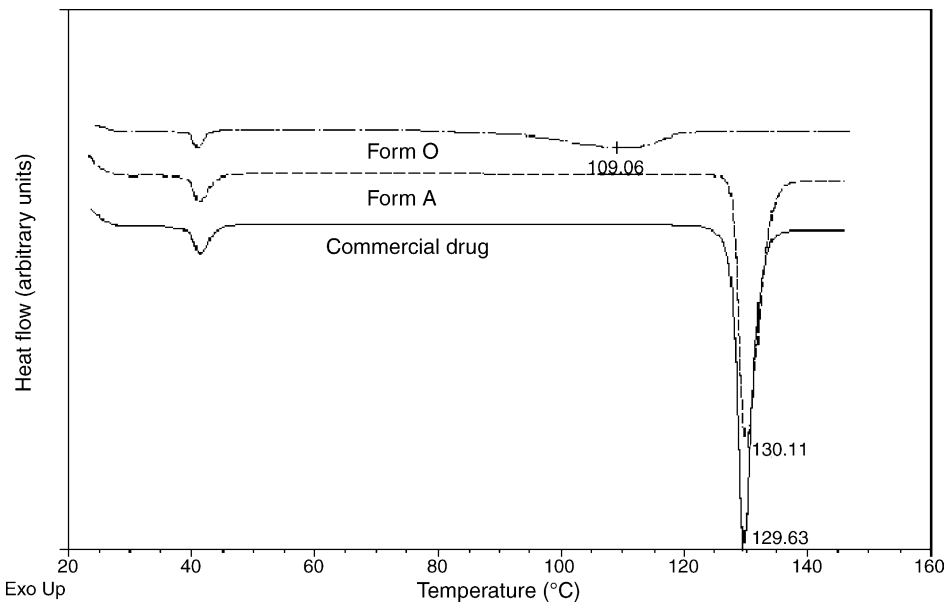

Fig. 2. DSC heating curves of form O, form A, and commercial tolbutamide.

Table 1
DSC results of Form A and Form O of tolbutamide

Form	Onset (°C)	Peak (°C)	Enthalpy (J/g)
Form A			
Peak 1	40–41	42–43	6–7
Peak 2	125–128	127–130	87–94
Form O			
Peak 1	40–41	41–42	4.6–6.2
Peak 2	94–98	102–111	43.5–54

sharp one at ∼130 °C. The first melting endotherm has been explained as a "simple rearrangement of hydrogen bonds" in the molecule (Leary et al., 1981). The second melting endotherm depicts the melting point of tolbutamide (126–132 °C). The DSC profile of the sample crystallized from 1-octanol (form O) is different from that of form A. The first melting endotherm appears duly around 40 °C. This is followed by a second, broad melting endotherm at about 109 °C (results summarized in Table 1) that indicate differences in melting behavior and thus a possibility of polymorph formation. The DSC profile of form A was identical to that of form I polymorph of tolbutamide (Simmons et al., 1972; Burger, 1975; Leary et al. 1981). The DSC profile of form O closely resembles form III, which shows a second melting endotherm between 98 °C and 118 °C (Rowe and Anderson, 1984).

The PXRD studies proved to be more conclusive since X-ray diffraction provides a fingerprint for polymorphic identification. The PXRD patterns of the samples show some striking differences. The PXRD pattern of form O shows a strong peak at 15.7°2θ, which is absent in the PXRD pattern of form A. A similar marker peak at 15.4°2θ was obtained in the PXRD pattern of form III polymorph of tolbutamide, as reported earlier (Kimura et al., 1999). Form A showed the same PXRD pattern as form I with marker peaks at 8.7° and 12.1°2θ. Fig. 3 shows the PXRD overlay of the two forms of tolbutamide.

The FTIR studies of these two forms showed some peak shifts for form O in the "C–H stretching region" of 2850–3000 cm^{-1} and in the S=O stretching frequency of 1350–1140 cm^{-1} as compared to that of form A. No evidence of solvent (1-octanol) binding was apparent for form O since a broad –OH stretch was not obtained at a frequency of 3400–3200 cm^{-1}. Since a comparison of the IR patterns of the two forms did not yield any major shift of peaks, this technique did not prove to be

