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Tablet formation and release from matrix tablets manufactured with cellulose acetate

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Abstract

Cellulose acetate has been successful in the production of matrix tablets but contradictory results exist also. Therefore, in this study it is used to elucidate the dependency of drug release from tablet formation and the factors influencing the microstructure of the tablet, such as densification, different particle size fractions, the dwell time during tableting and different drug concentrations. Tablets are produced on a single punch machine and on a hydraulic press. The tableting behaviour is judged from Heckel plots. Elastic recovery and crushing strength are measured. The resulting tablets are analysed by SEM, disintegration studies are performed and drug release is analysed. The produced tablets are of high robustness, tableting behaviour is plastoelastic. A high densification, that means a maximum relative density ($\rho_{rel,max}$) of at least 0.975 and particles of all sizes are necessary to produce tablets which are stable during disintegration studies for more than 8 h. Film-like structures were formed by partial fusion during tableting at temperatures higher than the glass transition temperature of the material. A reorganisation of the material occured. A dwell time of 10 or 20 s improved the formation of these structures. Tablets produced at high $\rho_{rel,max}$ or with longer dwell times resulted in controlled release tablets.

Keywords: Bonding; Tableting; Controlled release; SEM; Densification; Sintering

1. Introduction

The formation of tablets is a widely studied issue with the final aim of a better understanding of drug delivery from those tablets. As a result, drug release is dependent on the embedding of the drug during the formation of a tablet during compaction. The objective of this paper is to show the strong connection between the factors involved in tablet formation, the microscopic and submicroscopic properties of the final tablets and

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the drug release from these tablets. Cellulose acetate is chosen as the excipient to study this issue, because in the literature some contrary results are reported about its suitability as an excipient for controlled release tablets. Fengl et al. (1996, 1997) reported that cellulose acetate can be used to form a sustained release matrix and that both a hydraulic press and a rotary press were able to form satisfactory tablets. However, tablets formed on the rotary press included a small amount of plasticiser. Sanghvi et al. (1990), Agabeyoglu and Kaynar-Özdemir (1990) were also able to manufacture controlled release tablets. They both used a wet granulation technique prior to tableting. El-Khawas et al. (1993) prepared tablets by direct compression as well as after wet granulation. In all tablets prepared by direct compression a small amount of binder was included. Contrary to that, Abdallah et al. (1988) and Guyonnet et al. (1990) were not able to produce satisfactory tablets. Abdallah et al. (1988) concluded that the polymer failed in surrounding the drug particles properly. Guyonnet et al. (1990) were only able to produce controlled release tablets by coating the drug particles with a mixture of cellulose acetate and polyethyleneglycole prior to tableting. Based on these results different statements were made whether cellulose acetate is able to form a matrix or not. Therefore this polymer is expected to elucidate the processes necessary to form an immediate or controlled release tablet very clearly.

1.1. Tablet formation

The compression of powders and granules to form tablets is complex and persists in being poorly understood. Stages of the tableting process are (a) transitional repacking, (b) deformation at the points of contact, (c) fragmentation and/or plastic or elastic deformation, (d) bonding, (e) deformation of the solid body, (f) decompression, and (g) ejection (Parrott, 1990). The whole process up to the ejection of the tablet out of the die can be described with different models, e.g. porosity–pressure (Heckel, 1961a,b; Morris and Schwartz, 1995) and pressure–time (Dietrich and Mielck, 1985; Schmidt and Tenter, 1988; Shlieout and Zessin, 1994; Picker and Mielck, 1998) models. These models are helpful and give a lot of valuable information, but they are not able to describe the process of particle bonding in particular, which is of utmost importance for the final cohesion of the tablet (De Boer et al., 1978) and its dissolution properties. Other methods are used to characterise the properties of the formed tablet after compaction such as indentation hardness (Jetzer and Leuenberger, 1984) and the widely applied crushing strength (Fell and Newton, 1970). The strength of the interparticulate and intermolecular bonds for the whole compact shall be proved. Bonds can be formed by several mechanisms, described by three theories: the mechanical theory, the intermolecular theory and the liquid–surface film theory from which the last two are the most important (Parrott, 1990; Nyström et al., 1993). Hiestand and Smith (1991), Hiestand (1991, 1997a,b) explained the attraction of particles and the formation of bridges during tableting with a model for the process of tablet bonding. They explain that plastic deformation throughout the compaction–unloading cycle is responsible for bonding. The first 'ductile mechanism' model describes an isthmus formation during ductile extension, the second 'brittle mechanism' model describes direct tablet bonding without ductile extension. Although both of these models are useful approaches to describe tablet bonding, in general tablet bonding is a much more complicated process. It is important that the interparticle portion of the hydrostatic stress causes plastic deformation. Hüttenrauch showed that the activation of particles on a molecular level by crushing or milling contributes to tablet strength and an increased crushing strength means a higher amount of bondings formed in the tablet (Hüttenrauch and Keiner, 1976a,b). The time dependency of bond formation is shown by several authors (Rees and Rue, 1978; Larhrib et al., 1997). Hydrostatic stress evolves more at longer dwell times and high solid fractions than at low solid fractions.

1.2. Drug release

Drug release is dependent on the structures formed inside the tablet and the interaction of

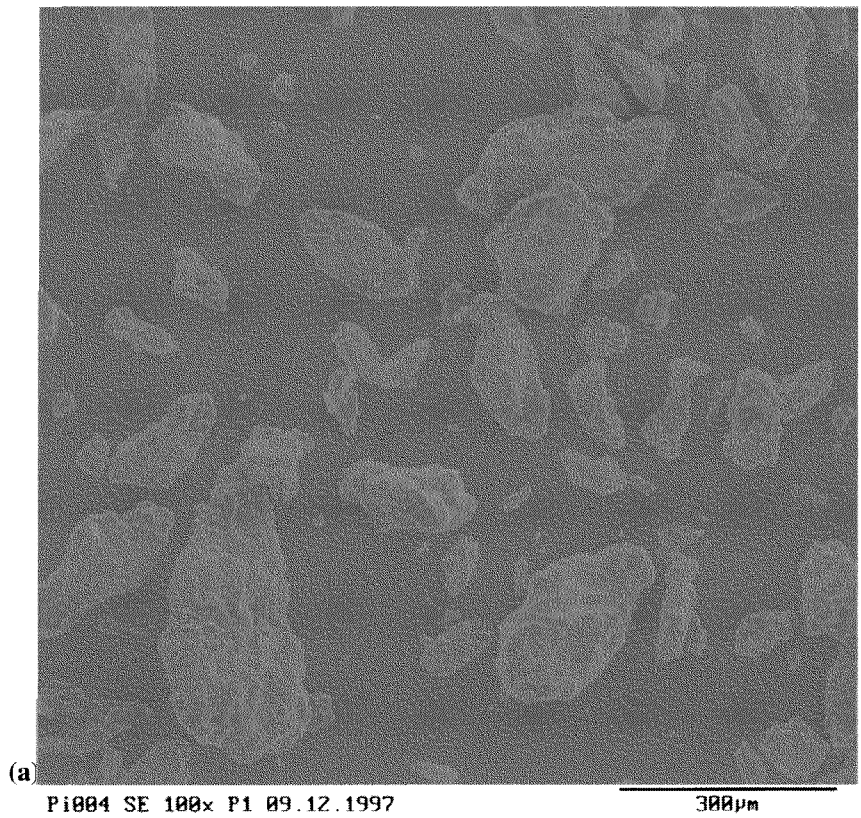


Fig. 1. Scanning electron micrographs of cellulose acetate powder at different magnifications.

these structures with gastric or intestinal fluid. The capillary microstructure of the tablets is formed during compaction and determines the penetration of the fluid (Carli and Simioni, 1981; Carli et al., 1981). Either an immediate release tablet is formed or a controlled release tablet. For an immediate release tablet the microstructure of the tablet has to be strong enough to withstand the mechanical influences up to the oral administration to the patient, but the bonds formed inside the tablet have to be weak enough to be segregated after penetration of the fluid, sometimes only possible by aid of a disintegrant. For a controlled release tablet the bonds formed inside the tablet and its structure have to be so strong that the sustained release of the drug is guaranteed. For hydrocolloid matrix tablets the structures responsible for the controlled release of drugs are mainly formed by the swelling process during penetration of the release medium. For matrix tablets not consisting of hydrocolloids this structure has to be formed already during the compaction process. Special conditions for producing such a tablet are necessary, including mainly the kind of material which is able to form such a matrix, usually a polymeric material. But why do some polymeric materials have the ability to form such a matrix and others not? There has to be general processes during tablet formation which are responsible for the stability of the tablet dependent on the physical properties of the material.

