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Evaluation of crystallinity and drug release stability of directly compressed theophylline hydrophilic matrix tablets stored under varied moisture conditions

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Abstract

The effects of relative humidity (RH) and compression pressure on drug/excipient crystal changes or drug release of theophylline tablets were studied using X-ray diffractometry (X-RD), differential scanning calorimetry (DSC) and dissolution analysis. A tablet formulation, containing hydroxypropyl methylcellulose (HPMC), microcrystalline cellulose (MCC) and anhydrous magnesium stearate was compressed at pressures such as 194.8 and 274.4 MPa, and stored at 23°C for 3 months under different RH values, ranging from 31 to 100%. Moisture sorption isotherms of all the tablets studied indicated sorption of large amounts of moisture at RH > 52%. Powder X-RD patterns of tablets stored at RH ≤ 52% indicated no change in crystallinity after 3 months, while in tablets stored at RH > 52%, theophylline monohydrate peaks were observed within 1 month and characteristic anhydrous theophylline peaks decreased. Peaks corresponding to pseudopolymorphs of magnesium stearate were also observed. DSC analysis of tablets stored at ≤ 52% revealed only the endothermic peak of theophylline at 277°C, while in tablets stored at > 52% RH, the endothermic peak of theophylline, and that of magnesium stearate pseudopolymorphs at 72°C were observed. Moisture sorption or crystal form was not affected by compression pressure. Drug release decreased as the compression pressure increased, and/or becomes inconsistent as a result of the formation of the less soluble theophylline monohydrate, partial hydration of the MCC and gelation of the HPMC. The drug dissolution data at the onset did not fit the Higuchi square-root model, but rather revealed a biphasic release pattern, indicative of faster, initial surface erosion followed by a slower diffusion-based mechanism from the gelled matrix. Higher RH resulted in a tendency towards a diffusion-only mechanism.

Keywords: Anhydrous theophylline tablet; Direct compression; Relative humidity; X-ray powder diffraction; DSC; Drug release; Theophylline monohydrate; Magnesium stearate pseudopolymorph

1. Introduction

The physical-chemical properties of pharmaceutical solids, such as flow, compaction, hardness and dissolution are dependent on the pres-

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ence of moisture and several reports have been made in the literature to this effect (Carstensen, 1977; Zografi and Kontny, 1987; Zografi, 1988; Ahlneck and Zografi, 1990; Kontny and Conners, 1992). In heterogeneous pharmaceutical solids or formulations, the study of moisture sorption is very complex, more so if both amorphous, non-hydrating and crystalline or crystalline/partly crystalline active ingredient/excipients are present. This is because amorphous excipients such as celluloses and starches can sorb enough moisture into their structures (as distinct from adsorption in which the water molecules are confined to the surface of the particles) to cause significant changes (swelling and gelation at high relative humidities) that will affect the overall properties of the formulation (Zografi, 1988; Ahlneck and Zografi, 1990).

In crystalline materials such as caffeine and theophylline in which hydrogen bonding is relatively weak, water molecules can produce hydrate stabilization primarily due to their space filling roles (Bryn, 1982; Zografi, 1988). The changes in the physical-chemical properties of these pharmaceutical solids may affect their bioavailability. It has been reported that there was a decrease in drug release from theophylline-microcrystalline cellulose pellets prepared by wet granulation due to the formation of additional binding between theophylline and microcrystalline cellulose and influenced by relative humidity (Herman et al., 1989). In another study the decrease in drug release was attributed to the formation of theophylline monohydrate (Herman et al., 1988). The formulation used in these investigations contained partially hydrating MCC and not a non-hydrating amorphous excipient like HPMC. In an earlier study, it was found that the anhydrous theophylline was more soluble than the monohydrate which has decreased bioavailability (Shefter and Higuchi, 1963).

The characterization of the crystal changes has often been performed by X-ray diffraction analysis (X-RD) and differential scanning calorimetry (DSC). The effect of moisture on single anhydrous theophylline crystals or the tablets of the pure components has been investigated using X-ray diffraction analysis (Naqvi and Bhattacharyya, 1981; Otsuka et al., 1990, 1991). The effect of hydration and tablet compression pressure on some of the physical-chemical properties of two anhydrous types of theophylline, compressed at 5, 10 and 15 MPa has been investigated. The workers reported that the hydration of both types decreased with increased tabletting pressure and that the change of theophylline to the monohydrate was achieved after 200 h (at 35°C and 95% relative humidity) in all the tablets (Otsuka et al., 1991). Some investigators (Muller, 1977; Ertel and Carstensen, 1988) studied the crystallinity of pure magnesium stearate and concluded that the trihydrate was formed at an RH > 50%.

In this study, we investigated the effect of moisture (using different relative humidities) on the crystal changes of anhydrous theophylline and excipients in a heterogeneous tablet formulation (containing MCC, HPMC and magnesium stearate) compressed at very high pressures on a commercial tablet press. X-RD, DSC and dissolution analysis were used in the evaluation of the crystallinity of the formulation components.