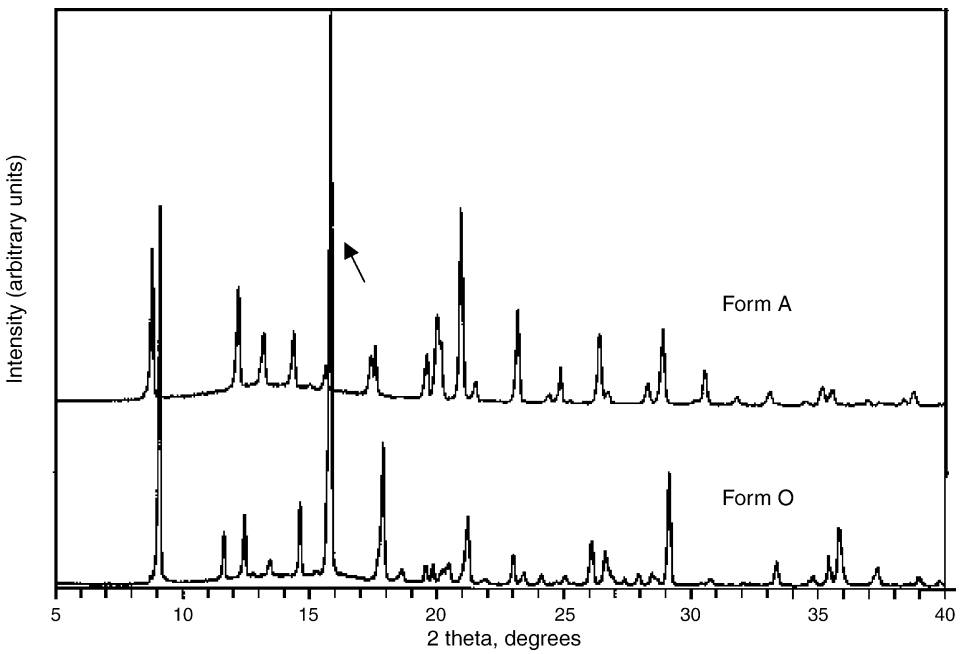

Fig. 3. PXRD patterns of form A and form O of tolbutamide (↑ indicates the marker peak).

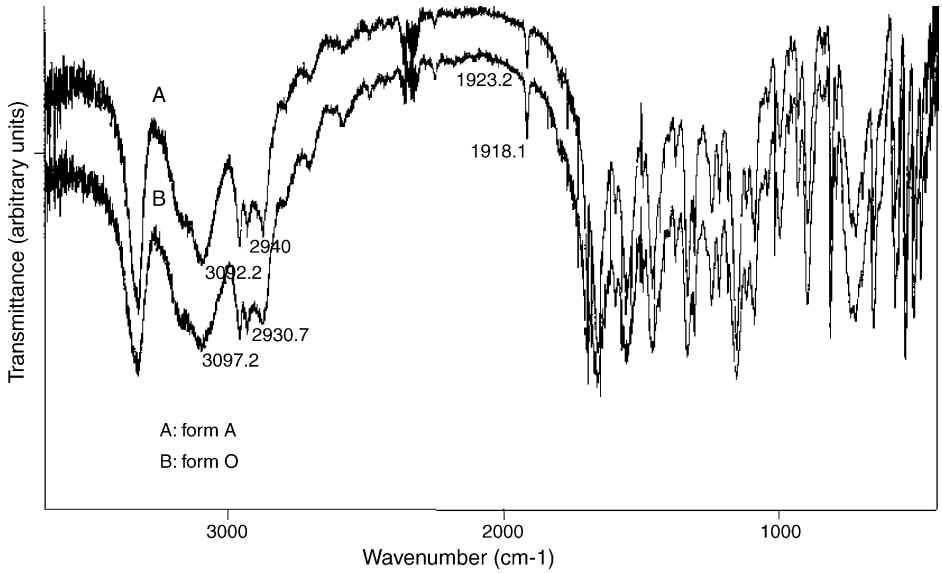

Fig. 4. FTIR patterns of form A and form O of tolbutamide.

very conclusive in the characterization of the two polymorphic forms. It has been proposed that this similarity in FTIR patterns of tolbutamide polymorphs is due to the presence of a "similar hydrogen-bonding network" (Kimura et al., 1999). The FTIR overlay of the two forms is shown in Fig. 4.

Optical microscopy of form A revealed large, isolated plate like crystals (Fig. 5). On the other hand, form O showed clusters of small, needle shaped crystals (Fig. 6). The visual confirmation of change in crystal habit of the two forms thus provided further evidence of existence of two different polymorphs. In a previous study (Kimura et al., 1999), the optical images of form I polymorph of tolbutamide showed plate like crystals and that of form III showed needle like crystals. Thus from all the characterization methods utilized so far, form A is identical to the form I polymorph and form O shows the closest resemblance to the form III polymorph.

3.2. Evaluation of untreated excipients and untreated drug-excipient physical mixtures

The DSC and PXRD profiles of cornstarch and talc were obtained, which agreed well with the literature. The PXRD profile of a 1:1 mixture of the excipients showed negligible crystallinity. A diffused PXRD pattern was obtained with two prominent peaks at of 9.1° and 28.2°2θ. To verify whether drug-excipient interactions are important to consider in this case, physical mixtures of drug: corn starch: talc at a ratio of 1:1:1were investigated in order to maximize the possibility of interaction of the three components. The DSC profiles of these mixtures do not show any evidence of interaction since all the major peaks of the individual components could be detected in the DSC pattern for both form A and form O mixtures (Fig. 7). PXRD studies showed no interaction for form A (Fig. 8) but some changes in were observed for form O (Fig. 9). In the 11°–14°2θ region, the 11.8°2θ peak was absent and there were some peak shifts for the drug-excipient mixture. Besides, the marker peak was not as prominent in the form O-excipient mixture as compared to that of Form O alone. Such changes probably do not indicate any significant interaction and could result due to the preferred orientation of the needle-like crystals in the PXRD holder. Thus, it was evident from both DSC and PXRD studies that a significant drug-excipient interaction did not exist in the physical mixture. Hence, tablets (for both the forms) were formulated containing 250 mg drug with 45 mg cornstarch as diluent and 5 mg talc. Physical mixtures of the same drug and excipient concentrations were also made for the humidity studies.

