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European Journal of Pharmaceutics and Biopharmaceutics 56 (2003) 101–110
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Potential of carrageenans to protect drugs from polymorphic transformation

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Received 11 November 2002; accepted in revised form 26 February 2003

Abstract

Carrageenans were analysed in mixture with polymorphic drugs to test their potential for minimising polymorphic or pseudopolymorphic transitions, which are induced by the tableting process. The κ-carrageenans Gelcarin® GP-812 NF and Gelcarin® GP-911 NF and the ι-carrageenan Gelcarin® GP-379 NF were tested in comparison to the well-known tableting excipients microcrystalline cellulose (MCC), hydroxypropyl methylcellulose (HPMC), and dicalcium phosphate dihydrate (DCPD). Amorphous indomethacin was chosen as model drug since its well-known recrystallisation behaviour can be mechanically stimulated. Further on, theophylline monohydrate was used. Its dehydration is induced by tableting. Pure materials and mixtures containing 20% (w/w) drug were compressed up to different maximum relative densities. The data obtained during tableting were analysed by three-dimensional (3D) modelling. Afterwards tablets were broken and examined by Fourier transform Raman spectroscopy in order to determine the degree of transformation inside the tablet. For quantitative interpretation, the intensities of representative bands were used. Thermal analysis was used additionally.

Using 3D modelling a decrease of plastic deformation can be noticed in the order HPMC > MCC > carrageenans, whereas DCPD represents an exception because of brittle fracture. Best hindrance of polymorphic transformation showed the carrageenans, the hindrance was slightly worse for HPMC. MCC and DCPD could not hinder transformation. A complete protection of the amorphous form could not be achieved. For theophylline monohydrate, the results were similar.

Keywords: Carrageenan; Indomethacin; Recrystallisation; Excipient; FT-Raman spectroscopy; Theophylline; Three-dimensional modelling; Dehydration; Polymorphic transition; Tableting

1. Introduction

Polymorphism is an important factor in pharmaceutical technology. About 40% of drugs processed into tablets exist in more than one polymorphic or pseudopolymorphic form. Since different modifications show different properties there is the possibility to select a form with optimal properties for a special problem. Stability problems arise frequently: at given conditions only one form is stable, others are metastable or instable [1,2]. Thus, polymorphic transitions described were often initiated by pharmaceutical operations [3–10].

Optimal solubility is the precondition for every effect in organism of a drug given orally. To achieve satisfactory solubility, advantages of specific polymorphic or especially amorphous forms should be used [11]. As a disadvantage, often amorphous materials already recrystallise at ambient conditions. Their ability to recrystallise is increased by pharmaceutical operations like milling, granulation, and tableting from which the materials obtain the energy necessary for activation [12].

Carrageenans have shown the ability to tablet α-amylase simultaneously reducing its inactivation caused by the tableting process [13]. This special ability can be attributed to their high elasticity which has been already described [14,15]. Tableting behaviour of carrageenans was evaluated by fitting the pressure–time function to the pressure–time plot and by fitting the Heckel function to the porosity–pressure plot. Parameters derived from these functions and

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doi:10.1016/S0939-6411(03)00037-7

also elastic recovery indicates that the materials could also be able to embed polymorphic drugs softly. Therefore, the objective of this study is to test the carrageenans whether they are able to avoid or reduce polymorphic transitions as they were able to reduce inactivation of α-amylase. In comparison frequently used tableting excipients as microcrystalline cellulose (MCC), hydroxypropyl methylcellulose (HPMC), and dicalcium phosphate dihydrate (DCPD) will be analysed. Amorphous indomethacin was chosen as the model drug in these mixtures.

For indomethacin, Yamamoto [16] described three polymorphic forms, α, β and γ. Similar and further forms were discussed in the literature [17–19]. At ambient conditions the amorphous form transforms only into the crystal γ modification [20]. Studies were usually performed by differential scanning calorimetry (DSC), X-ray diffractometry, and IR-spectrometry, recent investigations were also performed by Fourier transform (FT)-Raman spectroscopy [21–23]. Most of the studies were realised by using pure powdered indomethacin [24,25]. Until now only a few investigations exist analysing tablets consisting of indomethacin in mixture with excipients. Davies et al. [21] described the detection of 20% crystalline indomethacin in sodium alginate. Taylor and Langkilde [23] analysed even different polymorphic forms of drugs in tablets with excipients by FT-Raman spectroscopy. There are no investigations analysing polymorphic transitions in tablets induced by tableting using FT-Raman spectroscopy.