2. Materials and methods

2.1. Materials

Anhydrous theophylline and hydroxypropyl methylcellulose or HPMC (Methocel E10 CR®) were obtained as gifts from BASF, Knoll Fine Chemicals Division, Morris Plains, NJ and Dow Chemical Co., Midland, MI, respectively. Microcrystalline cellulose (Avicel PH 101®) was obtained from FMC Corp., Philadelphia, PA, while magnesium stearate was from Nuodex Inc., Piscataway, NJ.

2.2. Methods

2.2.1. Formulation and compression of tablets

Theophylline tablets were directly compressed using 300 mg anhydrous theophylline, 353 mg microcrystalline cellulose (MCC), 73 mg hydroxypropyl methylcellulose (HPMC) and 7.3 mg magnesium stearate. The powders were mixed for 5

min in a twin-shell blender at 30 rpm. Magnesium stearate was premixed in a planetary mixer with 20 times its quantity of Avicel, in order to prevent its agglomeration. Three different batches of the blend were compressed at 137.2, 194.8 and 274.4 MPa. pressure, respectively, at a machine speed of 25 rpm, using an 18-station fully instrumented, rotary tablet press (model HT AP 18SS-U/1, Elizabeth-Hata Inc., North Huntingdon, PA) equipped with 15/32 inch concave punches and dies. The high compression pressures were used with the aim of attaining a sustained release effect.

2.2.2. Content uniformity

Assays of the drug content of three tablets (in triplicate) were carried out by crushing previously weighed tablets in a mortar and pestle and placing 100 mg of the powder in a 10 ml flask, mixing adequately with water, filtering with a 0.45 μm filter and measuring the UV absorbance of the diluted portion at 271 nm with a Perkin Elmer UV-VIS spectrophotometer.

2.2.3. Moisture sorption studies

Saturated salt solutions were used to create 31, 52, 76, 95% relative humidities (RH) in respective humidity chambers. Water was used for the 100% RH chamber. 10 tablets compressed at the different pressures were weighed and placed in tared petri dishes. The dishes were placed uncovered along with the respective covers in the humidity chambers. At predetermined time intervals during the 3 month study period, the petri dishes were removed and the lids replaced on each dish before equilibrating for 30 min at room temperature. Each dish was weighed on an analytical balance and the percent weight gained, relative to the dry tablet weight, was recorded. The procedure was repeated until a near constant weight was reached.

The single components, theophylline, magnesium stearate, microcrystalline cellulose and hydroxypropyl methylcellulose, as well as the binary mixtures were hydrated for 1 week. The samples were evaluated for crystal changes using the X-ray powder diffraction method.

2.2.4. X-ray diffraction studies

X-ray diffraction analysis was performed using a Phillips PW 3710 scanner/PW 1830 generator with a CuKα anode at 40 kV and 40 mA. Random sample mounts were scanned between $2\theta = 5$ and 50°.

2.2.5. Thermal analysis

The heat of fusion of the pure components and the tablets was determined using a differential scanning calorimeter (DSC-50 Shimadzu) from 20 to 330°C. The sample, 5 mg (contained in a sealed aluminum pan), was analyzed at a heating rate of 10°C per min in static air.

2.2.6. Dissolution analysis

Tablets compressed at the three different pressures were similarly placed in the different humidity chambers and used for dissolution studies at predetermined time intervals. Dissolution was carried out using a USP paddle type II apparatus at 100 rpm. Simulated intestinal fluid, 900 ml (pH 7.2) was used at 37°C and the drug release was monitored for 12 h.

2.2.7. Hardness and thickness tests

The thickness and hardness of the tablets were determined using the Pharma Test® model PTB 311 tablet tester (Scientific Instruments Technology Corp., NJ).

3. Results

3.1. Content uniformity

The assayed drug content was within 100 ± 1.5% of the amount added to the formulation, on a per tablet basis.

3.2. Moisture sorption

Increased amounts of moisture were absorbed into the tablets at RH > than 52%. The pattern of absorption, although depicted as due to capillary condensation, is a likely result of moisture sorption into the polymer materials especially microcrystalline cellulose which makes up the ma-

jority of the tablet (Fig. 1). Compression pressure did not appear to affect the sorption pattern.

3.3. X-ray diffraction analysis

3.3.1. Tablets

The X-ray powder diffraction patterns of the tablets stored at 31 or 52% RH for 1 or 3 months have identical patterns with distinct peaks at $2\theta = 5$, 12, 15, 23, 25, 27 and 29°. Tablets stored above 52% RH also showed similarity in peak intensities. However, in contrast to tablets stored at $\leq 52\%$ RH, sharp hydrate peaks of theophylline monohydrate and pseudopolymorphs peaks of magnesium stearate were observed at $2\theta = 11$, 15 and 27°. Typical diffraction patterns for tablets stored at ≤ 52 and $> 52\%$ are shown in Fig. 2.