The aim of this study is therefore to elucidate the process of tablet formation and of drug release from such a tablet for a material which in the literature is reported to produce a matrix tablet (Agabeyoglu and Kaynar-Özdemir, 1990; Sanghvi et al., 1990; El-Khawas et al., 1993; Fengl

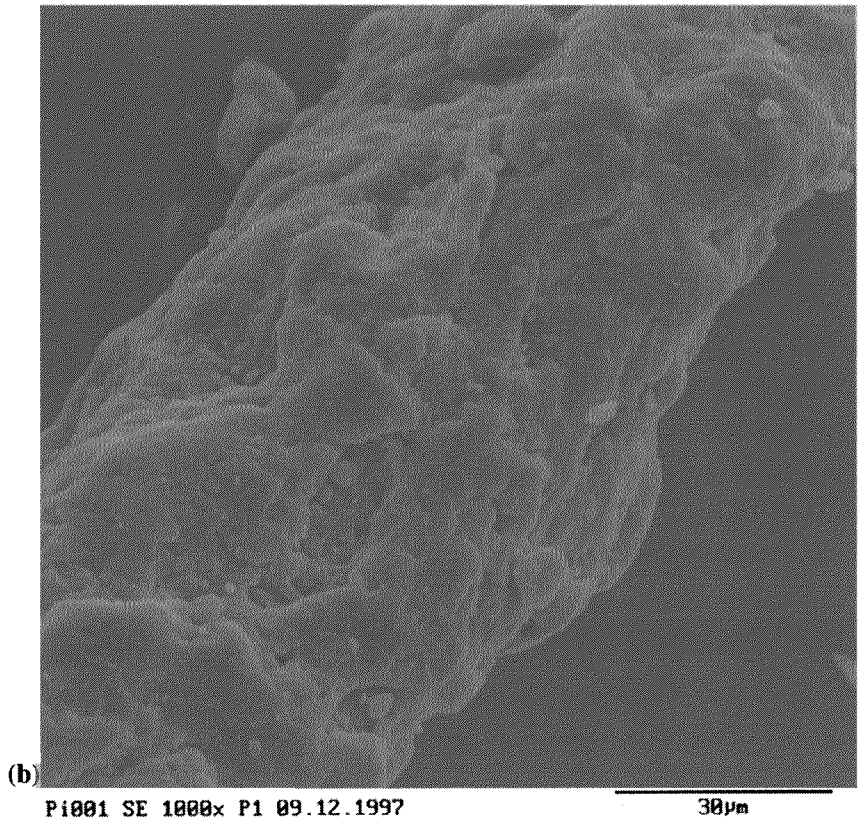


Fig. 1. (*Continued*)

et al., 1996, 1997) but for which production of a matrix tablet also failed. (Abdallah et al., 1988; Guyonnet et al., 1990). It has been reported that cellulose acetate and cellulose triacetate are not able to surround the particles and to form a stable matrix (Abdallah et al., 1988). In another study it was necessary to protect the matrix by coating from a too fast release (Guyonnet et al., 1990). What are the reasons for these contradictory results? Which mechanisms of tablet formation are necessary to produce a matrix tablet? Is this problem porosity dependent or is it dependent on the dwell time during tablet formation? All these questions have to be illustrated and explained for cellulose acetate and the results can be applied to other materials in a more general way.

2. Materials

Cellulose acetate CA-398-10, NF (Lot # AC-62505, Eastman, TN, USA) was used as the tableting excipient. The degree of substitution of this material containing 39.8% acetyl groups is between triacetate and diacetate. Theophylline monohydrate (Lot # 4072.2, Roth, Karlsruhe, Germany) was used as the model drug.

3. Methods

3.1. Powder and material properties

3.1.1. Particle size

A particle size analysis was performed in triplicate using laser diffractometry. (Sympatec Rodos

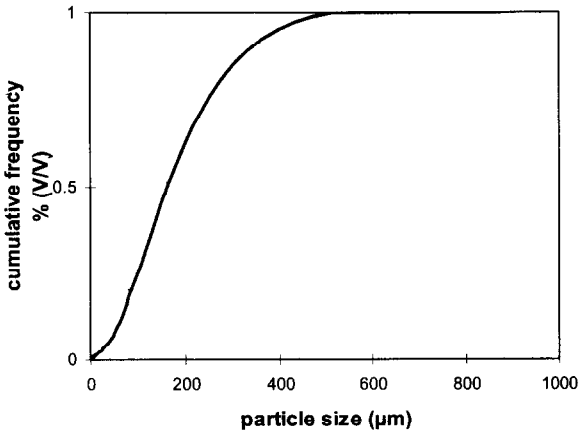


Fig. 2. Cumulative particle size distribution of cellulose acetate powder measured by laser diffractometry (mean, $n = 3$).

12 SR, Sympatec, Remlingen, Germany; pressure: 4 bar, injector beneath pressure: 60 mbar, focal distance 200 mm and measuring time: 25–35 s.) The mean particle size distribution was calculated.

3.1.2. Density

The true density was determined by a difference pressure pycnometer using helium (Accupyc 1330, Micrometrics, Norcross, USA) in triplicate. Bulk and tap density were determined with two repetitions in a weighed 250 ml cylinder using a volumeter (Erweka, Heusenstamm, Germany). Determinations were performed according to

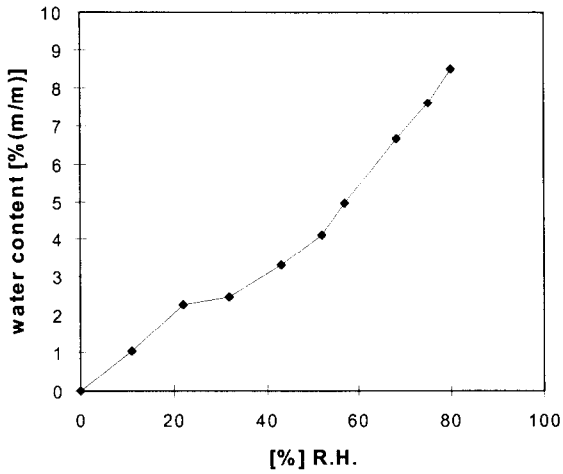


Fig. 3. Sorption isotherm of cellulose acetate (mean, $n = 2$).