Additionally mixtures with theophylline monohydrate have been tableted to verify the results. Theophylline transforms from the anhydrous form into the monohydrate and vice versa due to moisture and pharmaceutical operations like milling, granulation, and tableting. Caused by pressure the monohydrate loses its hydrate water [26,27].

Summarising, the aim of this study is to analyse by FT-Raman spectroscopy the recrystallisation of amorphous indomethacin and the dehydration of theophylline monohydrate in order to test the protection potential of the carrageenans for drugs undergoing polymorphic transitions due to tableting. The drugs will be analysed pure and in mixture with different excipients while studying powders as well as tablets.

2. Materials and methods

2.1. Materials

Model drugs used in this study were indomethacin (Synopharm GmbH, Barsbüttel, Germany, Lot # 9909B108) and theophylline monohydrate and anhydrate (Carl-Roth GmbH, Karlsruhe, Germany, Lot # 21835894 and Lot # 43418698). For the production of tablets several excipients were used: ι-carrageenan Gelcarin® GP-379 NF (Lot # ZA 502) and the two κ-carrageenans Gelcarin® GP-812 NF (Lot # ZB 502) and Gelcarin® GP-911 NF (Lot # ZC 502) from FMC Corp., Princeton, NY, USA. The various types of carrageenan differ in the amount of D-galactose-4-sulfate and 3,6-anhydro-α-galactose [14,15]. In comparison with these new tableting excipients two types of microcrystalline cellulose, Avicel® PH 101 (Lot # 6830C) and Avicel® PH 200 (Lot # 11939 C, MCC, FMC Europe N.V. Brüssel, Belgium), dicalcium phosphate dihydrate, Emcompress® (Lot # R19K, DCPD, Mendell, Patterson, NY, USA), and hydroxypropyl methyl cellulose Metolose® (Lot # 811610, HPMC, Shin-Etsu Chemical Co., Tokio, Japan) were analysed.

2.2. Methods

2.2.1. Preparation of indomethacin

Amorphous indomethacin was prepared directly before processing according to the Refs. [20,28]. The commercially available crystal γ form was melted at 165°C in little aluminium pans and quenched using dry ice. The solid melt is amorphous indomethacin. To get powdered amorphous indomethacin the glassy mass was lightly triturated in a mortar. By X-ray diffraction and Raman spectroscopy, it was proven that no recrystallisation occurred.

2.2.2. Production of mixtures

Mixtures containing 20% (w/w) amorphous indomethacin or theophylline monohydrate were produced with each of the excipients. Materials were mixed using a cubic mixer (Erweka Apparatebau GmbH, Heusenstamm, Germany) for 15 min at 30 rpm.

2.2.3. Tableting

The materials were tableted in an air conditioned room with a temperature of 23 ± 1°C and 45 ± 2% relative humidity. Tablets were produced on an instrumented single punch tableting machine (EK0/DMS Korsch GmbH, Berlin, Germany) with 11 mm flat faced punches. Equal true volumes of the substances were tableted up to different relative densities of the tablets at the maximum displacement of upper the punch ($\rho_{rel,max}$), as given in Table 1.

For DCPD the highest maximum relative density reached was 0.85, since high pressure is necessary for deformation. The maximum relative density can be defined as

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

where ρ_{max} is the density at minimum height of the tablet under load and ρ_{true} is true density.

Forces were measured by the calibrated strain gauges, and displacement of the upper punch was measured using an inductive transducer (W 20 TK, Hottinger Baldwin Meßtechnik Darmstadt, Germany). Signals were amplified and digitalised with the DMC plus system (Hottinger Baldwin Messtechnik GmbH, Darmstadt, Germany). Data were stored and analysed by a Macintosh computer with BEAM software (AMS, Flöha, Germany). The amount of

Table 1
Maximum relative densities used for compression of different excipients and mixtures of these excipients with drugs

Material	Maximum relative densities ($\rho_{rel,max}$)				
Pure excipients	0.72 ± 0.01	0.77 ± 0.01	0.80 ± 0.01	0.85 ± 0.01	0.89 ± 0.01
Mixtures with indomethacin	0.73 ± 0.01		0.81 ± 0.01		0.89 ± 0.01
Mixtures with theophylline					0.90 ± 0.01
DCPD pure or mixtures	0.72 ± 0.01	0.77 ± 0.01	0.80 ± 0.01	0.82 ± 0.01	0.85 ± 0.01

material for each tablet with a given maximum relative density was calculated and filled in the die for each compression cycle manually. For each condition 15 tablets were produced.

