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Dynamic solid-state and tableting properties of four theophylline forms

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Abstract

Relationships between solid-state, densification and compact properties of theophylline monohydrate (TMO), a mixture of forms (TMIX), and anhydrous polymorphs I (TA-I) and II (TA-II) were evaluated. Solid-state identification of powders and compacts was accomplished by powder X-ray diffraction. A compaction simulator was used to assess deformation behaviour of the powders and to prepare compacts. Porosity and tensile strength of the compacts were determined after 1, 24, and 168 h of storage at 22% relative humidity. TA-II was stable, whereas TA-I, TMIX and TMO partially transformed to the TA-II form during storage. All theophylline modifications primarily deformed by plastic flow. Increased water content decreased resistance towards densification and deformation of TMIX and TMO when compared to TA-II or TA-I, demonstrating viscoelasticity. Permanent densification behaviours of TMIX and TMO approached to that of TA-II during storage. Tensile strength of the different theophylline forms were practically equal after 1 h of storage. Tensile strength and porosity of TMIX and TMO compacts increased during the storage. Dynamic solid-state transformations from TMO, TMIX and TA-I to TA-II were associated with parallel changes in their densification and compact properties. The extent of these changes was also dependent on the materials' water content. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Theophylline; Polymorphic form; Hydrous form; Metastable form; Solid-state properties; Tableting properties

1. Introduction

To a large extent, the solid-state properties of solids, such as polymorphism, pseudopolymorphism and the crystal ordering/disordering of pharmaceutical materials control their processing behaviour and affect performance of the finished product (York, 1992). The influence of these solid-state properties on processing are likely affected by differences in molecular arrangements; i.e. crystal structure and subsequent crystal habit, crystal anisotropy, and particulate properties (Summers et al., 1976; York, 1992). Manufacturing processes, such as milling, granulation, drying

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and compression, can activate materials and induce phase transformations or metastable forms of drugs and excipients (Hüttenrauch, 1988; Wong and Mitchell, 1992; Ketolainen et al., 1995; Phadnis and Suryanarayanan, 1997). Unknown and uncontrolled changes in solid-state properties might cause problems in production; e.g. tablet compression, and also alterations in the performance of the product. Therefore, a fundamental knowledge and monitoring of solid-state properties and their relationships to physicotechnical properties is required to understand or even predict the tableting behaviour of pharmaceutical materials.

Theophylline, an oral bronchodilatator in asthma therapy, has been reported to exist in a monohydrate form (TMO) and an enantiotropic pair of anhydrous polymorphs I and II (TA-I and TA-II, respectively), where the TA-II is stable at room temperature (Suzuki et al., 1989; Suihko et al., 1997). Also, an anhydrous metastable form of theophylline, which is monotropic in respect to the stable TA-II, has been characterised (Phadnis and Suryanarayanan, 1997). These crystal forms of theophylline have different physicochemical properties which influence their processing and product performance. For example, it has been reported that TMO has better tableting and mechanical properties, e.g. lower elasticity and better compactibility, compared to the TA-II (Agbada and York, 1991). However, compression of the TMO activates its crystal lattice and induces dehydration of the crystal under dry conditions, which leads to a subsequent transformation to the metastable anhydrous form, and thereafter to the stable TA-II (Otsuka et al., 1993; Phadnis and Suryanarayanan, 1997). On the other hand, the anhydrous forms of theophylline can be converted to the TMO at high humidity (Otsuka et al., 1990). The TA-II has been found to be stable when subjected to mechanical activation; e.g. trituration or compression (Chan and Doelker, 1985; Phadnis and Suryanarayanan, 1997).

However, it is still not known how these well characterised crystalline forms of theophylline behave during tableting or storage. The aim of this study was to assess the solid-state stability of these four theophylline forms during a dynamic compression process and subsequent short-term storage in a dry environment. An additional goal was to evaluate the densification and deformation behaviours and compact mechanical properties of these forms and to evaluate alterations in their compact properties as a function of solid-state transformation during the storage.

2. Materials and methods

2.1. Materials

Anhydrous theophylline (Sigma Chemicals, USA) was dissolved in distilled water at 60°C to form a supersaturated solution. When the solution was slowly cooled, needle-like TMO crystals were formed. After drying at room temperature the obtained crystals were gently dispersed with a mortar and pestle, and passed through a 100 μm sieve (used throughout hereafter). A mixture of theophylline forms (TMIX), which contained a large fraction of the anhydrous metastable form, was prepared by vacuum drying the TMO ($\varnothing \leq$ 100 μm) at 25°C and 2×10^{-4} torr for 24 h (Phadnis and Suryanarayanan, 1997). TA-II was produced by heating the TMO ($\varnothing \leq 100$ μm) at 110°C for 24 h (Suzuki et al., 1989). Using the same sieve fraction in preparing TMO, TMIX and TA-II resulted in products of identical size distribution. TA-I was recrystallised by heating the TA-II in hermetically sealed glass tubes for 5 h at 250°C (Suzuki et al., 1989). All products were stored in a desiccator at 20°C and 22% relative humidity (RH) for as short time as possible, in order to avoid gratuitous solid-state transformations of the samples.