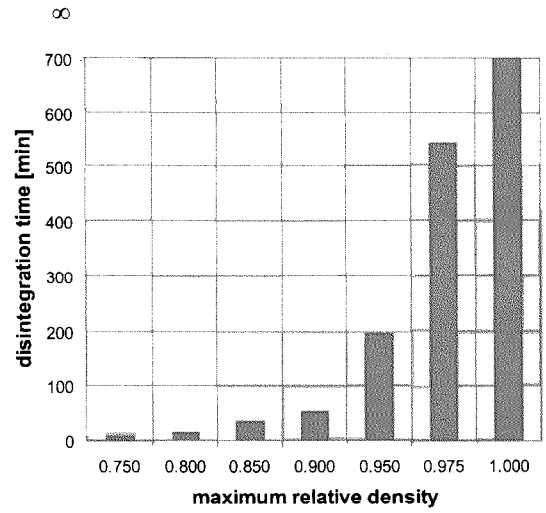


Fig. 4. Disintegration time of cellulose acetate tableted to different $\rho_{rel,max}$ on a single punch machine (mean, $n = 5$)*.

Pharmacopoeia Europaea (Europäisches Arzneibuch, 1997).

3.1.3. Water content

The content of water for the material used for tableting was determined by thermogravimetric analysis in triplicate (Polymer laboratories Thermal Sciences LTD, TG 1000/1500, Polymer Laboratory Surrey, United Kingdom). Additionally, sorption isotherms were recorded gravimetrically after equilibration over saturated salt solutions (Greenspan, 1977) in duplicate.

3.1.4. Glass transition temperature

Differential scanning calorimetry analysis (DSC 200, Netzsch Gerätebau, Selb, Germany: heating rate 20°C between 20 and 200°C) was performed in triplicate. Pinholed pans were used for the first and the second heating. Samples were analysed in closed pans for determining the glass transition of the moist material. The glass transition temperature was calculated as the midpoint of the glass transition step.

3.2. Preparation of materials

The materials, cellulose acetate and theophylline monohydrate, were physically mixed in a mixer with fixed wide-necked bottles (250 ml,

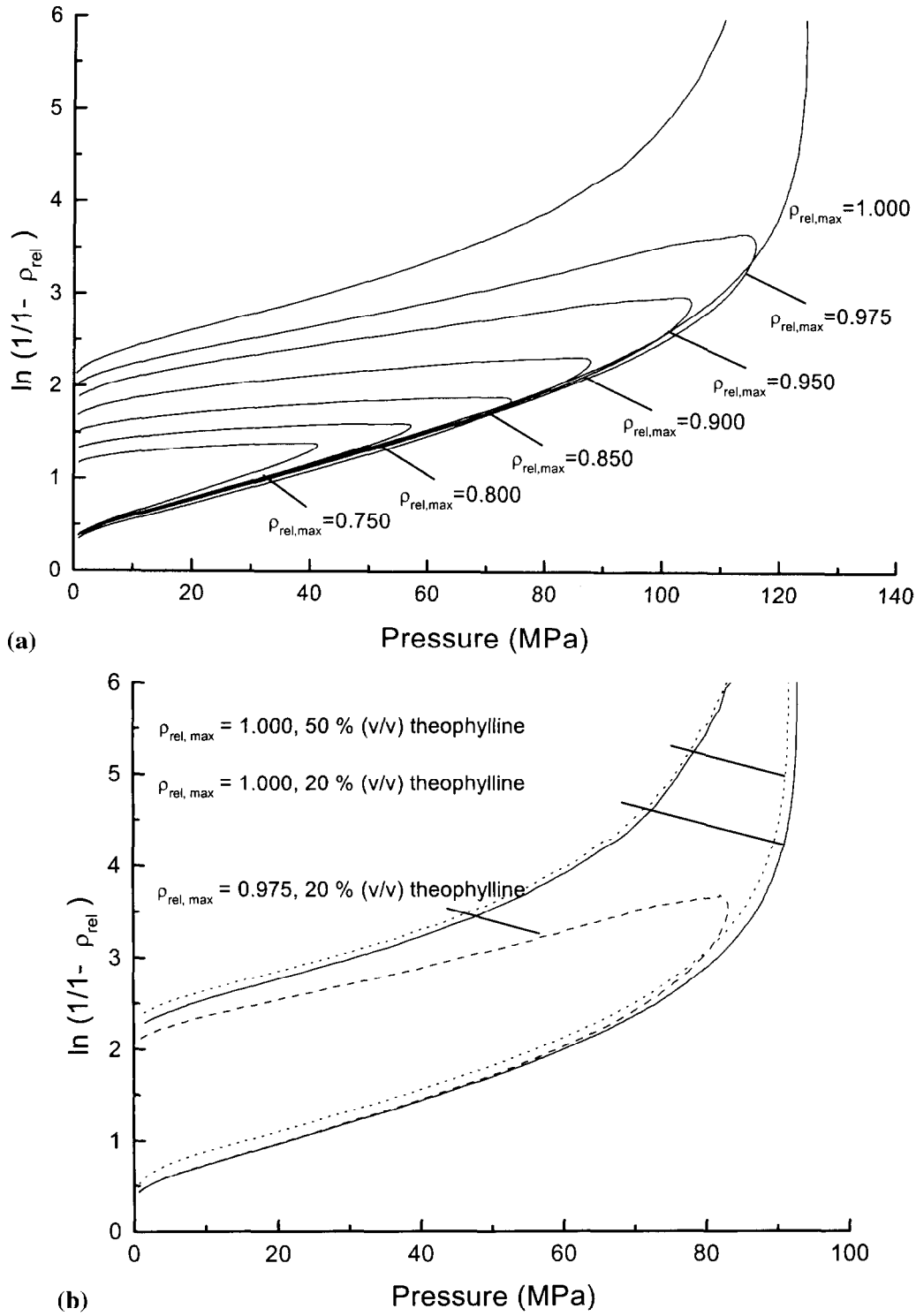


Fig. 5. Heckel plots of cellulose acetate tableted to different $\rho_{rel,max}$ (a) without theophylline and (b) with different concent of theophylline.

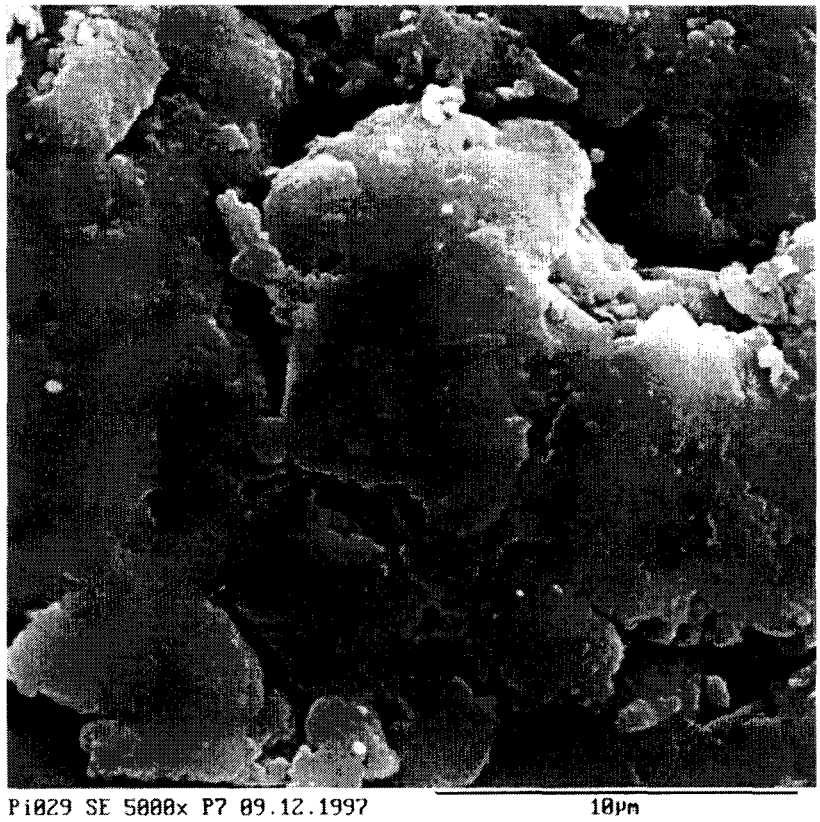


Fig. 6. SEM of the surface of a cellulose acetate tablet containing 20% (v/v) theophylline tableted to a theoretical $\rho_{rel,max}$ of 1.000 before release studies.