Analysis of tableting data was performed for all pure excipients and mixtures. The collected data of five compression cycles were used to calculate pressure and $ln(1/(1-D_{rel}))$ according to Heckel [29,30] where D_{rel} is the relative density. Three dimensional (3D) data plots were produced using normalised time and pressure and $ln(1/(1-D_{rel}))$. A twisted plane was fitted to the data [31]

$$z = \ln\left(\frac{1}{1-D_{rel}}\right)$$

$$= ((t - t_{max})(d + \omega p_{max} - p) + (ep) + (f + dt_{max}) \quad (2)$$

where D_{rel} is relative density, t the time and p is the pressure,

$$d = \frac{\delta \ln(1/(1-D_{rel}))}{\delta t}, \qquad e = \frac{\delta \ln(1/(1-D_{rel})}{\delta p},$$

$$f = \ln\left(\frac{1}{1-D_0}\right)$$

where t_{max} is normalised time at maximum pressure, p_{max} the maximum pressure, ω is the twisting angle at t_{max} and D_0 the relative density at $t = 0$.

When d is increasing the plasticity due to time is increasing. When e is increasing the plasticity due to pressure is increasing. A low ω means a lot of fast elastic decompression. The three parameters d (time plasticity), e (pressure plasticity), and ω (which indicates fast elastic decompression) were calculated using Matlab® software. They are represented in 3D-parameter plots, which are characteristic for the deformation mechanism.

2.2.4. Differential scanning calorimetry

Amorphous indomethacin and the crystal γ form of indomethacin were analysed from 25 to 200°C in pinholed pans. For analysis of theophylline monohydrate and anhydrate from 25 to 300°C closed pans were necessary. For all experiments a heating rate of 10 K min^{-1} was used (DSC, Netzsch Gerätebau, Selb, Germany).

2.2.5. FT-Raman spectroscopy

Pure materials, mixtures, and tablets were analysed using FT-Raman spectroscopy in order to monitor the recrystallisation of amorphous indomethacin and the dehydration of theophylline monohydrate. The spectra were collected on a Bruker RFS 100/S FT-Raman spectrometer (Bruker Optik GmbH, Ettlingen, Germany) using a diode-pumped Nd:YAG with an operating wavelength of 1064 nm. Typical spectra were acquired with 200 scans and a laser power of 125 mW at the sample location. The interferograms were apodised with the Blackman-Harris four-term function and subjected to Fourier transformation to give spectra with a resolution of 4 cm^{-1}.

Powder samples were placed in glass test tubes. To study the transformation of the drugs inside the sample, the tablets were broken, and the laser beam was focused on the fractured surface. Powders and tablets containing amorphous indomethacin were measured at the day of production and after storage of 14 and 28 days. Those containing theophylline monohydrate were studied at the day of production and after storage of 1, 4, 8, and 16 days. Between the measurements the samples were stored in closed glass test tubes in an air conditioned room at 23 ± 1°C and 45 ± 2% relative humidity. For each mixture three powder samples and five tablets were studied.

For quantitative analysis the peak height of bands belonging to two forms (generally described with the letters A and C) of a drug were evaluated. Since the bands of the two forms overlap, it is necessary to apply the procedure developed by Kontoyannis [32] for calcium oxalate hydrate and already used for indomethacin by Taylor and Zografi [22]. As illustrated in Fig. 1, the intensity ratio $I(\nu_1)I(\nu_2)$ can be derived from the spectrum of a mixture of the forms A and C. Obviously, this ratio is related to the amount x_A and x_C of the form A and C, respectively, as follows

$$I_R = \frac{I(\nu_1)}{I(\nu_2)} = \frac{x_C C(\nu_1) + x_A A(\nu_1)}{x_C C(\nu_2) + x_A A(\nu_2)} \quad (3)$$

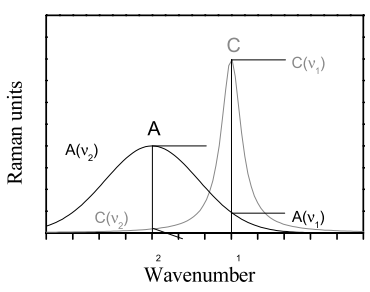

Fig. 1. Two overlapping Raman bands and parameters for analysis model.

where $x_A + x_C = 1$ and $C(\nu_1)$, $C(\nu_2)$, $C(\nu_1)$, and $A(\nu_2)$ are defined in Fig. 1.