2.2. Identification of crystal modifications

Powder X-ray diffraction (XRD) patterns were obtained from a Philips PW1820 ADP1700 Automated Powder diffractometer System (Philips, The Netherlands) under the following conditions: Ni filtered CuK_a radiation ($\lambda = 0.15418$ nm), 50 kV voltage, 40 mA current, automatic divergence slit (irradiated sample length 12.5 mm), receiving slit 0.1 mm, scatter slit 4° with a proportional

detector, step size 0.03°, sample time 1.00 s, and peak angle range 5–30.02°. Data were collected and analysed by the Philips PC-APD software package. Mass fractions of the different theophylline forms in the samples were calculated by determining the background corrected integrated intensities of the characteristic peaks with the PC-APD's Fit Profile program. The characteristic two theta peaks were analysed between 10.01–12.41°, 6.29–7.70°, 8.00–10.49° and 7.79–9.50°, for TA-I, TA-II, TMIX and TMO, respectively. Samples were stored the first 24 h under RH 0% (silica gel). After the XRD measurements the samples were moved to RH 22% and reanalysed after total storage of 168 h.

2.3. Determination of physical properties

The material density was determined with a pycnometer (Multipycnometer MVP-1, Quanta Chrome, USA), using helium as a measuring gas, and values were expressed as the mean of five parallel measurements.

Scanning electron micrographs of the powder samples, coated with gold (Sputter Coater II E 5100, Polaron Equipment Ltd., England), were obtained with a JEOL JSM-35 electron microscope (JEOL Ltd., Japan) using an acceleration voltage of 15 kV at a magnification power of 200. The equivalent Martin diameter was determined for about 300 particles from each sample. The ratio between equivalent diameters of a sphere having the same area and a sphere having the same perimeter was taken as the shape factor (Rumpf, 1990). Larger values of the shape factor indicated particles that were becoming more regular, and unity represented a totally spherical particle.

The water content of the samples was determined by a Karl Fischer titrimeter (Mettler Dl 35 Karl Fischer Titrimeter, Mettler Toledo AG, Switzerland). Hydranal®-solvent (Riedel de Haën AG) and Hydranal®-titrant five were used. The results were expressed as the mean of three parallel measurements.

2.4. Powder compression

The compression studies were performed using a compaction simulator (PuuMan Oy, Finland). Compressed powders were initially weighed individually, and manually poured into the die (10 mm in diameter) to produce flat faced compacts with a theoretical thickness of 1.7 mm at zero-porosity while taking into account the material densities. Single-sided sawtooth-profiles (i.e. constant punch movement) with a punch velocity of 60 mm/s and compression pressures of 50, 70, 100 and 150 MPa were used ($n = 5$ for each material at each pressure). The compacts were made with a die-wall lubrication by treating the punch and die wall with a 2% w/w suspension of magnesium stearate in acetone before each test. During compression, upper and lower punch forces and displacements were monitored. For further analysis the obtained compression displacement data were corrected with upper and lower punch deformation.

Evaluation of consolidation behaviour of the powders was determined according to the Heckel equation (Heckel, 1961a,b):

$$\ln 1/(1 - D) = k \times P + A \quad (1)$$

where D represents the relative density, which relates to the packing fraction (i.e. the ratio between the apparent density of a powder bed and the material density) to the applied pressure, P. The slope of the linear portion, k, was expressed as the reciprocal, K, and represents mean yield pressure (Paronen, 1987). A constant, A, was the extrapolated intercept of the y-axis. Two different methods were used for obtaining data from the Heckel equation (Paronen and Juslin, 1983). The first was the tablet-in-die method, in which the applied pressure and packing fractions of the powder column were determined during the compression process. The second method was the ejected-tablet method, in which the packing fractions were determined by measuring the compact weight and dimensions 1, 24 and 168 h after ejection from the die.

2.5. Porosity and tensile strength of compacts

Crushing strength of the compressed theophylline compacts were determined by using a CT5 Universal Tester (Engineering Systems Ltd., UK) with a constant cross head velocity of 1 mm/s.

The compacts were stored for 1, 24, or 168 h under RH 22%, and the volumetric dimensions and the weight of compacts were measured before measuring crushing strength. Porosity was calculated by using the weight, dimensions and material density of the compacts. Tensile strength of the compacts was derived according to Fell and Newton (1970). The results presented are the means of five determinations.

3. Results and discussion

3.1. Physical properties of powders

The material density of the TA-I was higher than that of the other forms (Table 1). The material density of the TMIX was intermediate being between that of the TA-II and TMO. Since TMIX was unstable the measured material density was only a best approximation of the actual material density. These values were used for material densities of compacts after 1 h storage. The measured material densities multiplied with corresponding weight fractions of the form in question, obtained by XRPD, were used in calculating of material densities of compacts with specified contents of theophylline forms at the specified time point, i.e. after 24 and 168 h storage.