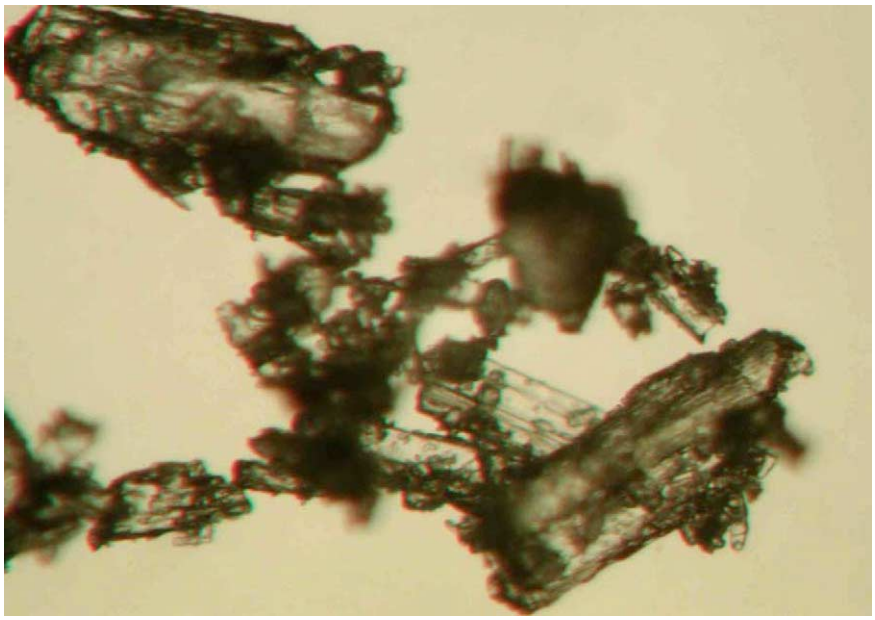

Fig. 5. Polarized light microscopy image of form A.

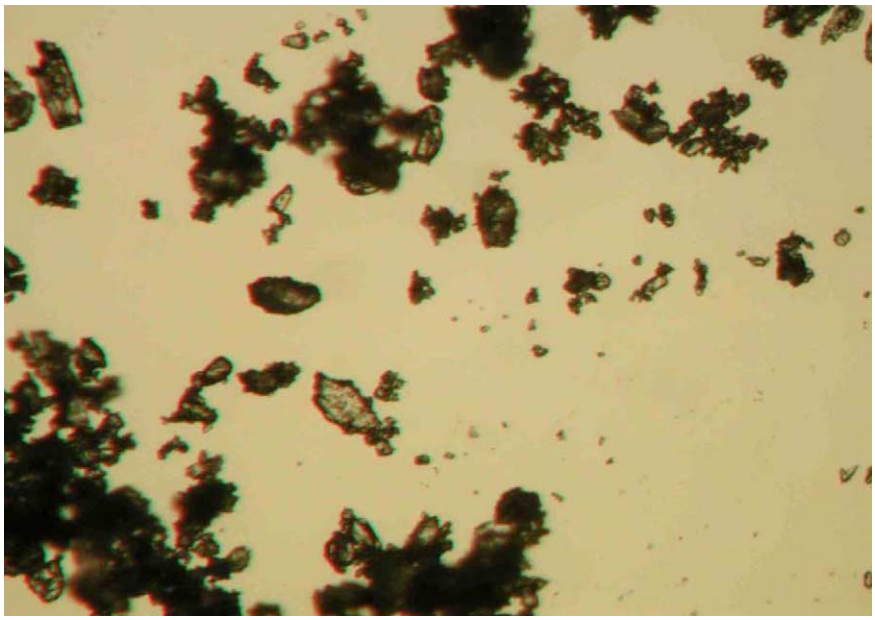

Fig. 6. Polarized light microscopy image of form O.