15 min, 30 rpm, AR 400, Erweka, Heusenstamm, Germany) prior to tableting. The mixing ratio were calculated as true volumes (v/v).

For disintegration studies cellulose acetate was divided by sieving (Retsch, Haan, Germany) in three particle size fractions: <75, 125–212, >212 μm.

3.3. Tableting

3.3.1. Eccentric tableting machine

Tableting was performed on an instrumented single punch tableting machine (EK0/DMS, No. 1.0083.92, Korsch, Berlin, Germany) with 11 mm diameter flat faced punches. The relative humidity during tableting was in between 40 and 50% r.h. Equal true volumes of the substances were tableted to different maximum relative densities of the tablets, $\rho_{rel,max}$: 0.750, 0.800, 0.850, 0.900, 0.950, 0.975, 1.000 (precision 0.001).

$$\rho_{rel,max} = \frac{\rho_{max}}{\rho_{true}} \quad (1)$$

where: $\rho_{rel,max}$, maximum relative density; ρ_{max}, density at minimum height of the tablet under load; ρ_{true}, true density.

Equal true volumes were chosen to gain about the same porosity of the tablets under load. Even when volume reduction of the different materials is different during compression this method describes in a visual way the distribution of the material in the tablet. The tablet height and therefore the volume at maximum densification under load were held constant at 3.000 ± 0.001 mm (corrected for elastic deformation of the punches). The depth of filling was held constant at 13 mm

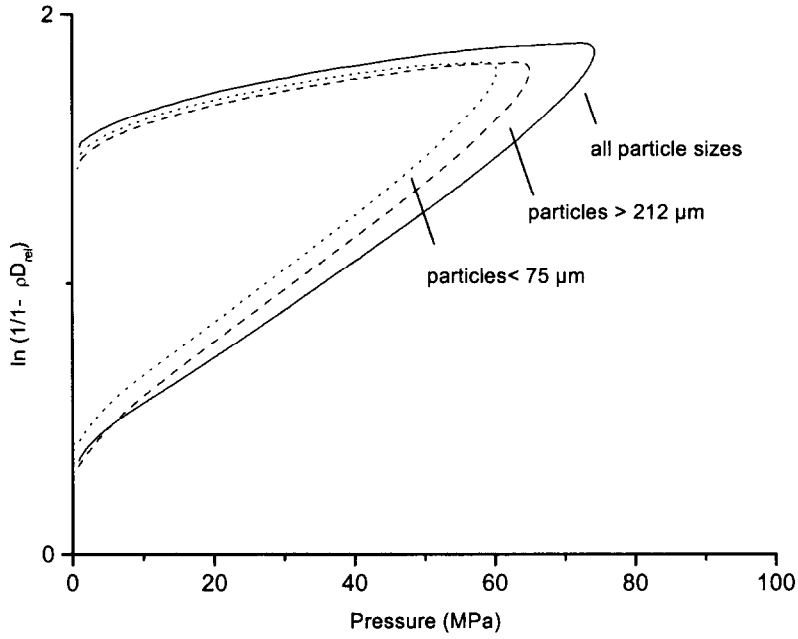


Fig. 7. Heckel plots of cellulose acetate fractions tableted to a $\rho_{rel,max}$ of 0.850.

and the compression rate was 10 rpm. Forces were measured by the calibrated strain gages and displacement of the punch faces was measured using an inductive transducer (W 20 TK, Hottinger Baldwin Meßtechnik, Darmstadt, Germany). The amount of material necessary for each tablet with a given $\rho_{rel,max}$ and always the same apparent density was calculated. The powder was manually filled into the die and one compaction cycle was performed. Fifteen single tablets were produced at each condition. No lubricant was used to avoid its influence on dissolution properties. The die was polished after each 15 tablets made at one condition with ethanol, it was not cleaned in between because no powder was remaining in the die.

Force and distance signals were amplified and digitised with the DMC plus system (Hottinger Baldwin Meßtechnik, Darmstadt, Germany). Data were stored and analysed by a Macintosh computer with BEAM Software (AMS, Flöha, Germany). For analysing tableting data, only data >1 MPa were used. Always five compression cycles were analysed starting with the 6th tablet.

The Heckel-function (Heckel, 1961a) was fitted to the Heckel plot. For calculating the slope of the Heckel-function, all data pairs (pressure and displacement) up to the maximum pressure are divided into ten equal groups and linear regression is performed. The group with the lowest slope is selected and this group is enlarged by data pairs until the standard deviation is more than 6-fold. The slope is calculated for the last regression line. The Heckel slope was judged in combination with recovery of the tablet up to the point at which the upper punch leaves the surface of the tablet (elastic recovery after decompression).

3.3.2. Mechanical characterisation of the tablets

Elastic recovery according to Armstrong and Haines-Nutt (1972) was calculated after 24 h (micrometer screw, Mitotuyo, Tokyo, Japan).

Additionally, the diametrical crushing strength of five tablets was determined directly after ejection (Erweka crushing strength tester, Type TBH28, Erweka, Heusenstamm, Germany). The used strain rate was 2.3 mm/s.

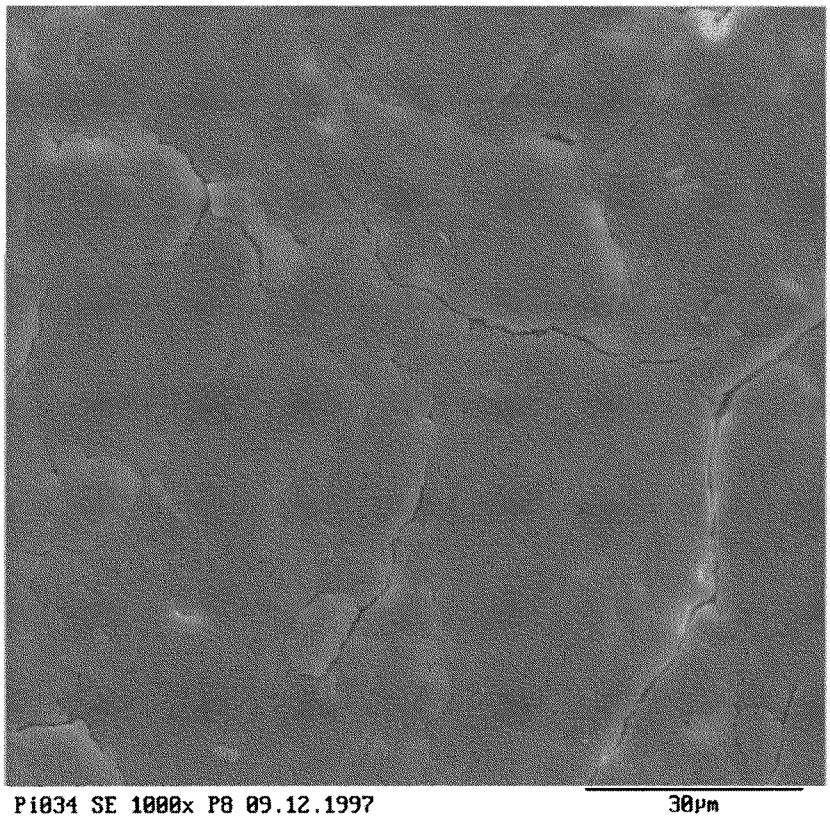


Fig. 8. SEM of the surface of a cellulose acetate tablet tableted on a hydraulic press with a compression pressure 113.3 MPa and a dwell time of 20 s before release studies.