The amount of the form C is given by

$$x_C = \frac{I_R - \frac{A(\nu_1)}{A(\nu_2)}}{I_R\left(1 - \frac{C(\nu_2)}{C(\nu_1)} \cdot \frac{C(\nu_1)}{A(\nu_2)}\right) + \frac{C(\nu_1)}{A(\nu_2)} - \frac{A(\nu_1)}{A(\nu_2)}} \quad (4)$$

The various ratios must be determined separately as follows

$\frac{C(\nu_2)}{C(\nu_1)}$ from the spectrum of the drug form C

$\frac{A(\nu_1)}{A(\nu_2)}$ from the spectrum of the drug form A

$\frac{C(\nu_1)}{A(\nu_2)}$ from the spectra of mixtures of A and C

Knowing these ratios it is very straightforward to deduce the amount x_C from the intensity ratio $I_R = I(\nu_1)/I(\nu_2)$.

3. Results and discussion

3.1. Tableting behaviour of mixtures

Fig. 2 shows 3D parameter plots of excipients, pure and in mixture with the drugs. HPMC shows the highest e and ω values (see Fig. 2(b)). The tableting behaviour of mixtures and pure materials is very similar. The high pressure plasticity e and the low fast elastic decompression (high ω value) indicate the highest plastic deformation for HPMC in comparison to all materials examined. Avicel® PH 101 and Avicel® PH 200 (see Fig. 2(a)) show lower e and ω values. Avicel® PH 101 with a lower particle size (manufacturer specification: mean particle size 50 μm) deforms more plastically than Avicel® PH 200 (manufacturer specification: mean particle size 200 μm). The tableting behaviour of mixtures with indomethacin and theophylline is similar to that of the pure excipients. For carrageenans, the e and ω values are clearly lower than those for MCC and HPMC. The deformation is less plastic and the low ω values present a higher portion of fast elastic decompression. This is similar to the results as analysed by Heckel plots and fitting of the pressure–time function [14,15]. Furthermore, there are differences between the different types of carrageenans. The κ-carrageenans, Gelcarin® GP-812 NF (Fig. 2(b)) and Gelcarin® GP-911 NF (Fig. 2(c)) show higher d, e, and ω values than the ι-carrageenan, Gelcarin® GP-379 NF (Fig. 2(d)). Thus, in comparison to all others analysed, Gelcarin® GP-379 NF is the most elastic excipient. The tableting behaviour of carrageenans in mixture is clearly influenced by the drugs. Mixtures with indomethacin and theophylline deform more plastically than the pure excipients. DCPD shows strongly decreasing ω values. In this context it has to be kept in mind that it is the only material showing brittle fracture during tableting.

Summarising, an order regarding the plastic deformation of the pure excipients and also in mixture with drugs can be set up: DCPD < ι-carrageenan < κ-carrageenan < MCC (200 μm) < MCC (50 μm) < HPMC. With regard to its brittle fracture during deformation DCPD represents an exception. Thus ι-carrageenan shows the highest portion of elastic deformation.

3.2. Thermal investigations

Fig. 3 shows DSC curves of amorphous and crystalline indomethacin and theophylline monohydrate and anhydrate. In agreement with literature the melting of crystalline indomethacin occurs at 163°C. For amorphous indomethacin a glass transition (1) at 36°C and crystallisation (2) partially to the α form but mostly to the γ form takes place at about 100°C. Melting of the α form (3) can be weakly seen at 161°C, and the γ form melts at 163°C [19,20]. The glass transition temperature and recrystallisation of amorphous indomethacin have already been investigated as a function of relative humidity, temperature, and mechanical treatment [33–35]. Our results are in agreement.

Theophylline anhydrate melts at 275°C. The monohydrate shows two additional endothermic reactions at 80 and about 170°C. The double peak at about 80°C contains the dehydration and evaporation of the crystal water [36,37]. The second endotherm can be associated with further water loss as described by Picker [27].

3.3. Interpretation of FT-Raman spectra

3.3.1. Indomethacin

The Raman spectra of amorphous indomethacin and its crystal γ form are identical to those described in literature [22]. Differences between the two forms are well apparent, particularly in the wavenumber range from 1500 to 1800 cm^{-1}. The carbonyl stretching bands were selected for the quantitative analysis. For crystalline indomethacin the carbonyl stretching vibration appears at 1698 cm^{-1} while that of amorphous indomethacin appears at 1680 cm^{-1} [28].