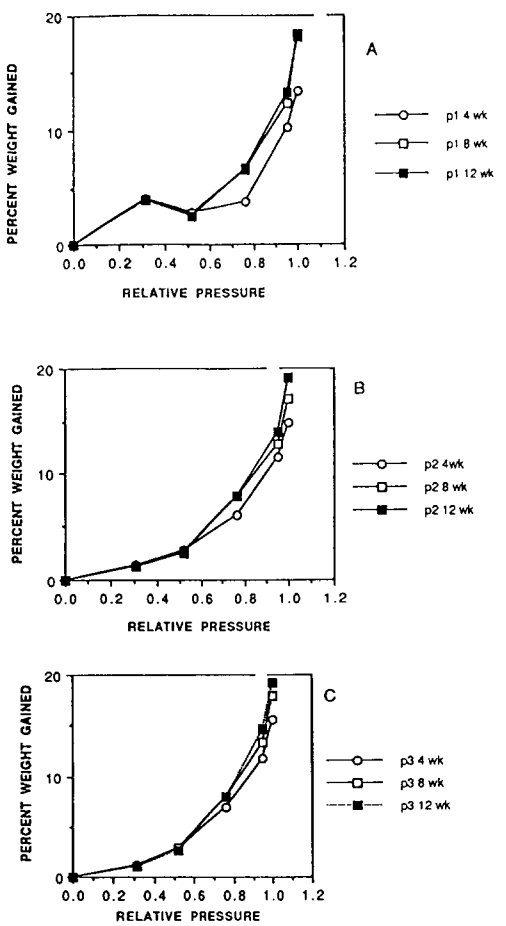

Fig. 1. Moisture sorption isotherms of directly compressed theophylline tablets during storage. (A) Pressure 1 (137.2 MPa); (B) pressure 2 (194.8 MPa); (C) pressure 3 (274.4 MPa).

3.3.2. Single components

To confirm the presence of theophylline monohydrate and magnesium stearate pseudopolymorphs, the single components in the tablet formulation were hydrated at 100% RH for 1 week at room temperature. Hydration was conducted at 100% RH for this period because, from previous work of some investigators (Otsuka et al., 1991), it was reported that hydration of pure theophylline tablets at 95% RH, (at 35°C) was achieved after 200 h. The crystal transitions to the hydrate forms of theophylline and magnesium stearate are shown in the X-ray diffraction patterns in Fig. 3 and 4. The peak observed at $2\theta = 27°$ corresponds to another hydrate peak of theophylline while those at $2\theta = 20$, 21 and 23° correspond to the pseudopolymorphs of magnesium stearate. Broad peaks of partially crystalline microcrystalline cellulose and amorphous hydroxypropyl methylcellulose are also depicted. However, the magnesium stearate peaks cannot be observed in the diffraction of the tablet powder, irrespective of the storage conditions, due to overlaps by the broad peaks of the celluloses.

3.3.3. Binary components

Hydroxypropyl methylcellulose did not have any effect on the X-ray diffraction of the other components. This is shown in the hydrated physical binary mixtures of the components (Fig. 5). Theophylline/Avicel peaks were identical to those usually seen in the tablet samples while the theophylline/magnesium stearate binary mixture revealed the hydrated theophylline peaks and those of magnesium stearate pseudopolymorphs. Theophylline/HPMC peaks were identical to those from hydrated theophylline, an indication that HPMC did not interfere with the crystal properties of the other components.

3.3.4. Compression pressure

Similar diffraction patterns were observed for tablet formulations compressed at the three pres-

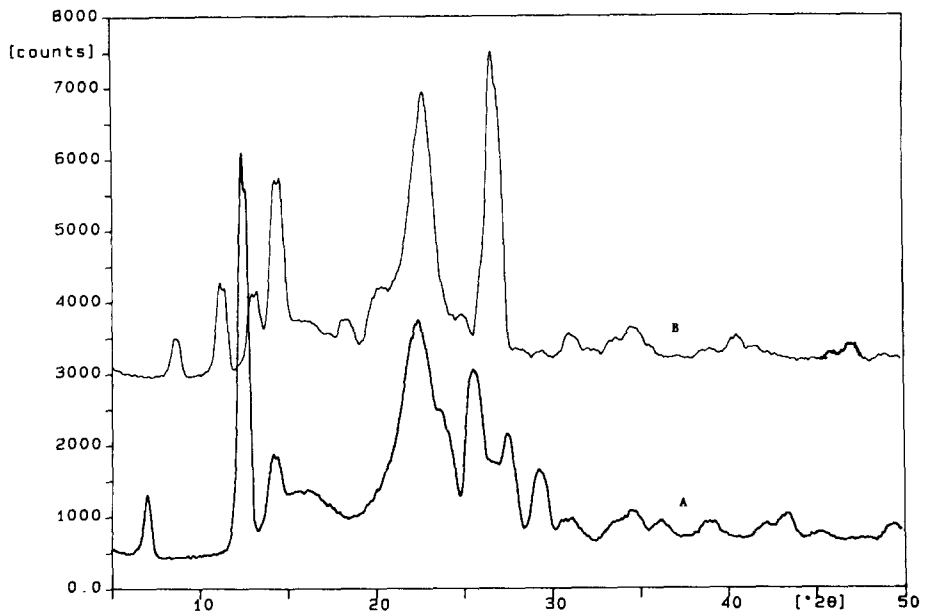

Fig. 2. Typical X-ray powder diffraction pattern of directly compressed theophylline tablets stored at ≤ 52% RH (A) and at > 52% RH (B) for 3 months.