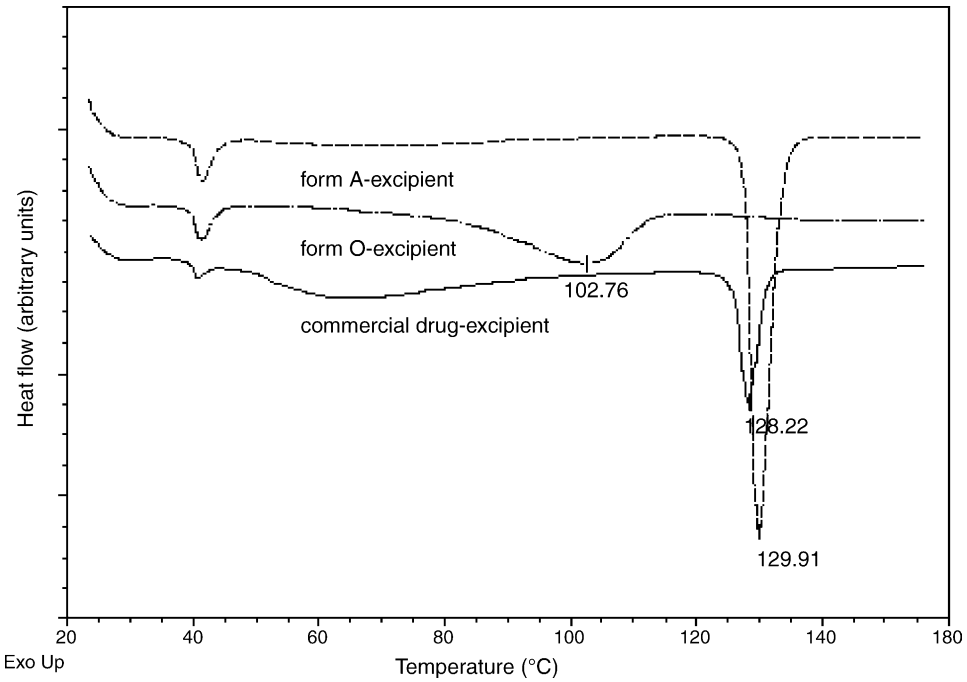

Fig. 7. DSC heating curves of drug-excipient mixtures: form A, form O, and commercial drug.

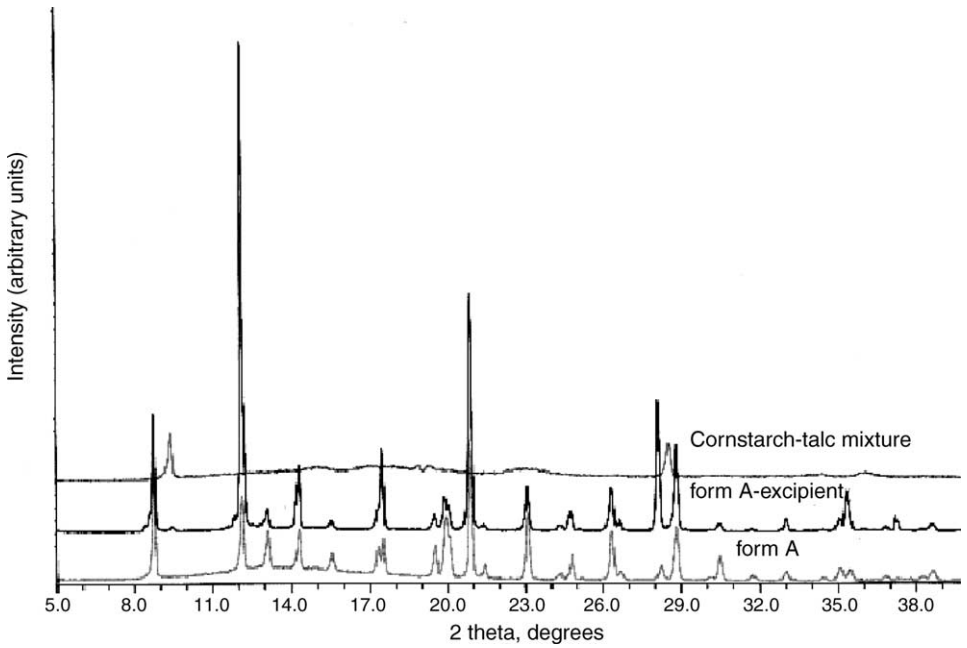

Fig. 8. PXRD patterns of excipients, form A-excipient mixture, and form A.

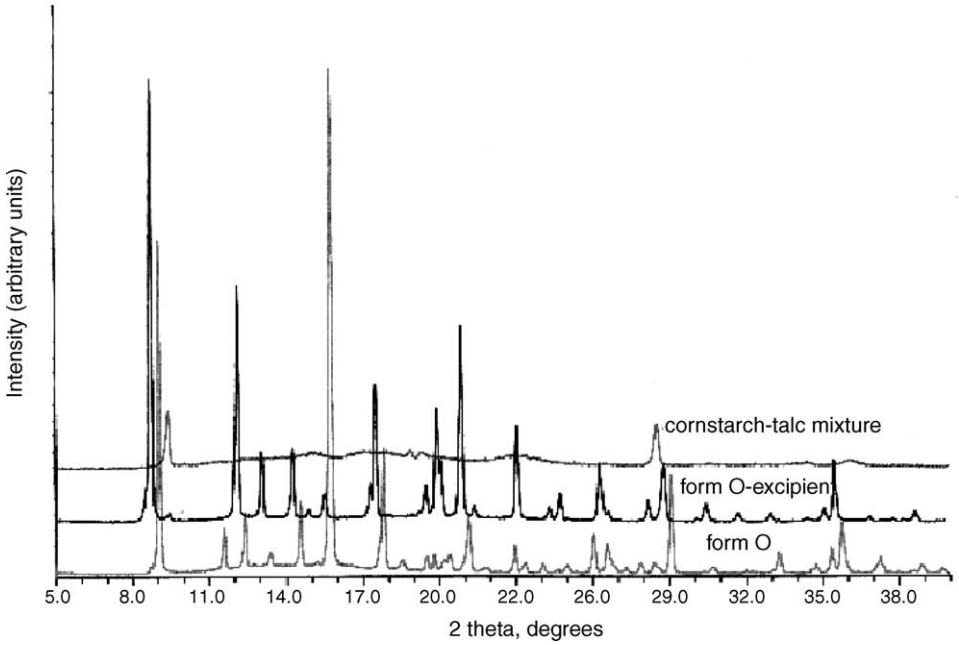

Fig. 9. PXRD patterns of excipients, form O-excipient mixture, and form O.