3.3.3. Hydraulic press

Tablets of 13 mm diameter and a weight of 400 mg were produced on a hydraulic press (SPECAC 15.000, VEB, GDR) with flat faced punches. The peak pressure of 37.7, 75.4 or 113.3 MPa was held constant for a dwell times of 10 and 20 s. Ten tablets were produced at each pressure and dwell time.

3.4. Disintegration studies

Disintegration of the tablets was measured up to the complete disintegration into particles ≤ 2 mm in a disintegration tester (Erweka, Heusenstamm, Germany) or up to 8 h respectively in a paddle apparatus in distilled water at 37°C for five tablets. Standard deviation was calculated.

3.5. Drug release

Drug delivery was analysed using the paddle method according to USP XXIII in distilled water (900 ml, 37 ± 0.5°C, 100 rpm) for 8 h. Samples of 10 ml medium were drawn and substituted by distilled water. The resulting concentrations of drug in the release medium were determined in appropriate intervals spectrophotometrically (Spectronic 601, Milton Roy, Obertshausen, Germany). The content of drug was determined at peak maximum (theophylline monohydrate: 271 nm). The release of six tablets was determined and means and standard deviations were calculated.

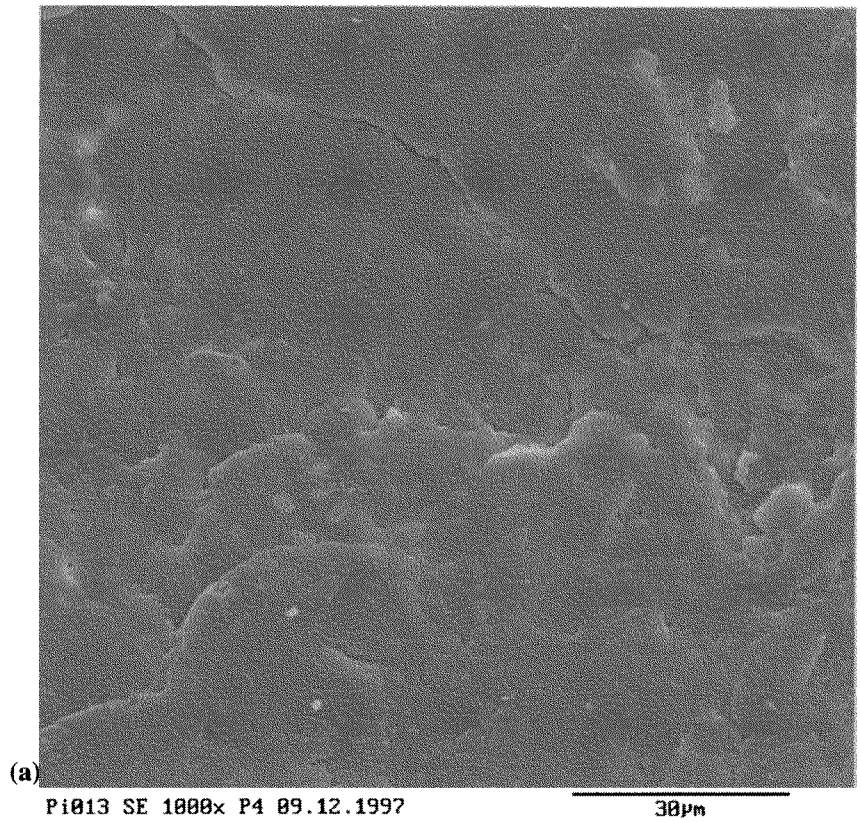


Fig. 9. SEMs of the (a) surface and the (b) inside of a cellulose acetate tablet tableted on a hydraulic press with a compression pressure of 113.3 MPa and a dwell time of 20 s after release studies.

3.6. Microscopic photography and scanning electron microscopy (SEM)

From dried tablets photographs (Pentax p 30 N) were taken with a magnification of 10.

Vacuum oven dried samples of the powder and the tablets before and after release studies were mounted on a sample holder and coated with coal/gold/coal. The samples were examined with a scanning electron microscope (model JEOL 6400, Tokyo, Japan) at an accelerating voltage of 15 or 5 kV depending on the sample.

4. Results and discussion

4.1. Powder and material properties

Particle shape is shown in Fig. 1(a) and (b) by SEM. The particles of cellulose acetate have an irregular, often oblong shape and they show the fibrous nature of the material, especially for particles of a medium size. The bigger ones seem to be aggregates. The fine structure in Fig. 1(b) shows a kind of molten and dropped structure with intramolecular pores. The particle size was characterised according to Fig. 2. The re-

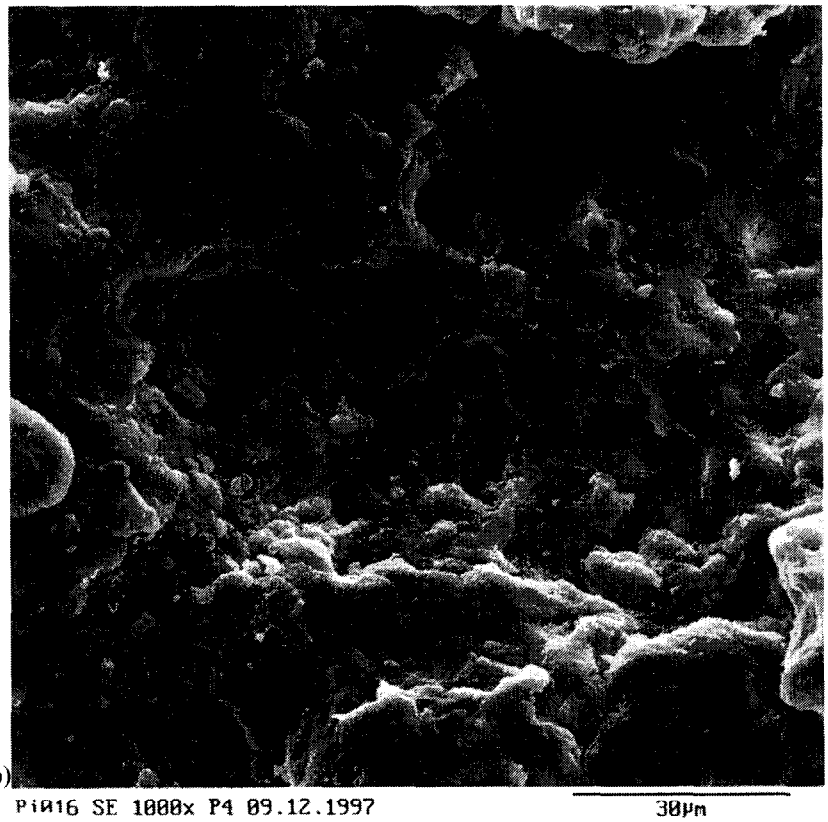


Fig. 9. (*Continued*)

sults of the analysis by laser diffraction show a slightly larger particle size due to the measuring method which pretends round particles.

Fig. 3 shows the water sorption behaviour of the material up to 80% relative humidity (r.h.) (mean standard deviation: 0.09% (m/m)). Cellulose acetate is able to absorb and adsorb water which will influence the bonding of this material during compaction. The material tableted contained 2.53% (w/w) water determined by thermogravimetric analysis. Hydrogen bondings may be formed and be responsible for tablet strength and release behaviour.