The mean Martin's particle diameter was the smallest for the recrystallised TA-I, and the shape of the particles was generally elongated (Table 1). TA-I had the most irregular particles of all the forms studied, and micron-sized needle-like particles were adhered to surfaces of the larger ones (Fig. 1). The other three forms had almost equal mean Martin's particle diameter, but the shape and texture of the various particle surfaces varied. TMO had the most regular shaped particles and a relatively smooth particle surface. TMIX had a slightly more regular particle shape and surface than TA-II, which had a very uneven particle surface with numerous small particles adhered to larger ones. The theophylline modifications originated from the same starting material; i.e. TMO passed through a 100 μm sieve. Heat-dried TA-II and vacuum-dried TMIX were the dehydrated forms of TMO. Thus, irregular particle surfaces of TA-II and TMIX were a consequence of dehydration, and subsequent collapse and rearrangement of the crystal structure, as reported earlier (Suzuki et al., 1989; Suihko et al., 1997).

Both the TA-I and TA-II contained a small amount of water as a result of the low ambient humidity during storage, whereas TMIX also contained residual crystal water in the crystal lattice which corresponded to the fraction of monohydrate in the crystals (Table 1). The water content of TMO was equal to that of the theoretical water amount (9.1% w/w) in the crystal lattice of theophylline monohydrate.

Table 1
Physical properties of the theophylline forms[a]

Theophylline form	Material density (g/cm^3)	Martin's diameter (μm)	Particle shape factor	Water content (% w/w)
Anhydrous form I	1.522 (0.001)	16 (29)	0.77 (0.11)	0.1 (0.1)
Anhydrous form II	1.484 (0.005)	25 (24)	0.81 (0.08)	0.1 (0.1)
Mixture of forms	1.478 (0.005)	24 (22)	0.83 (0.07)	2.5 (0.1)
Monohydrate	1.470 (0.001)	26 (25)	0.85 (0.07)	9.1 (0.1)

[a] Standard deviations are listed in parentheses.