3.3. Evaluation of the hydrated physical mixtures

The DSC overlays of form A-excipient mixture (Fig. 10) and form O-excipient mixture (Fig. 11) do not show any change in the thermal profiles of the drug after exposure to different humidity conditions. The PXRD profiles of tableting mixtures of both form A (Fig. 12) and form O (Fig. 13), at different humidity conditions do not show any changes from the control either. This indicates that there has been no change in the two forms (in the tableting mixture) under all humidity conditions studied.

3.4. Drug release studies

The drug release profiles of the hydrated tablets versus the control (two different compression pressures, and 3 humidity conditions) are shown in Figs. 14 and 15 for form A, and Figs. 16 and 17 for form O. The drug release patterns of hydrated form A tablets (45%, 75% and 95%) was largely similar to that of the control. Statistical analysis did not show any significant variations within the dissolution patterns for form A hydrated tablets under the effects of pressure and humidity, except in one case. The 90 min time point at 95% RH with a 2500 lbs pressure, showed a statistically significant higher drug release value (Fig. 14). However, in the opinion of the authors, a reasonable physical explanation for this phenomenon is unlikely and the data point can be construed as an artifact. In the case of form O, the 95% humidity conditioned tablets showed a consistently lower drug release rate than those subjected to 45% and 75% RH conditions. This was observed for both the 2500 as well as 5000 lbs compaction pressures. A summary of percentage drug release values is shown in Table 2 (form A tablets) and Table 3 (form O tablets). Increasing the compression

Table 2
Drug release (%) from form A tablets under the various experimental conditions after 90 min

Relative humidity	Compression pressure (lbs)	
	2500	5000
Control	78%	75%
40%	90%	71%
75%	84%	72%
95%	124%	70%

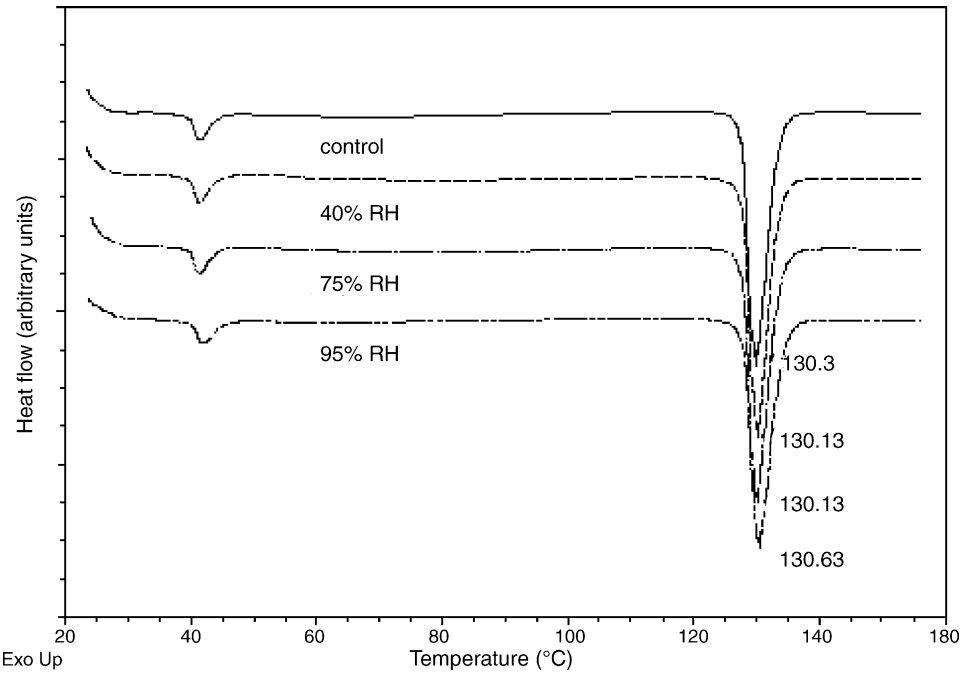

Fig. 10. DSC heating curves of form A tolbutamide-excipient tablet mixtures for control, 40% RH, 75% RH, and 95% RH samples.