The determined midpoint for the glass transition temperature of the dry material is 154.1 ± 0.1°C for the first and the second heating. The glass transition region between 149.1 and 159.0°C is relatively small and thus the result is very accurate. Glass transition is lowered by the amount of 2.53% (w/w) water to 66.9 ± 1.3°C. Thus the material used is in the glassy state. During tableting higher temperatures are most probable and thus bonding will be possible between particles in the rubbery state by fusion or melting according to the liquid–surface theory. Because cellulose acetate is not water soluble these bonds cannot be segregated in the release medium like hydrogen bonds.

The density values determined were like follows: 1.35 g/cm^3 true density (measured by helium pycnometry), 0.40 g/cm^3 tap density and 0.34 g/cm^3 bulk density. Thus the volume reduction from bulk density to a theoretical $\rho_{\text{rel. max}}$ of '1.000' will be fourfold and most of this process will occur during tableting because the arrangement of particles during tapping without the influence of force is relatively low. The low tap density shows this. Thus during tableting a lot of density changes are expected influencing the release from these tablets.

Table 1
Data of the compressibility of the cellulose acetate and mixtures of cellulose acetate and theophylline monohydrate at different maximum relative densities ($\rho_{rel,\,max}$)

Maximum relative density	Particle size fraction	Theophylline monohydrate (% (v/v))	Maximum upper punch pressure (MPa)	Heckel slope (MPa-1)	Elastic recovery during decompression (%)	Elastic recovery after 24 h (%)	Crushing Strength after 24 h (N)
0.750	All	0	41.69 (0.41)	0.0184 (0.0001)	8.93 (0.28)	19.46 (0.13)	82.3 (5.7)
0.800	All	0	57.76 (1.95)	0.0157 (0.0004)	8.54 (0.27)	18.39 (0.13)	115.0 (4.0)
0.850	All	0	73.13 (1.16)	0.0155 (0.0001)	8.90 (0.45)	17.66 (0.12)	160.6 (4.0)
0.900	All	0	86.73 (1.35)	0.0158 (0.0003)	10.49 (0.28)	19.03 (0.12)	208.8 (14.0)
0.950	All	0	102.29 (2.06)	0.0163 (0.0002)	12.92 (0.45)	19.67 (0.16)	265.6 (19.6)
0.975	All	0	116.32 (1.00)	0.0154 (0.0006)	12.25 (0.25)	19.51 (0.14)	299.0 (18.2)
1.000	All	0	124.99 (1.07)	0.0160 (0.0005)	13.13 (0.35)	20.01 (0.17)	310.4 (13.3)
0.850	<75 μm	0	59.17 (0.68)	0.0175 (0.0005)	8.51 (0.18)	20.00 (0.14)	133.0 (6.8)
0.850	>212 μm	0	64.22 (0.39)	0.0171 (0.0001)	9.20 (0.25)	22.00 (0.12)	115.6 (4.0)
0.975	All	20	109.98 (0.74)	0.0160 (0.0003)	10.86 (0.24)	18.61 (0.12)	202.0 (20.1)
1.000	All	20	123.23 (1.43)	0.0161 (0.0004)	11.81 (0.24)	18.93 (0.17)	229.6 (22.0)
1.000	All	50	120.77 (1.06)	0.0153 (0.0002)	10.95 (0.28)	16.47 (0.18)	161.0 (6.0)

Mean, standard deviation given in parentheses.

4.2. Tableting behaviour and release from differently formed tablets

4.2.1. The influence of densification on bonding

For proving whether the particles are able to form a stable matrix disintegration tests were performed. The results are given in Fig. 4. The tablets were manufactured from pure cellulose acetate without magnesium stearate because magnesium stearate is known to reduce bonding capability (De Boer et al., 1978). All tablets with a $\rho_{rel,max}$ value less or equal to 0.950 disintegrated in less than 8 h. Disintegration time increased with $\rho_{rel,max}$, which means that an increase in bonding occurs more when a specific distance between the particles has been overcome. Only tablets having a $\rho_{rel,max}$ value of less or equal to 0.975 resulted in controlled release tablets. They were more than 8 h stable in the disintegration apparatus. All the others were not mechanically stable enough to withstand the mechanical influences in water during a disintegration test or in a paddle apparatus. Obviously plastic deformation and mechanical interlocking of the particles are able to produce a stable tablet but the particles can be very easily segregated by the release medium. The reason is that the hydrogen bonds which are responsible for the mechanical stability of the tablet can be solved by the release medium. Bonding can be imagined as for microcrystalline cellulose (Albersheim, 1975) which disintegrated very readily. When a densification higher or equal to 0.975 is reached the tablets are not only stable during disintegration studies, they also show a very high crushing strength. This means that the type of bonding in the tablets is changing. Heckel plots can give further insights (Fig. 5(a)). The principle deformation mechanisms are the same for tablets with and without theophylline (Fig. 5(b)). The slope of the Heckel-function remains similar. But Fig. 5(a) shows that with increasing $\rho_{rel,max}$ the plot gets a more round shape at the necessary maximum pressure. The response of the material produces a constant pressure during further densification, which means that the pressure is no longer increasing during densification. A hydrostatic stress is occurring and according to Hiestand (1997b) the interparticle portion of the hydrostatic stress contributes to bonding because it produces plastic deformation of the particles. At the same time, the elastic recovery after decompression and after 24 h is increasing (Table 1). This means that the part of elastic deformation is increasing. Since strong bonds are already formed between the particles it can be expected that the tablet on the whole is now reacting like a viscoelastic body which means that it undergoes deformation characterised by a combination of elastic deformation and viscous flow (Müller, 1995). This viscoelasticity contributes to bonding. The bonds will be formed by fusion and sintering of the particles because at these high pressures it is most probable that temperatures higher than the glass transition temperature of the material (67°C) are occurring inside the tablet (Larhrib et al., 1997). The density of liquids is usually higher than the density of solids. Only by melting a theoretical $\rho_{rel,max}$ of '1.000' becomes possible. Structural changes are occurring. For a tablet containing a low amount of theophylline, fusion and sintering can be seen by a SEM-photograph at a $\rho_{rel,max}$ of '1.000' (Fig. 6). The structure formed will be responsible for the controlled release. The bonds formed cannot be solved by the release medium. Controlled release cannot occur when this structure is not formed because the hydrogen bonds formed at lower $\rho_{rel,max}$ can be dissolved. However, are there other factors than densification which can influence the formation of this sintered structure?

4.2.2. The influence of particle size on bonding

Since sintering or fusion can occur more easily when the surface area is higher, it was expected that using only fine particles would result in stable tablets and using only coarse particles would result in very unstable tablets. But tablets produced with different particle size fractions of material all showed a sudden disintegration. Disintegration tests for tablets with a $\rho_{rel,max}$ of 0.850 containing only particles smaller than 75 μm, bigger than 212 μm or in between 75 and 250 μm all disintegrated at once, faster than those made from the whole particle size fraction. This showed that all particle sizes including fine and coarse particles are necessary to produce the formation of bonding and