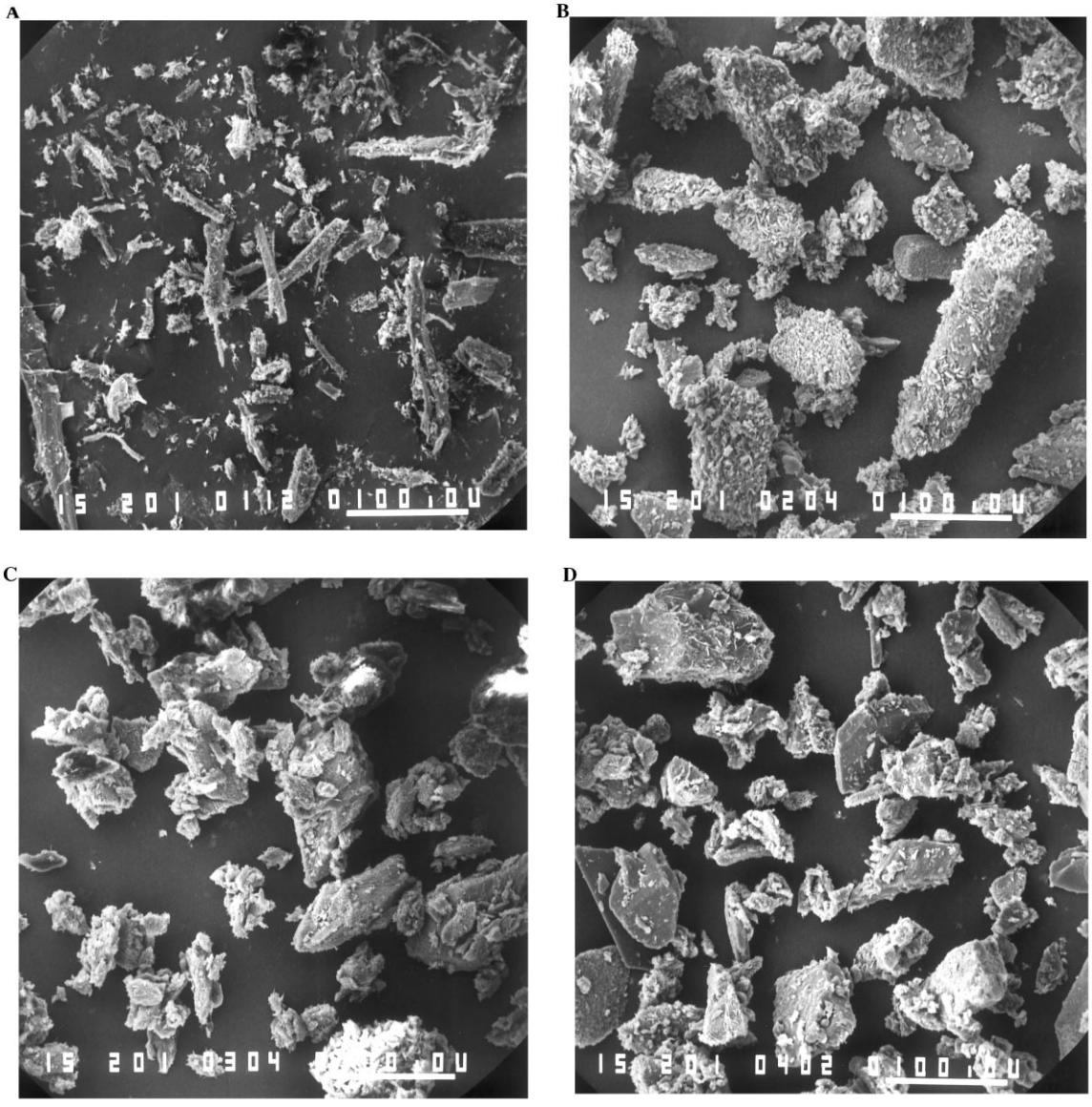

Fig. 1. Scanning electron micrographs of theophylline anhydrous form I (A), anhydrous form II (B), a mixture of forms (C), and the monohydrate (D). Bar is 100 μm.

3.2. Solid-state stability of powders and compacts

The TA-I, TA-II and TMO forms were essentially identical to XRD patterns reported by Suzuki et al. (1989). The vacuum-dried powder was a mixture of TA-II, the metastable anhydrous form and TMO, hereafter referred to as the mixture of forms (TMIX). TA-I partially transformed (4–9% w/w) to TA-II during storage of the compacts (Fig. 2). The TA-II was perfectly stable under compression and during storage. The TMIX powder contained 79% TA-II after 168 h storage. In compacts, this change was even more pronounced. After 24 h storage compacts of the TMIX contained 56–59% (w/w) TMO and 31–41% TA-II, whereas the fraction of the metastable