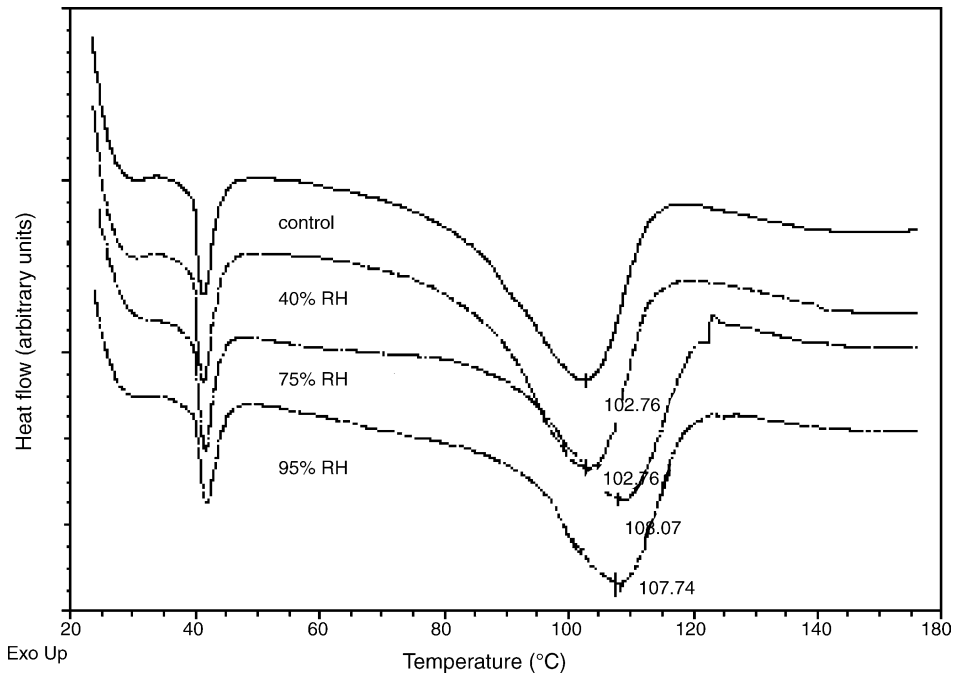

Fig. 11. DSC heating curves of form O tolbutamide-excipient tablet mixtures for control, 40% RH, 75% RH, and 95% RH samples.

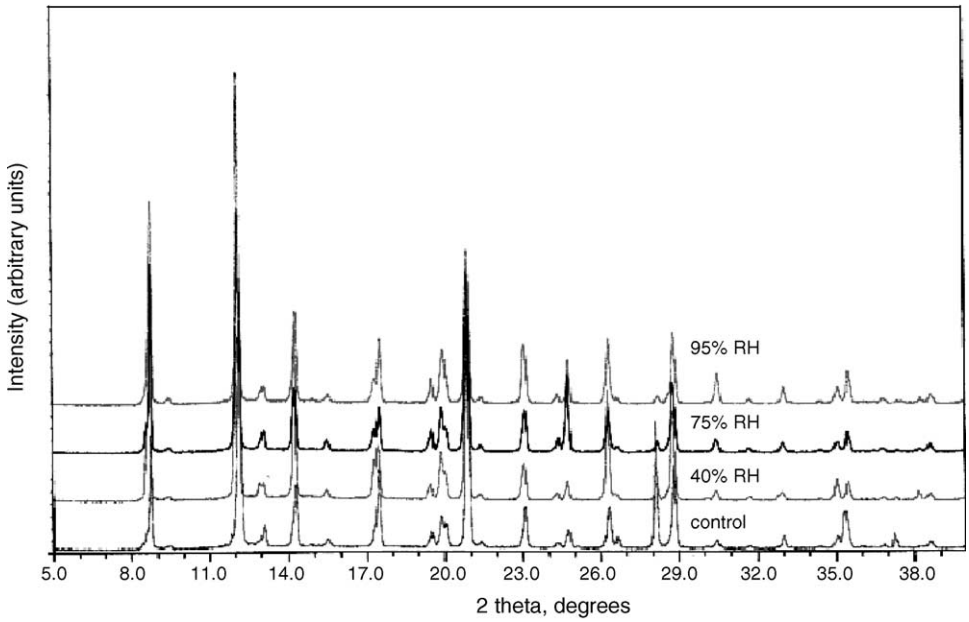

Fig. 12. PXRD patterns of form A tolbutamide tablet mixture for 95% RH, 75% RH, 40% RH, and control samples.

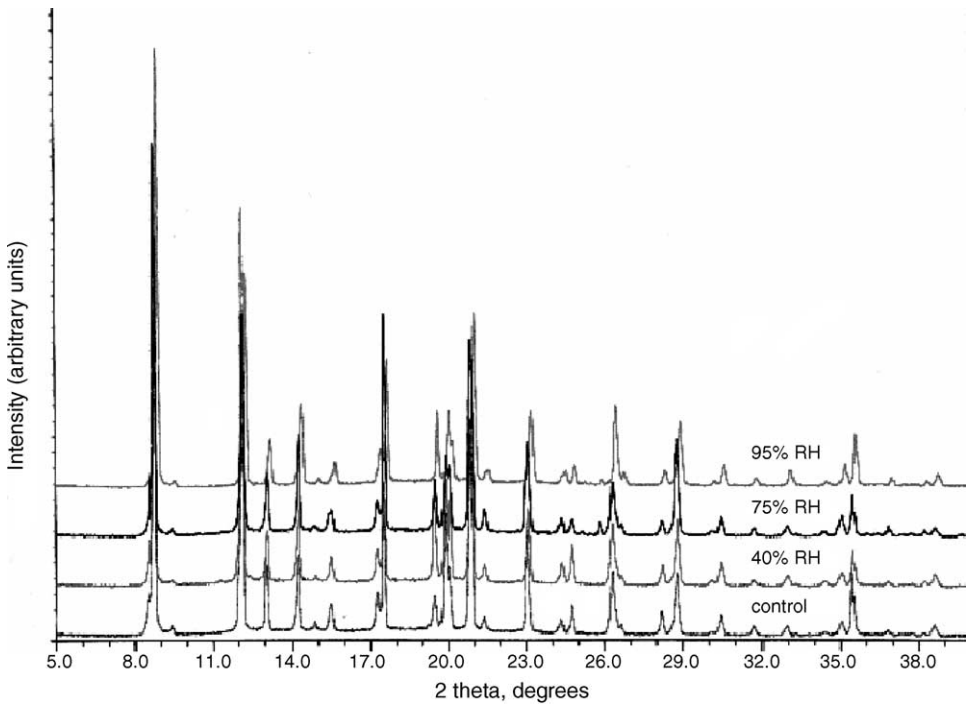

Fig. 13. PXRD patterns of form O tolbutamide tablet mixture for 95% RH, 75% RH, 40% RH, and control samples.