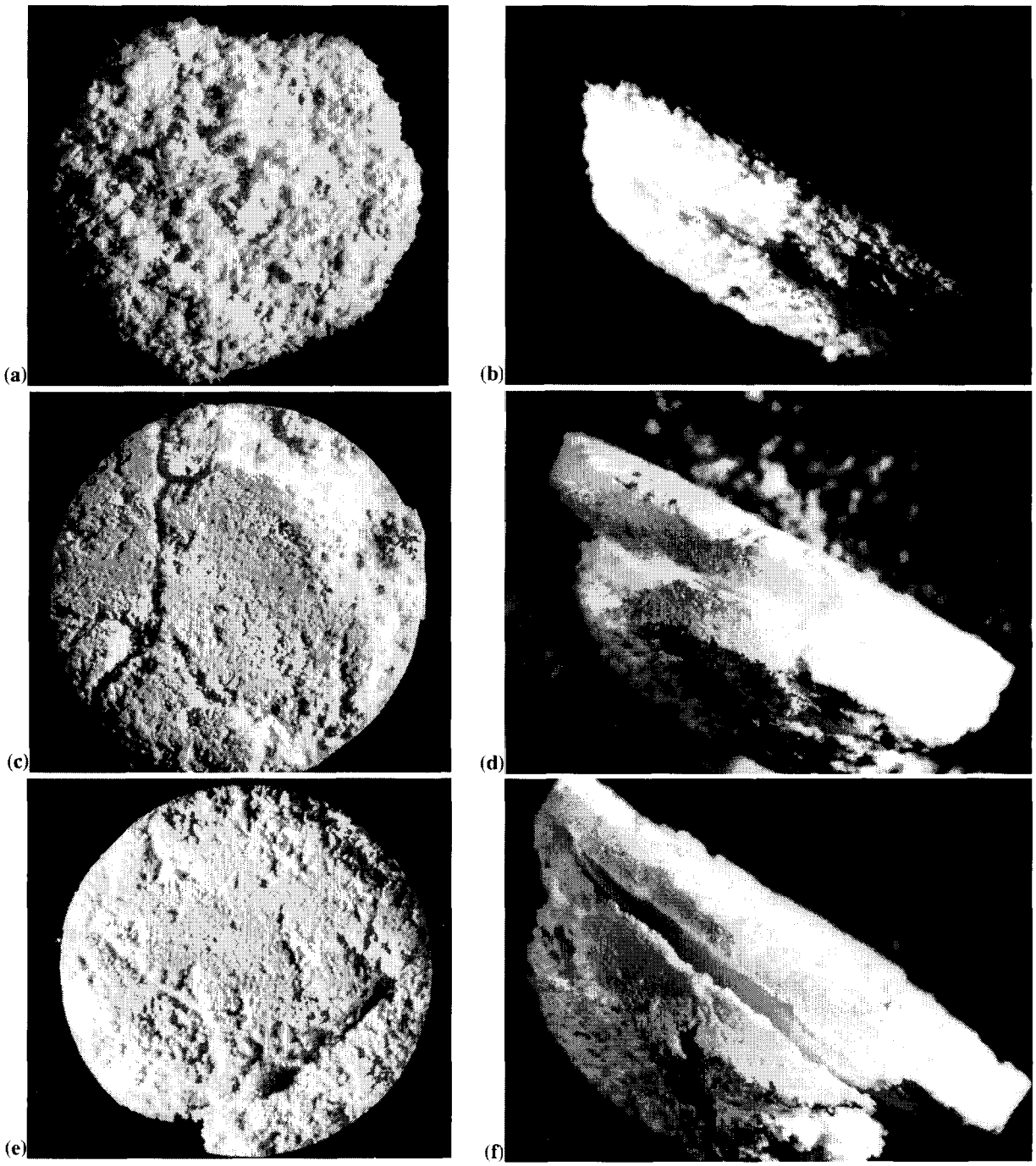


Fig. 10. Photographs* (original magnification × 10) of dry cellulose acetate tablets after release studies: (a) surface and (b) edge of a tablet tableted to a $\rho_{rel,max}$ of 0.975 which contained 20% (v/v) theophylline; (c) surface and (d) edge of a tablet tableted to a $\rho_{rel,max}$ of 1.000 which contained 20% (v/v) theophylline; and (e) surface and (f) edge of a tablet tableted to a $\rho_{rel,max}$ of 1.000 which contained 50% (v/v) theophylline.

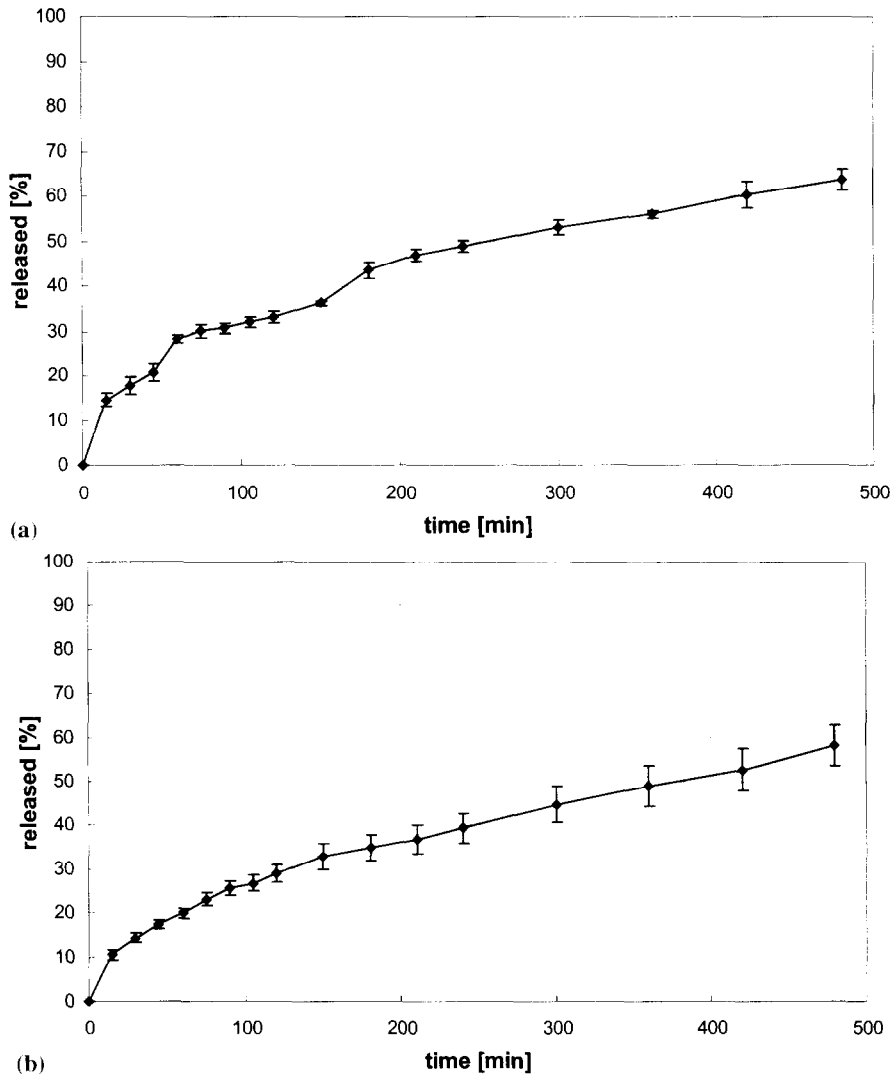
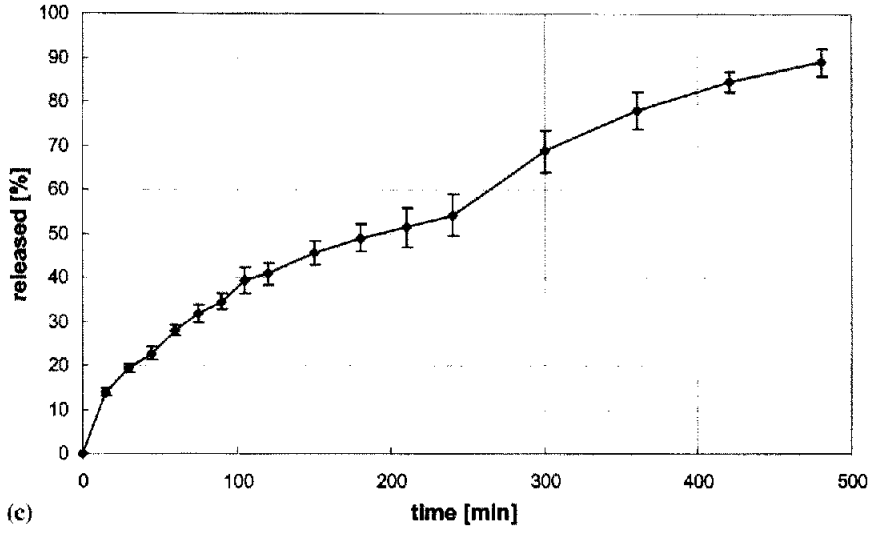