sures and stored below RH 31%. The diffraction patterns of similar tablets stored at 100% RH were also identical, although different (due to hydrate peaks) from those of tablets under 31% RH, an indication that these high pressures alone did not affect the crystallinity of the tablets (Fig.

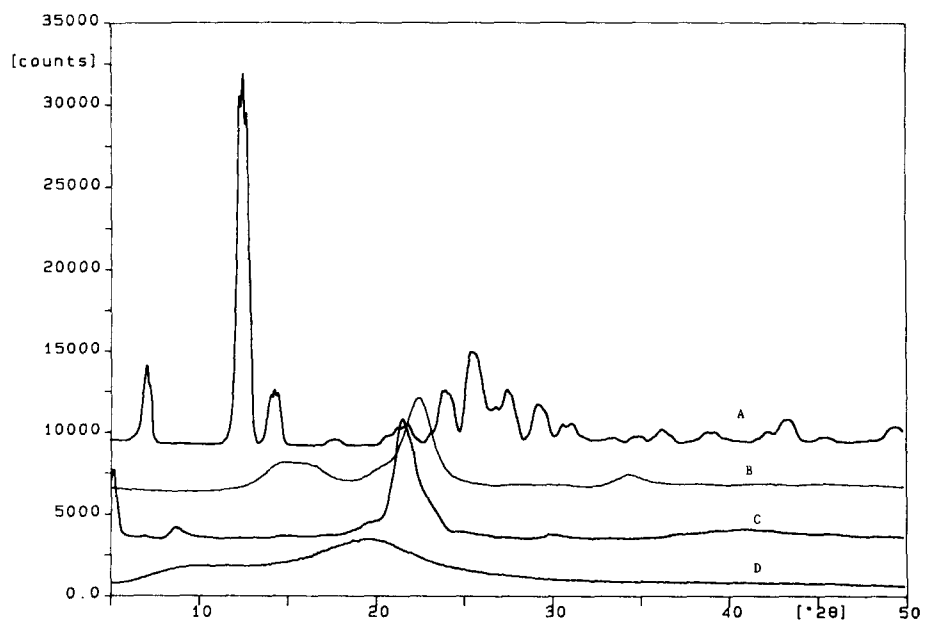

Fig. 3. X-ray powder diffraction patterns of individual components of tablet formulation. (A) Theophylline; (B) MCC; (C) magnesium stearate; (D) HPMC.

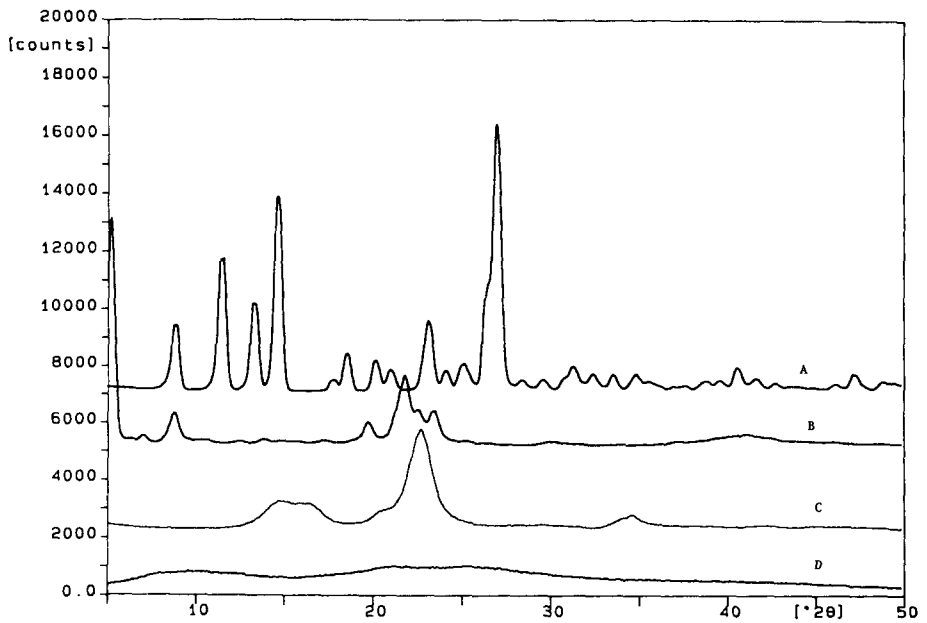

Fig. 4. X-ray powder diffraction patterns of individual components of tablet formulation, hydrated at 100% RH for 1 week. (A) Theophylline; (B) magnesium stearate; (C) MCC; (D) HPMC.