As shown in Fig. 4 the bands of the amorphous and crystalline form overlap. For calibration the Raman spectra of 11 physical mixtures of amorphous and crystalline indomethacin in the range from 0 to 100% were acquired. In this way the following ratios were determined

$$\frac{C(\nu_2)}{C(\nu_1)} = 0.0396, \qquad \frac{A(\nu_1)}{A(\nu_2)} = 0.3430,$$

$$\frac{C(\nu_1)}{A(\nu_2)} = 3.4741$$

where C represents crystalline indomethacin and A represents the amorphous form.

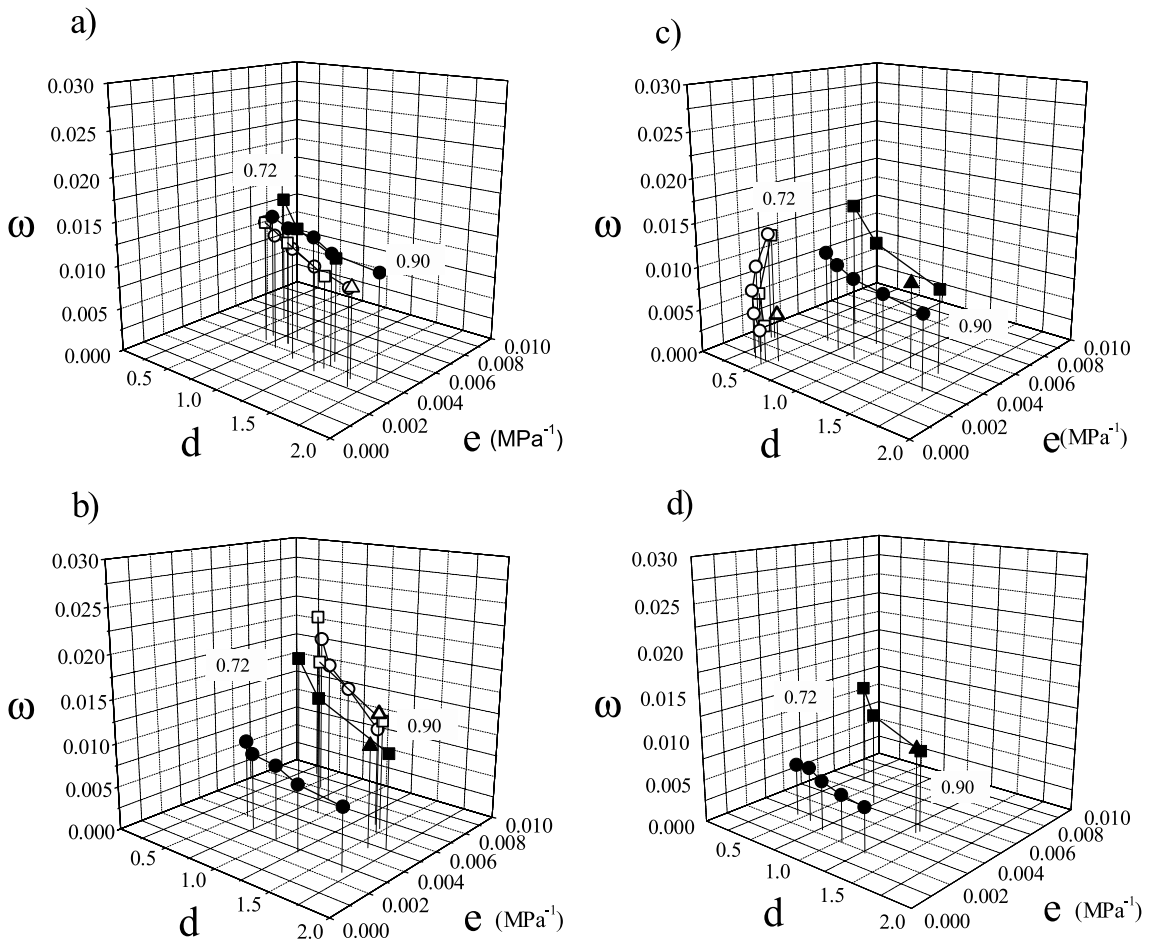

Fig. 2. 3D parameter plots of different excipients pure and in mixture with 20% (w/w) amorphous indomethacin or theophylline monohydrate (a) Avicel PH 200 (○), with indomethacin (□), with theophylline (△); Avicel PH 101 (●), with indomethacin (■); (b) HPMC (○), with indomethacin (□), with theophylline (△); Gelcarin GP-812 NF (●), with indomethacin (■), with theophylline (▲); (c) DCPD (○), with indomethacin (□), with theophylline (△); Gelcarin GP-911 NF (●), with indomethacin (■), with theophylline (▲); (d) Gelcarin GP-379 NF (●), with indomethacin (■), with theophylline (▲).