Fig. 11. Release from cellulose acetate tablets (mean and standard deviation, $n = 6$) (a)* tableted to a $\rho_{rel,max}$ of 0.975 containing 20% (v/v) theophylline, (b)* tableted to a $\rho_{rel,max}$ of 1.000 containing 20% (v v) theophylline, (c)* tableted to a $\rho_{rel,max}$ of 1.000 containing 50% (v/v) theophylline and (d) tableted with 113 MPa and a dwell time of 20 s.

thus a stable tablet. Packing is best when the fine particles are in the void spaces between the bigger particles and this indicates also that the particles have to be in very close contact, otherwise, mechanical interlocking which also contributes to Looking at the SEM-photograph (Fig. 8) one can no longer distinguish single particles at a low pressure of 37.7 MPa and a dwell time of 10 s. The particles are melted together in a film-like structure. The dissolution medium is not able to disrupt the tablets. Fig. 9(a) and (b) shows the structure of a tablet densified with 113.0 MPa and a dwell time of 20 s on the surface (a) of the tablet and inside the tablet (b). The fused structure can be seen not only on the surface but also inside the tablet. This clearly indicates that the longer dwell time caused higher temperatures which facilitate fusion. The hydrostatic stress which occurs at



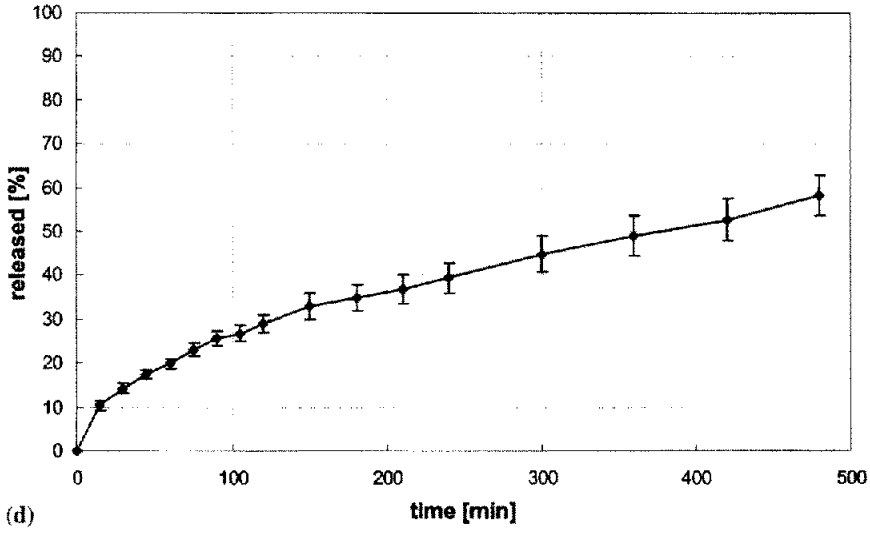


Fig. 11. (*Continued*)

high $\rho_{rel,max}$ on a single punch machine on a hydraulic press is consisting for a longer time interval.

4.2.4. The release process from highly densified tablets

Since only tablets produced at a $\rho_{rel,max}$ of 0.975 or '1.000' were stable for 8 h in the dissolution medium, these tablets were used for analysing release properties. These tablets slowly eroded but were stable over 8 h in the disintegration tester. Fig. 10 shows photographs of the dried tablets after release, Fig. 11 shows the corresponding release curves. The photographs show that erosion especially took place at the edge where the tablets were less fused. The hydrogen bonds responsible for the mechanical stability of the tablet can be dissolved, whereas bonding formed by fusion cannot be dissolved. For all these tablets a bursting at the edge can be observed. Bursting proceeded after the intrusion of water into the tablet when the pressure developed by the penetrated water was high enough (Carli et al., 1981; Carli and Simioni, 1981). Both the bonding mech-

anisms, hydrogen bonding and fusion, are responsible. The release curves show an increase of drug concentration in the release medium for the $\rho_{rel,max}$ of 0.975 after 1 h and for the $\rho_{rel,max}$ of '1.000' after 4 h. This indicates that after this times in the release medium bursting occurs. Therefore, the time of tablet bursting is different for different $\rho_{rel,max}$ but not for different concentrations of drug. The drug concentration determines the rate of release (Fig. 11(b) and (c)). The densification of the excipient is responsible for the burst effect. This is remarkable because the difference in ρ of the final tablet after 24 h is low (about 20%). Different inner structures resulting from different bonding mechanisms must have been formed. At the $\rho_{rel,max}$ of 0.975 less fusion is possible. Because tablets produced on a hydraulic press were stable over 8 h in the disintegration tester without showing erosion at the edges, it was assumed that these tablets show no sudden increase in drug concentration. Studies performed by Fengl et al. (1996) showed this. A release study on tablets produced on a hydraulic press confirmed these results (Fig. 11(d)). A long dwell time and thus a hydrostatic stress remaining for some seconds is necessary to allow enough bonding by fusion. The properties of the amorphous polymer are influenced. The polymer chains reorganise at these pressures held for a relatively long time and cohesion inside the tablet increases. Fusion of the polymer is the dominating bonding mechanism compared to strong hydrogen bonding which is responsible for the mechanical stability of the tablet produced on a tableting machine at lower $\rho_{rel,max}$.

5. Conclusions

The results show that it is only possible to produce a matrix tablet with cellulose acetate for controlled release applications by using longer dwell times. Thus it becomes obvious why contradictory results were reported in the literature (Abdallah et al., 1988; Agabeyoglu and Kaynar-Özdemir, 1990; Guyonnet et al., 1990; Sanghvi et al., 1990; El-Khawas et al., 1993; Fengl et al., 1996, 1997). Without longer dwell times and the hydrostatic stress evolving during this process the bonding in the cellulose acetate matrix is dominated by hydrogen bonding which can be dissolved by the release medium. At lower $\rho_{rel,max}$ the tablets disintegrate at once, at higher $\rho_{rel,max}$ the tablets burst after some time. Only when a reorganisation of the material occurred throughout the tablet were the tablets stable during release. Higher temperatures than the glass transition temperature occurring during the tableting process throughout the material are necessary to cause fusion which is responsible for the stability of these matrices. This is the case by using longer dwell times during compaction on a hydraulic press. Since it is not practicable to use this machine during regular manufacturing processes, for using this material for controlled release applications it is necessary to change the mechanism of bonding to improve the stability of the tablet. This could be accomplished by including an additional excipient which deforms plastically (El-Khawas et al., 1993). Abdallah et al. (1988) already mentioned that the particles have to be surrounded. Following these results a material used for controlled release tablets should bond more easily by fusion. A more plastic deformation of the material and thus a higher portion of interparticulate hydrostatic stress throughout the compaction-unloading cycle is necessary.

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Data marked with * are taken from a 'Diplomarbeit', which was supervised by the corresponding author during six months: Bikane, F., 1997. Eignung von Celluloseacetat als Matrixbildner; Tablettierverhalten in Mischung mit Calciumhydrogenphosphatdihydrat (Emcompress®). Diplomarbeit Martin-Luther-Universität Halle-Wittenberg.

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