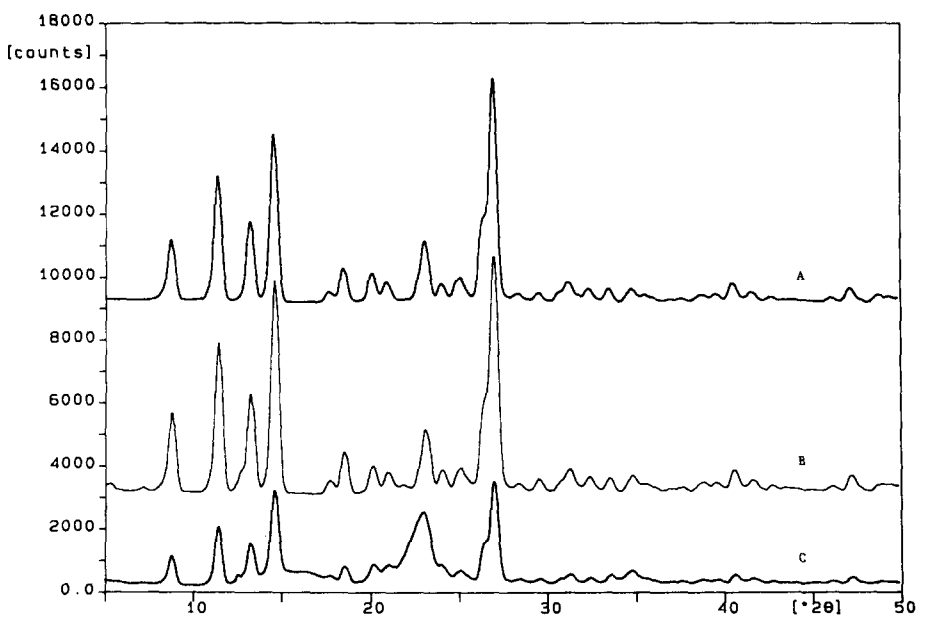

Fig. 5. X-ray powder diffraction patterns of binary physical mixtures of tablet formulation components, hydrated at 100% RH for 1 week. (A) Theophylline/MCC; (B) theophylline/magnesium stearate; (C) theophylline/HPMC.

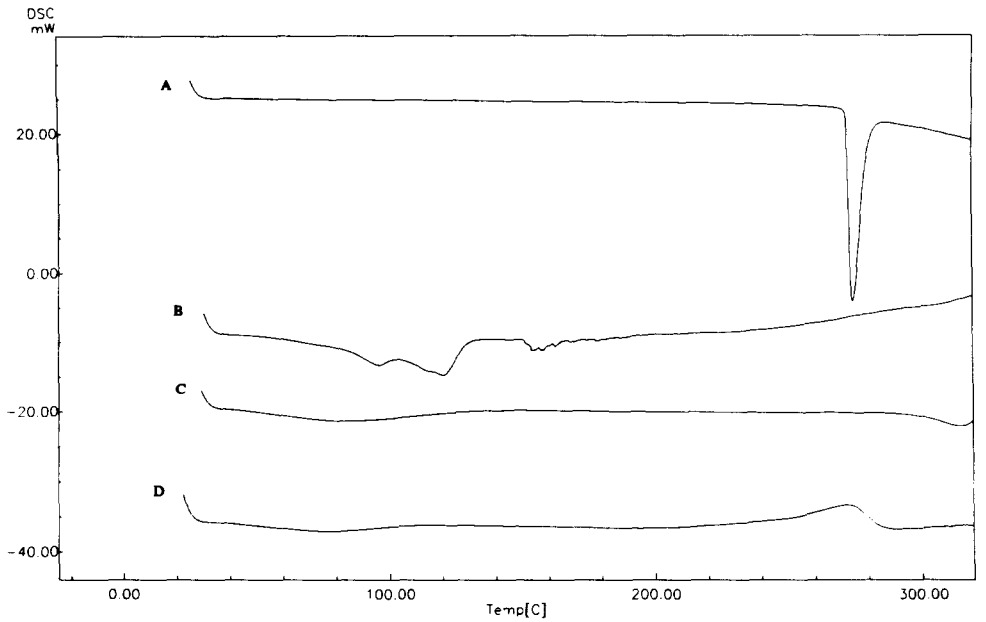

Fig. 6. Differential scanning thermograms of single components. (A) Anhydrous theophylline; (B) magnesium stearate; (C) microcrystalline cellulose; (D) hydroxypropyl methylcellulose.