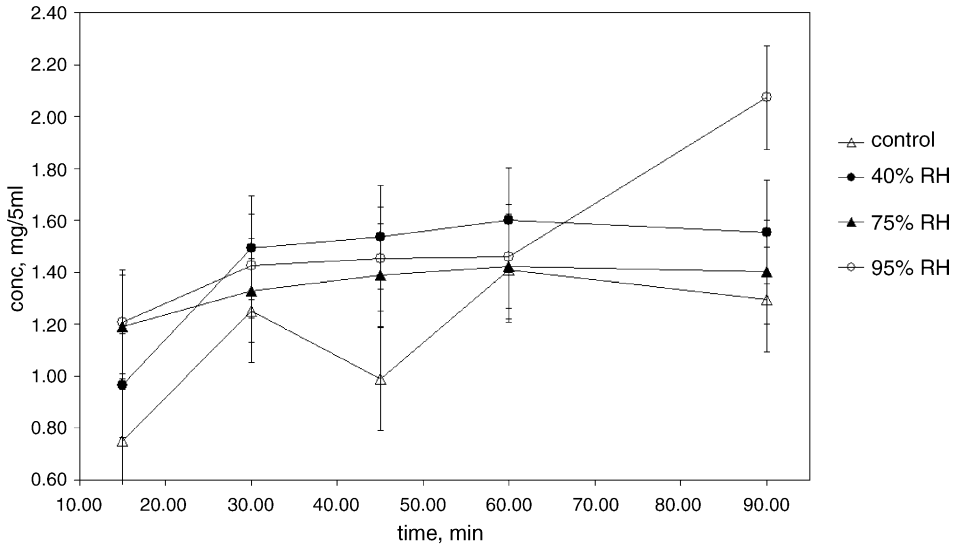

Fig. 14. Dissolution profiles of form A tolbutamide tablets (2500 lbs).

pressure causes the formation of harder tablets, which in turn prolongs the disintegration process of the tablet and hence delays the deaggregation. This decreases the drug release rate, and is supported by the lower drug release values (%) of the form A and form O tablets (2500 lbs versus 5000 lbs) in Tables 2 and 3. The effect of RH on the in vitro release profile was the most significant for form O tablets, as corroborated by statistical analysis. Poor drug release was observed for form O tablets exposed to 95% RH at both 2500 lbs and

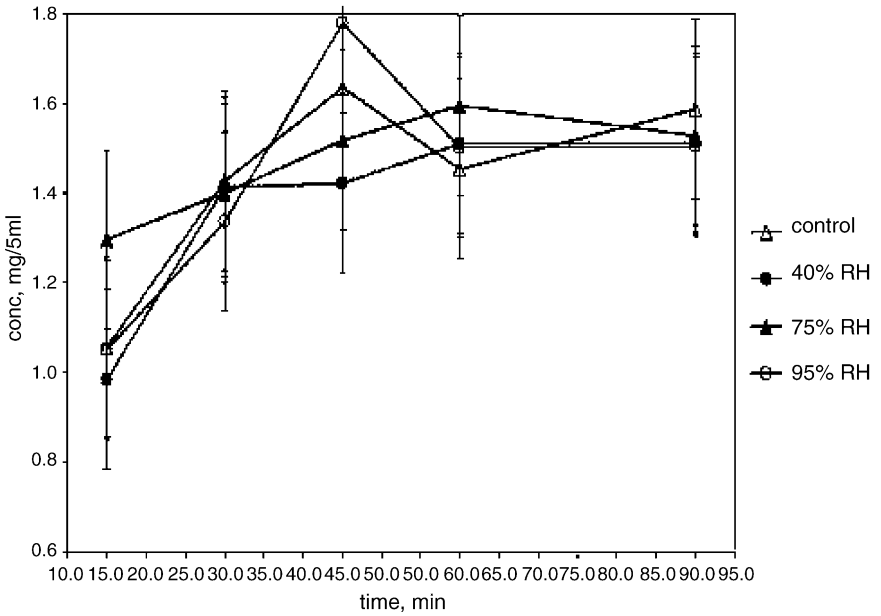

Fig. 15. Dissolution profiles of form A tolbutamide tablets (5000 lbs).