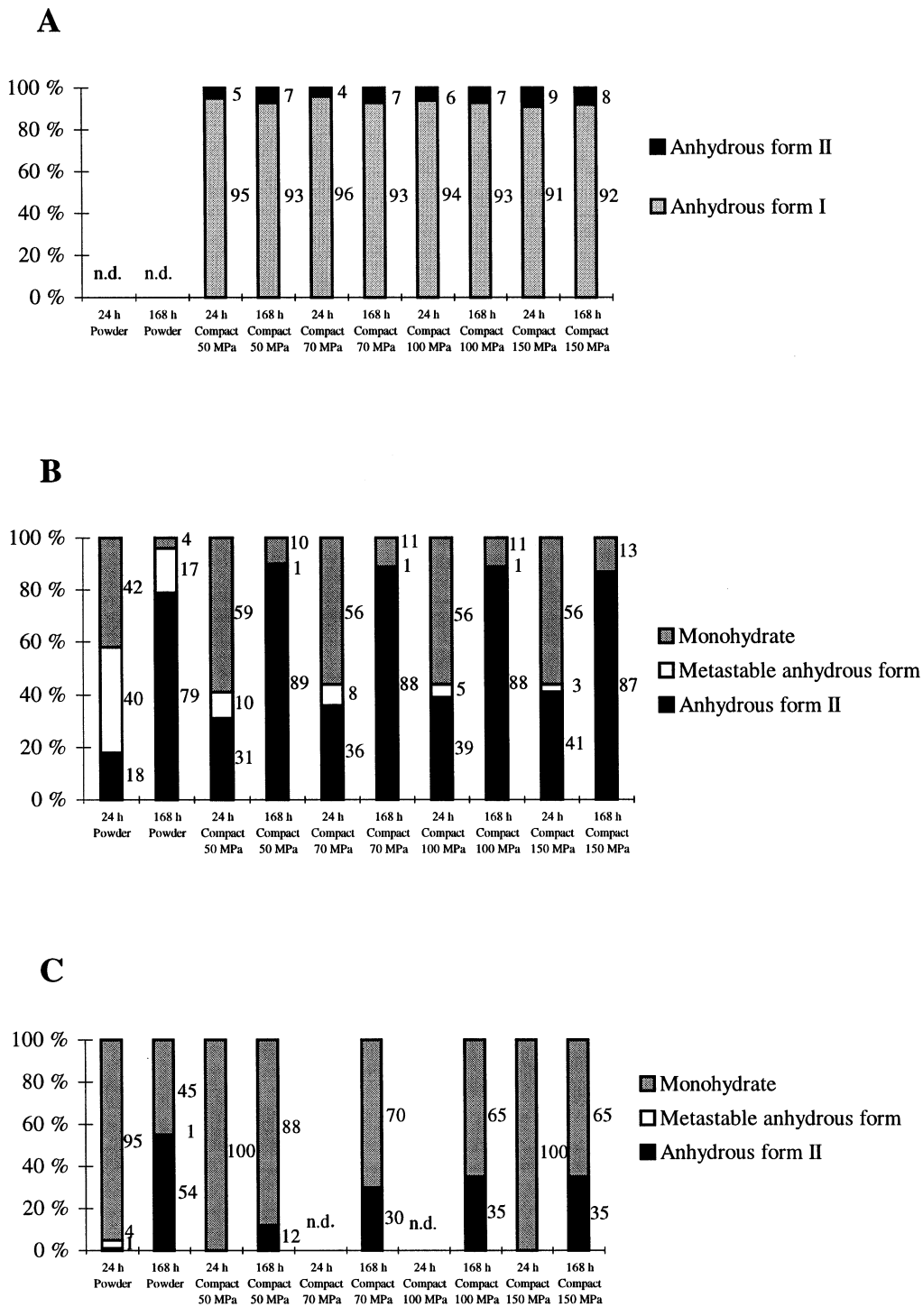

Fig. 2. Relative fractions (%) of theophylline anhydrous form I (TA-II) (A), a mixture of forms (TMIX) (B), and the monohydrate (TMO) (C) in the powders and compacts determined by X-ray powder diffractometer. Numeric values of relative fractions are presented in the right-hand side of the column, and n.d., not determined.

anhydrous form was less than 10% in each. After 168 h storage the compacts contained approximately 88–89% TA-II, 10–11% TMO and only 1% of the metastable anhydrous form. Increasing the compression pressure increased the transformation rate of the TMIX towards TA-II. The TMO powders contained 4% of metastable anhydrous form and 1% of TA-II already after 24 h storage, and 54% was transformed to the stable TA-II after 168 h storage. In compacts, the stability of the TMO improved, especially in those compressed under low pressures, and the rate of dehydration and consequent transformation to the TA-II was considerably lower (12–35%) than in powder form (54%). Traces of amorphous theophylline were not detected in the XRD studies.

Otsuka et al. (1993) reported that TMO loses water after compression and that dehydration is diminished by decreased porosity of the compact. Our results are contradictory, as TMO compacts compressed under high pressures (100 and 150

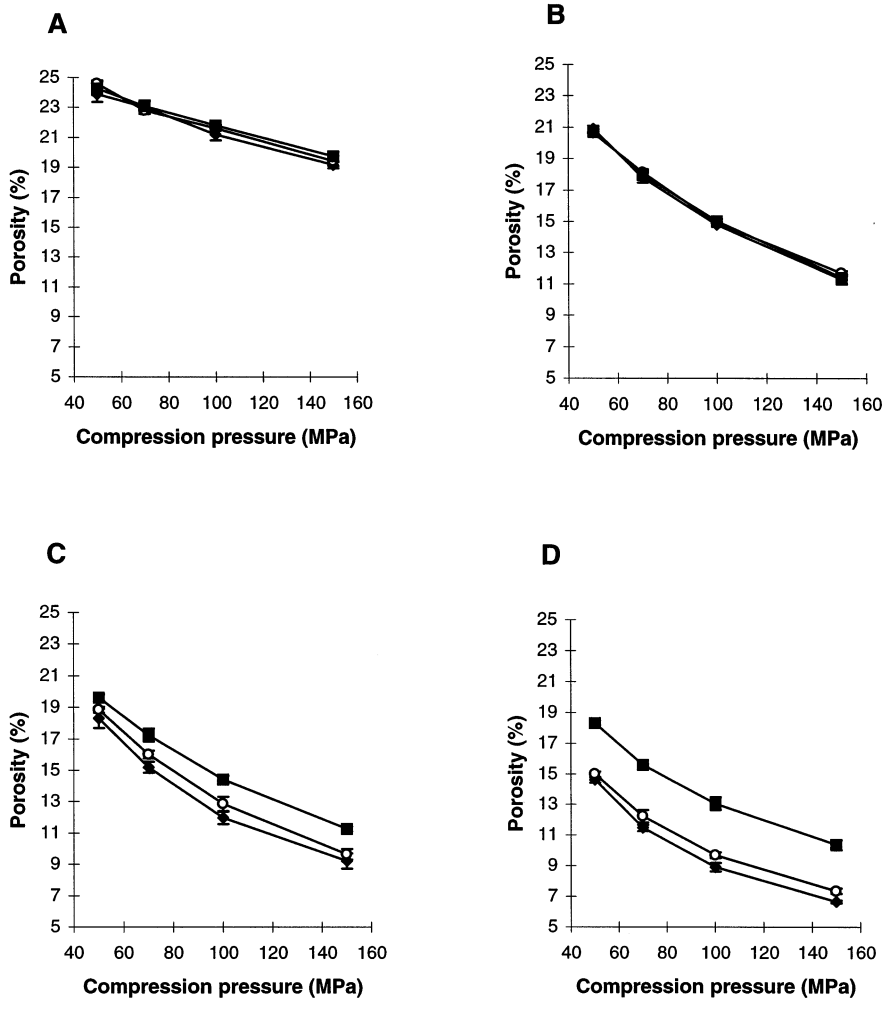

Fig. 3. Compact porosity of theophylline anhydrous form I (A), anhydrous form II (B), a mixture of forms (C), and the monohydrate (D) as a function of compression pressure after 1 (◆), 24 (○) and 168 h (■) of storage. Standard deviation is shown as y-error bars.