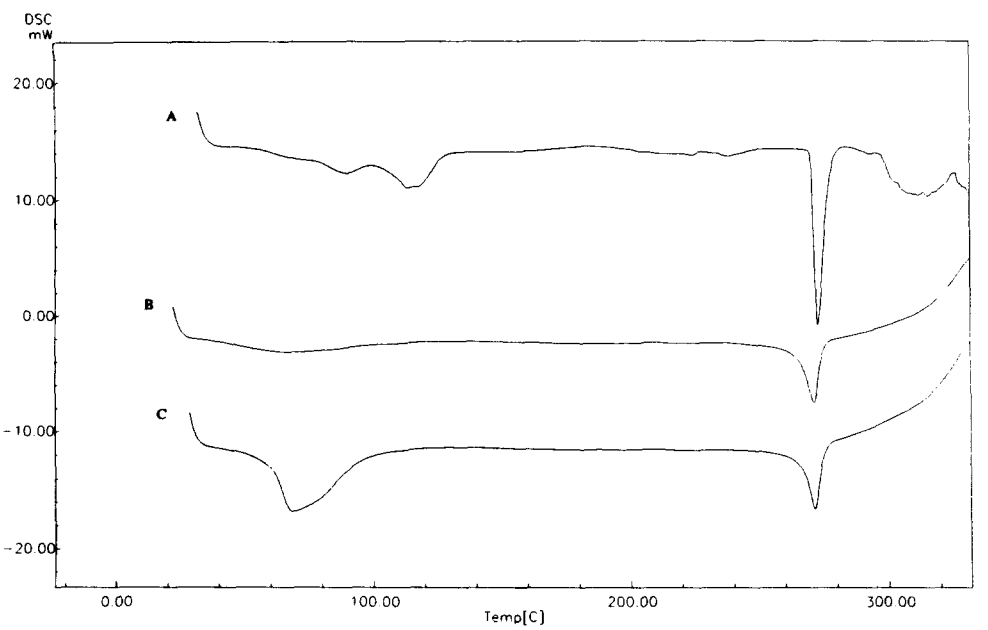

Fig. 7. Differential scanning thermograms of the physical mixture of the tablet components (A), tablet stored at RH $\leq$ 52% (B) and tablets stored at RH > 52% (C).

2A and B). This is noteworthy because the compression at the high pressures was conveniently achieved using the commercial rotary tablet press referred to earlier.

3.4. DSC

DSC of the individual single components showed an endotherm at 277°C for anhydrous theophylline. Two endothermic peaks at 98 and 110°C for magnesium stearate were observed (Fig. 6). There was no peak observed for the non-crystalline HPMC, while for the semi-crystalline microcrystalline cellulose, a small broad peak was seen at 90°C. In the thermogram of the physical mixture, the two endothermic peaks of magnesium stearate and that of anhydrous theophylline were observed (Fig. 7). For tablets stored at $\leq$ 52% RH, only the endothermic peak of anhydrous theophylline was observed at 277°C, while for tablets stored at $\geq$ 52% RH (i.e., 76, 95 or 100% RH), the same peak was observed at 277°C in addition to another distinct peak at 72°C. Typical thermograms are also presented in Fig. 7.

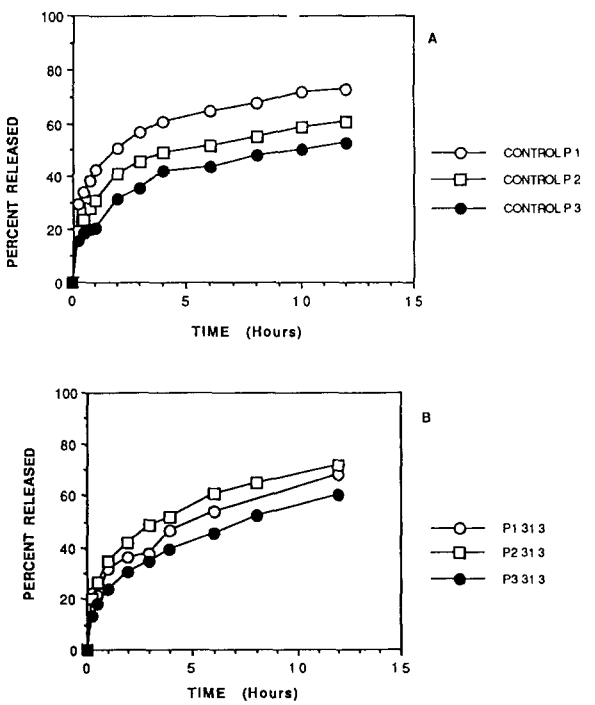

Fig. 8. Typical drug release profiles of tablets compressed at different pressures on day 1 or at 1 month (A), and at 3 months under RH $\leq$ 52% (B): P1 = 137.2 MPa; P2 = 194.8 MPa; P3 = 274.4 MPa.