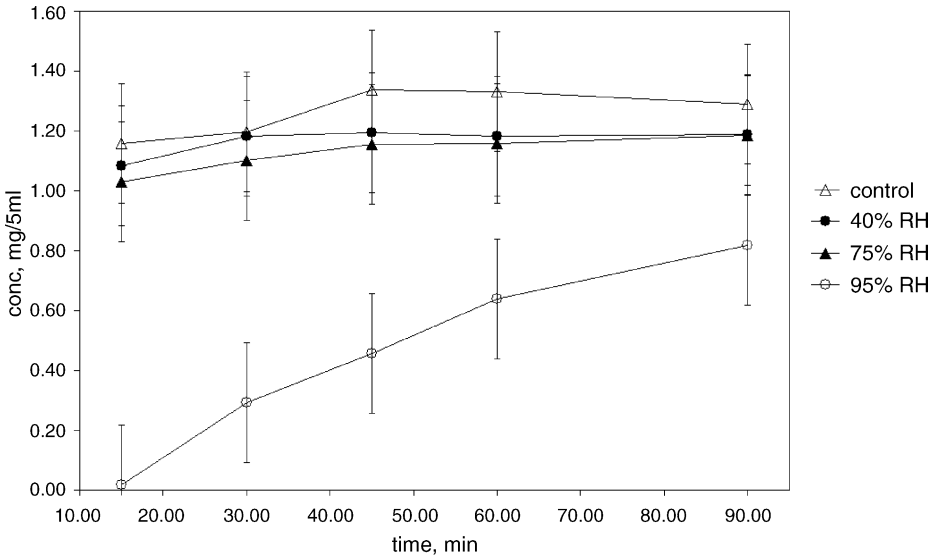

Fig. 16. Dissolution profiles of form O tolbutamide tablets (2500 lbs).

5000 lbs compression pressures (Table 3). One possible explanation for such a decreased release may be the surface gelation of the cornstarch (15%, w/w) present per tablet. At lower RH, the tablet disintegrates and the drug release takes place mainly by the surface erosion mechanism but at higher RH conditions, erosion of the tablet matrix is retarded due to gelation and hence drug release occurs by mainly by diffusion, rather than erosion (Roy et al., 2003). It is interesting to note that form A does not conform to this hypothesis. Another possible reason could be that form O is unstable as compared to form A. Low release rates result from the formation of other poorly soluble polymorphs of tolbutamide as a result of solvent-mediated phase tran-

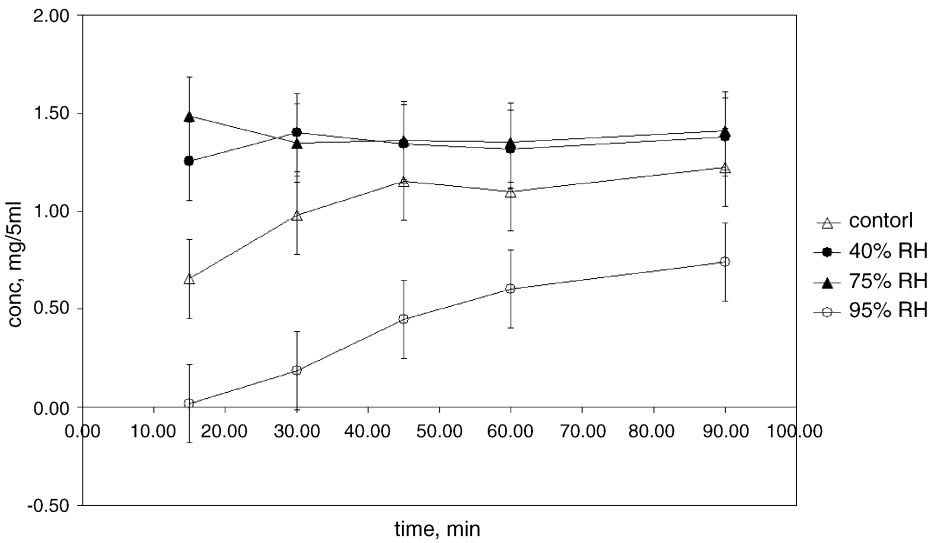

Fig. 17. Dissolution profiles of form O tolbutamide tablets (5000 lbs).

Table 3
Drug release (%) from form O tablets under the various experimental conditions after 90 min

Relative humidity	Compression pressure (lbs)	
	2500	5000
Control	90%	73%
40%	83%	75%
75%	81%	74%
95%	49%	45%

sitions. These explanations, however, are speculative at this point and warrant further investigation.

4. Conclusion

Acetonitrile and 1-octanol have been used for the preparation of two polymorphic forms of tolbutamide. From the DSC, PXRD, optical microscopy and dissolution studies it was concluded that form A (from acetonitrile) is the same as form I polymorph and form O (from 1-octanol) is similar to form III polymorph previously reported by other workers (Simmons et al., 1972; Burger, 1975; Leary et al. 1981; Kimura et al., 1999). Although considerable controversy exists over the stability of these two forms, the present study showed both form O and form A to be stable at room temperature. Optical microscopy revealed large, isolated plate like crystals for form A and clusters of small, needle shaped crystals for form O. The study of the effects of humidity and compression pressure on the crystalline properties and dissolution characteristics of the two forms in the prepared tablets showed that there is no drug-excipient interaction in the test physical mixtures (1:1:1 ratio of drug, corn starch and talc). In the tableting mixtures containing 250 mg drug, 45 mg cornstarch and 5 mg talc, there was no significant change in the crystalline properties of both forms after exposure to 40%, 75% or 95% RH. The dissolution study of the tablets (hydrated and control) for the two forms did not show any significant variation for form A ($\alpha = 0.5$). The hydrated tablets of form O exposed to 95% RH showed a consistently low drug release profile for both 2500 lbs and 5000 lbs compression pressures. Thus form A is a robust candidate for further formulation development.

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