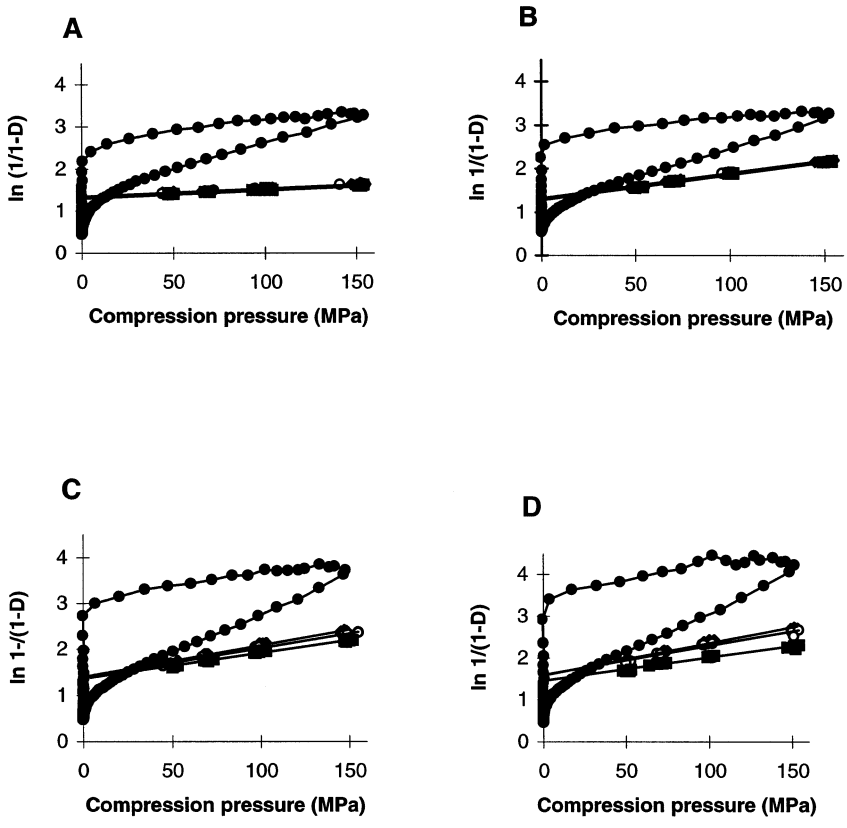

Fig. 4. Heckel tablet-in-die (●) and Heckel ejected-tablet plots after 1 (◆), 24 (○) and 168 h (■) storage of theophylline anhydrous form I (A), anhydrous form II (B), a mixture of forms (C), and the monohydrate (D).

MPa) resulted in low porosity (Fig. 3), and the degree of dehydration during storage in a dry environment was higher than in compacts compressed under lower pressures (50 and 70 MPa). This difference might result from different experimental settings, particularly since the dehydration of TMO is sensitive to ambient conditions (Suihko et al., 1997). Interestingly, TMO was more unstable in powder form than in compacts. Thus, it seems that the TMO was not significantly stressed under compression and also the compact structure protected TMO from dehydration. TMIX contained less of the metastable anhydrous form in compacts than in powder form. Part of the metastable anhydrous form that is present in TMIX could transform to the stable TA-II during storage in the ambient dry environment. It also seems that part of the metastable anhydrous form could transform to TMO. However, the results obtained are not sufficient to deduce the mechanism of this transformation.

3.3. Deformation behaviour

The propensity towards total densification and deformation of the theophylline forms was evaluated on the basis of porosity–pressure data using the Heckel tablet-in-die method (Fig. 4). TMO had the lowest K_d-values; i.e. it had the lowest resistance towards densification and total particle deformation, including both elastic and plastic components (Table 2) (Duberg and Nyström, 1986). The TMIX also had a relatively low K_d-value, and TA-II had a lower value than TA-I.

The Heckel equation is very sensitive to small errors, as low as 1% in material density (e.g.

Gabaude et al., 1999). In addition, both TMO and TMIX showed dynamic transformation towards TA-II during the storage, which reflected a change in their material densities. Thus, the K_d-values for TMO and TMIX were also determined by using the material densities of TA-II and TMIX, as well as TA-II and TMO, respectively. The calculated K_d-values for TMO were 61 ± 2 (from the material density of TA-II) and 57 ± 2 (from TMIX), and for TMIX 66 ± 3 (from TA-II) and 58 ± 2 MPa (from TMO). These values were between those of TA-II and TMO, demonstrating that the deformation behaviour of the compressed TMO and TMIX powders were significantly different when compared to each other or with TA-II (Table 2).