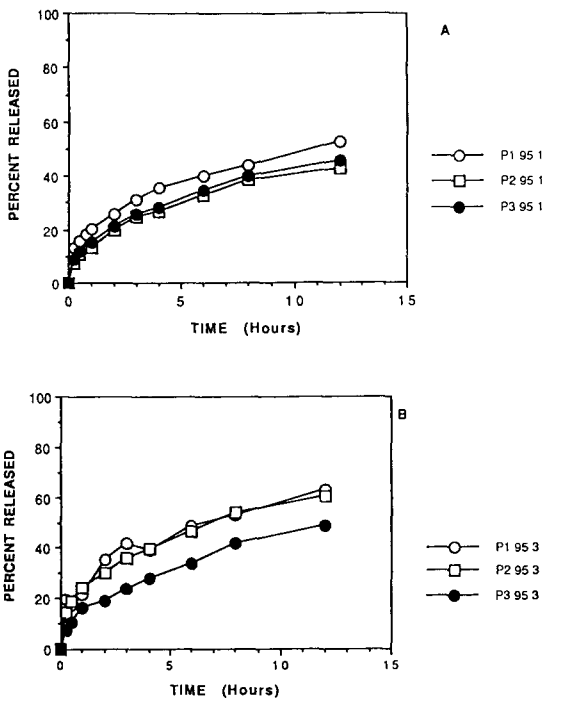

Fig. 9. Drug release profiles of tablets compressed at different pressures and stored at 95% RH for 1 month (A), or 3 months (B): P1 = 137.2 MPa; P2 = 194.8 MPa; P3 = 274.4 MPa.

3.5. Drug release

The drug release profiles of tablets compressed at the three pressures showed a sustained release pattern on day 1, with T_{50} (time taken for 50% of the drug to be released into the dissolution medium) ranging from 2 to 4 h, and a decrease in drug release as the pressure increased. Below 52% RH, drug release was more stable as seen in Fig. 8, where the total amount of drug released and the T_{50} were similar for samples stored for 3 months, to those obtained on day 1. Above 52% RH (e.g., 95% RH), drug release was inconsistent and decreased with increase in relative humidity (Fig. 9). For example, drug release generally decreased in tablets stored under 95% RH at 1 month interval, whereas after 3 months

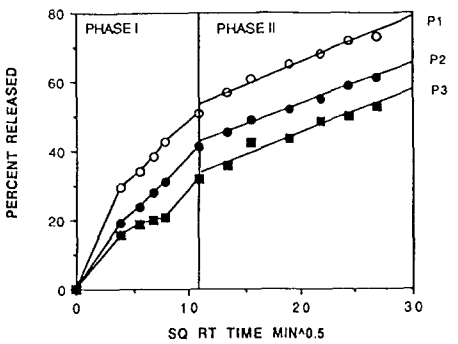

Fig. 10. Higuchi model of drug release data of control theophylline tablets: P1 = 137.2 MPa; P2 = 194.8 MPa; P3 = 274.4 MPa.

the drug release increased. Tablets compressed at 274.4 MPa pressure showed an increase in drug release after storage for 3 months, an observation due to the expansion of the tablets (or increase in thickness) upon moisture sorption and consequent formation of softer tablets that disintegrated faster.

The drug release for the control tablets stored at RH $\leq$ 52% was biphasic in nature and did not fit the Higuchi square-root model (Fig. 10). Phase I was due to the faster release (due to erosion of the drug from the surface of the tablet within the first 2 h), prior to gelling of the tablet. Phase II fitted the Higuchi model, since the tablet, having gelled on the surface in the dissolution medium, allows for diffusion of the drug into the dissolution medium. The drug release data for tablets stored at > 52% RH (e.g., 95% RH) were best described by the Higuchi square-root of time model as demonstrated by the higher correlation

Table 1
Correlation coefficients from regression analysis of dissolution data fitted to Higuchi model

	Storage conditions of theophylline tablets		
	Control	RH 31% at 1 month	RH 95% at 1 month
Pressure 1	0.876	0.922	0.982
Pressure 2	0.915	0.967	0.991
Pressure 3	0.949	0.962	0.994

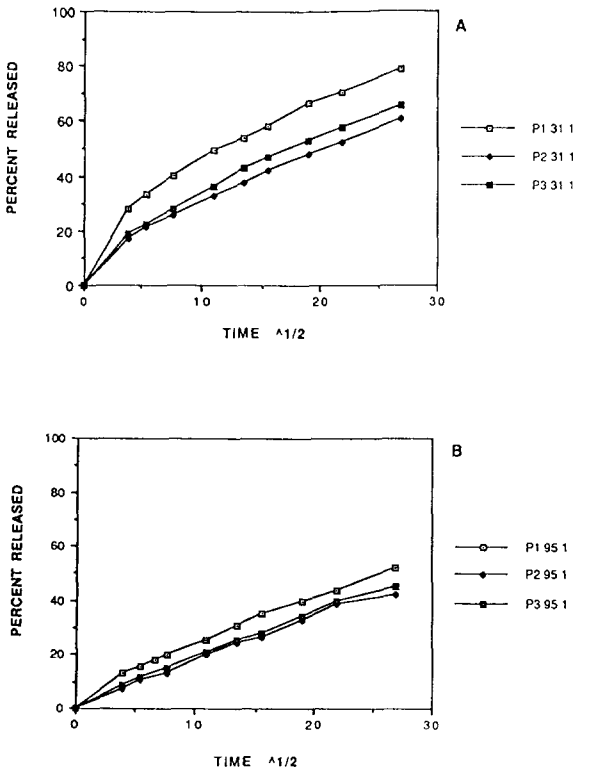

Fig. 11. Higuchi model of drug release data of theophylline tablets and stored at 31% RH (A), and 95% RH for 1 month: P1 = 137.2 MPa; P2 = 194.8 MPa; P3 = 274.4 MPa (B).