The K_p-values obtained after 1 h storage showed similar rank order for the theophylline modifications than the K_d-values when using the Heckel ejected-tablet method, which describes the tendency of a material to densify permanently (Table 2, Fig. 4). Again the TMO had the lowest K_p-value; i.e. the easiest deformability. The TMIX and TA-II also had relatively low K_p-values, whereas TA-I had a considerably high K_p-value, indicating high elasticity. During storage, the K_p-values of the TA-I and TA-II remained constant. However, the K_p-values of the TMIX and TMO increased during the storage, and were greater than that of the TA-II after 168 h.

The fast elastic recovery of material during the decompression can be evaluated by using the downward part of the Heckel tablet-in-die plot (Fig. 4); i.e. K_{ef} -values in Table 2 (Duberg and Nyström, 1986; Paronen, 1987). According to this parameter TMO was highly prone to fast elastic deformation; i.e. it had a low K_{ef}-value. The TMIX was more elastic than the anhydrous forms and TA-I showed more fast elastic behaviour than the TA-II.

Analysis of the porosity–pressure data using the Heckel methods indicate that the theophylline modifications deformed primarily by plastic flow. The water present in the crystal lattice of the TMIX and TMO powders significantly decreased the resistance towards densification and enhanced elastic deformation when compared to TA-II. The liberated water of TMO has been shown to act as a lubricant in the compacted powder bed, reducing interparticulate friction and deformation resistance (Agbada and York, 1991). In this study, the effect of this liberated water is considered as an aid to dynamic compact densification in the die and increasing elastic recovery of the compact. During storage, TMIX and TMO compacts were dehydrated and transformed towards TA-II. This increased their K_p-values; i.e. it affected their permanent densification behaviour. The K_p-values approached, and were eventually slightly greater than, that of TA-II. Thus, densification and deformation properties of the theophylline modifications were related to solid-state structure and water content.

Table 2
K-values obtained from Heckel tablet-in-die ($r > 0.998$) and ejected-tablet ($r > 0.983$) methods of the theophylline forms[a,b]

Theophylline form	Tablet-in-die		Ejected-tablet		
	K_d	K_{ef}	K_p		
			1 h	24 h	168 h
Anhydrous form I	83 (2)	299 (13)	476	455	526
Anhydrous form II	76 (1)	352 (33)	169	175	172
Mixture of forms	63 (2)	283 (51)	145	154	179
Monohydrate	52 (2)	177 (25)	130	143	182

[a] K_d refers to total deformation of the material under compression. K_{ef} refers to fast elastic recovery of the material during decompression. K_p refers to permanent deformation of the material after viscoelastic recovery.
[b] Standard deviations are listed in parentheses.

The difference between the *K*-values obtained from the Heckel tablet-in-die and ejected-tablet methods, and the relatively high K_{ef}-value (i.e. low fast elastic recovery of compacts) indicate that TA-I has a viscoelastic component in its deformation behaviour. In previous studies, it was concluded that the more stable polymorph at room temperature had more exclusive resistance against densification, exhibited less elasticity and formed stronger compacts than the less stable form (Summers et al., 1976; Roberts and Rowe, 1996). According to total deformability of powders under compression, the anhydrous polymorphic forms of theophylline seemed to be somewhat exceptional because the more stable TA-II at room temperature was more easily deformed than TA-I. However, TA-I possessed higher elasticity than TA-II. In addition, TA-I had the smallest mean particle size of the studied theophylline forms, which could increase resistance to densification under compression (Roberts and Rowe, 1986). Thus, the particulate properties of TA-I could have led to higher resistance against total particle deformation under compression, which does not seem to be an intrinsic crystal property of the TA-I.

3.4. Porosity and tensile strength of compacts

After 1 h of storage, rank order in decreasing compact porosity of the theophylline modifications was as follows: TA-I > TA-II > TMIX > TMO (Fig. 3). The porosity of compacts made of the anhydrous forms remained unchanged, whereas porosity of compacts made of TMIX and TMO increased markedly during storage, especially between 24 and 168 h, with simultaneous small decrease in both weight and volumetric dimensions.

TA-II formed slightly stronger compacts than the other forms when compared on porosity levels of 20 and 15% for TA-I and TMIX/TMO, respectively, whereas TMO formed slightly weaker compacts (Fig. 5). During storage tensile strength of compacts made TA-I and TA-II remained practically unchanged. The tensile strength of compacts made of TMO and TMIX increased markedly during the storage, and was greater than that of the TA-II compacts after 24 h storage.

Wong and Mitchell (1992) have found that chlorpromazine hydrochloride hemihydrate, and also a partially dehydrated hemihydrate, formed stronger compacts than stable anhydrous form I, which on the other hand formed significantly stronger compacts than the metastable anhydrous form II. This behaviour of the chlorpromazine hydrochloride modifications is rather close to that of the theophylline modifications in this study. Strength increased for the TMO and TMIX compacts between 1 and 24 h storage is caused presumably by viscoelastic deformation of the compressed particles (Alderborn and Ahlneck, 1991), which correlates with the observed deformation behaviour of these materials. Between 24 and 168 h storage dehydration and transformation of these compacts towards the TA-II increased interparticulate bonding. The dimensions of these compacts slightly decreased simultaneously, and thus, the increased porosity was primarily due to dehydration of the compacts. Strengthening of the compacts between 24 and 168 h storage could be a combination of two mechanisms. Firstly, rearrangement of solid material at particle surfaces i.e. crystallisation of metastable anhydrous form to the stable TA-II form. Secondly, crystallisation of dissolved theophylline between adjacent particles during the dehydration and movement of water towards the compact's surface (Down and McMullen, 1985; Ahlneck and Alderborn, 1989).

4. Conclusions

During short-term storage in low RH, metastable TA-I, TMIX and TMO crystallised towards stable TA-II. Under compression the theophylline modifications primarily deformed by plastic flow. Water present in TMIX and TMO enhanced their densification when compared to the anhydrous forms TA-I and TA-II. The tensile strength of the theophylline forms were almost equal after 1 h storage. However, porosity and strength of TMIX and TMO compacts increased substantially during their transformation towards TA-II. Thus, tableting properties of the various

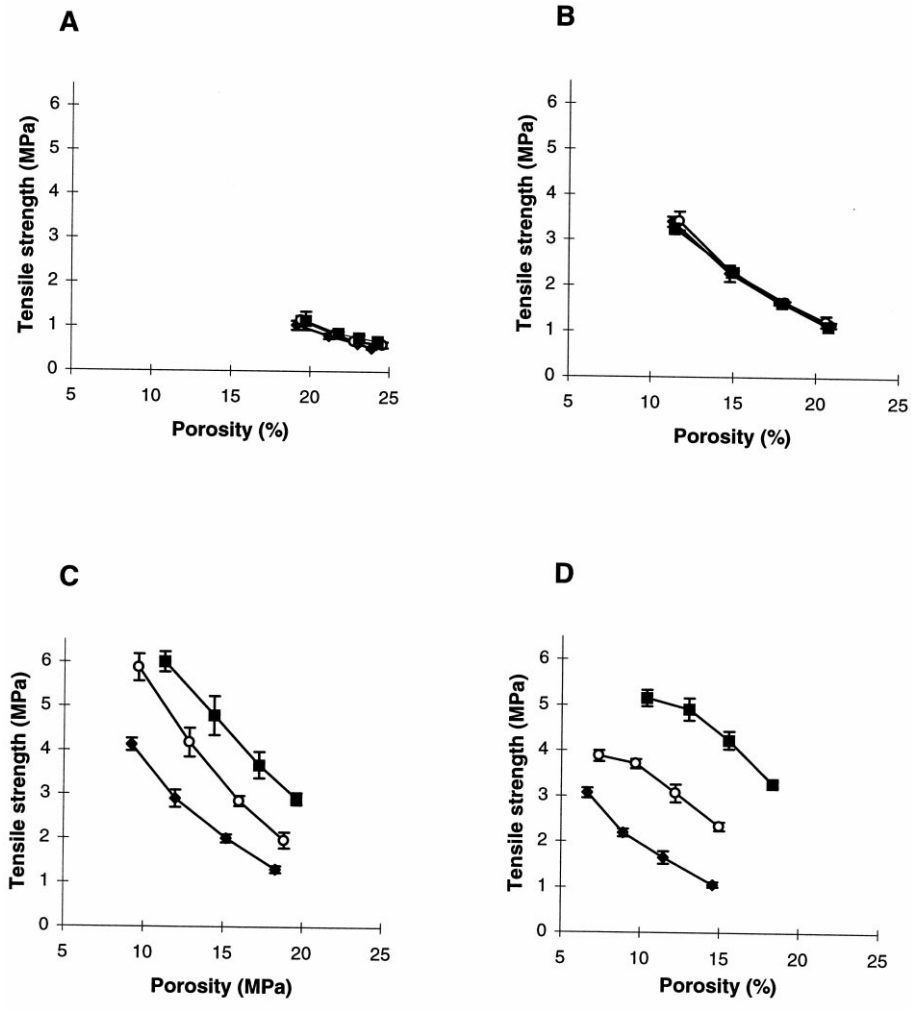

Fig. 5. Tensile strength of theophylline anhydrous form I (A), anhydrous form II (B), a mixture of forms (C), and the monohydrate (D) compacts as a function of compact porosity after 1 h (◆), 24 h (○), and 168 h (■) of storage. Standard deviation is shown as *y*-error bars.

theophylline forms were related to their solid-state structure, water content and changes in both of these characteristics during storage.

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