coefficients of the regression analysis (Table 1). This is indicative of a diffusion mechanism, a result of microgelling of the tablet matrix at the higher RH (Fig. 11).

3.6. Hardness and thickness

The initial average hardnesses for tablets compressed using 137.2, 194.8 and 274.4 MPa pressures were 13.88 ± 1.45, 18.46 ± 0.83 and 20.60 ± 1.95 Kp, respectively, while the respective thickness values were 2.44 ± 0.01, 2.40 ± 0.01 and 2.34 ± 0.03 mm. After storage for 3 months, hardness decreased while thickness increased with increase in RH. For example, at 76% RH, the hardness decreased to 7.46 ± 2.5, 11.7 ± 0.87 and 11.60 ± 1.20 Kp, respectively, for the three pressures and the thickness likewise increased to 6.46 ± 0.03,

6.32 ± 0.04 and 6.15 ± 0.02 mm. The hardness and thickness of tablets stored at 95 and 100% RH for 3 months could not be determined because the samples became so soft that they deformed during testing.

4. Discussion

A significant amount of moisture was sorbed to the tablets stored at relative humidity greater than 52% due to change in polymer chain conformation caused by the entry of water into the polymeric structure of the MCC and the HPMC (Zografi and Kontny, 1987). Moisture sorption into these polymers also aided in the crystal change of anhydrous theophylline to its monohydrate and that of the magnesium stearate to its pseudopolymorphs. The distinct change in the uptake isotherm after 52% RH is consistent with the literature in which anhydrous magnesium stearate was reported to hydrate to the trihydrate at RH > 50% (Ertel and Carstensen, 1988).

The sharp X-ray diffraction peaks of theophylline monohydrate and those of magnesium pseudopolymorphs observed in tablets stored at RH $\geq$ 52% correlate with the sorption isotherms. These indicate that above 52% RH, there was a change in crystallinity of anhydrous theophylline to the monohydrate and the conversion of magnesium stearate to its pseudopolymorphs. The increase in peak intensity of the tablet samples at $2\theta = 20$ and 27° after storage for 3 months is an indication of continued change of the two components into the hydrate forms. Increasing the compression pressure did not affect the crystal transition.

From the X-ray diffraction patterns of the single and binary physical components, it is seen that the presence of partially hydrating MCC and the non-hydrating HPMC did not affect the X-ray diffraction of the other components in the tablet formulation.

The characteristic DSC endotherm of anhydrous theophylline at 277°C, observed in tablets stored at RH $\geq$ 52%, was due either to that of the theophylline that recrystallized as the anhydrous form, or to anhydrous theophylline that did not completely convert to its monohydrate. The second endotherm, observed at a lower temperature (72°C) was that of magnesium stearate trihydrate or its pseudopolymorph, or it could be a result of an interaction between partially hydrated MCC and the magnesium stearate. It has been reported (Rowe, 1988) that magnesium stearate interacts with MCC through weak adhesive intermolecular bonds. The fact that this peak was not seen at RH $\leq$ 52% is consistent with a previous report (Ertel and Carstensen, 1988), but more difficult to interpret.

The general decrease in drug release in tablets stored at RH $\geq$ 52% is due firstly to the formation of theophylline monohydrate and magnesium stearate trihydrate, and secondly, to gelation with resultant swelling of the hydrophilic matrix (indicated by increase in thickness of tablets) and consequent decrease in drug release. This showed that aside from the hydrated theophylline and magnesium stearate, the cellulose components which also sorbed moisture with consequent gelation (in the case of HPMC) within the tablet matrix contributed to the instability of drug release. Consequently, the release mechanism changed from biphasic to the diffusion-only type.

5. Conclusions

Storage of directly compressed theophylline tablets stored at relative humidity greater than 52% resulted in crystal changes of anhydrous theophylline to its monohydrate and that of the magnesium stearate to its pseudopolymorphs. Although the partially hydrating MCC and gelation of the non-hydrating HPMC did not affect the X-RD of theophylline tablets, these components made the drug release very unstable and caused alteration in the release mechanism. Controlling the humidity of the environment to below 52% can prevent the hydration and instability of drug release of theophylline tablets containing excipients such as cellulose polymers. The stability problems involving change in crystallinity of drugs like anhydrous theophylline can be better understood by the use of different analytical techniques such as those used in this study.

Acknowledgements

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