The calibration curve can be described by the linear regression $y = 0.9995x$ with a correlation coefficient $r = 0.9917$. The coefficient of determination R^2 was 0.9812. Thus, it is possible to analyse the crystallinity of indomethacin in powder mixtures and in tablets.

Fig. 5 shows that the Raman spectra of indomethacin tablets are dependent on the storage time. There is no recrystallisation at day 0 in powder or in tablets (Fig. 5(b)). After 14 days of storage the influence of pressure is slightly noticeable. In tablets more crystalline indomethacin can be found than in powder. After 28 days these differences are much more clear. Recrystallisation in tablets in comparison to powder is doubled. However, no direct influence of different maximum relative densities on the extent of recrystallisation can be seen.

3.3.2. Theophylline

Raman spectra of theophylline monohydrate and anhydrate are identical to those described in literature [23]. Here distinct band shifts appear. The aliphatic =CH stretching band was chosen for quantitative analysis. For theophylline monohydrate aliphatic =CH stretching vibration appears at 3121 cm^{-1}, while that of theophylline anhydrate appears at 3108 cm^{-1}. For calibration the same method as for indomethacin was used. The following ratios were determined

$$\frac{C(\nu_2)}{C(\nu_1)} = 0.1846, \qquad \frac{A(\nu_1)}{A(\nu_2)} = 0.1728,$$

$$\frac{C(\nu_1)}{A(\nu_2)} = 0.6244.$$

Here C represents theophylline anhydrate and A represents theophylline monohydrate.

The dehydration of theophylline monohydrate not only depends on pressure but is also influenced by humidity, temperature, and the porosity of the sample [36,38–41]. Thus, the transformation in tablets is slower than in powder (see Fig. 6) regarding to the larger surface area of powder particles. The transport of water vapour is faster. Therefore, to quantify the hindrance of various excipients due to

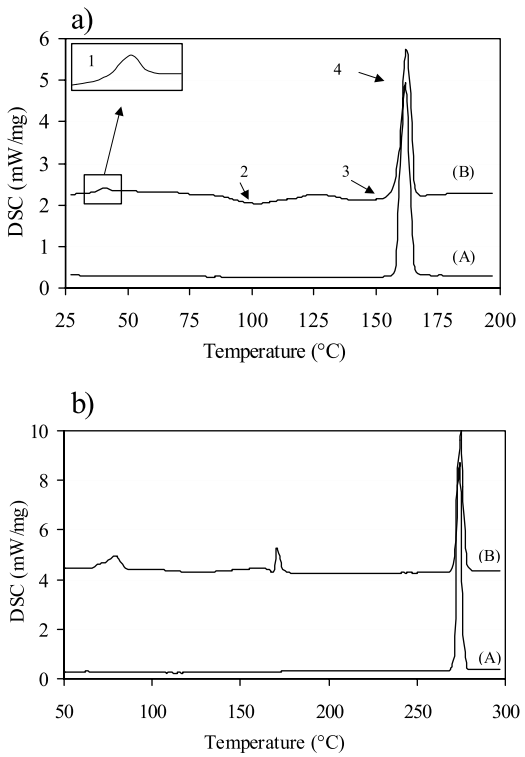

Fig. 3. DSC diagram of: (a) crystalline γ indomethacin (A) and the amorphous form of indomethacin (B) (1 glass transition, 2 crystallization, 3 melting of the α form – weak, 4 melting of the γ form) and, (b) theophylline anhydrate (A) and theophylline monohydrate (B).

tableting, only the results of one-day storage were interpreted. Here, the influence of tableting exceeds the influence of the environmental conditions.

3.4. Influence of tableting excipients on transformation of model drugs

Since only the transformation of the drugs should be analysed, bands of excipients should not appear in the region of the spectra, which was used for quantitative analysis. The spectra of all excipients used are shown in Fig. 7. An analysis is clearly possible.

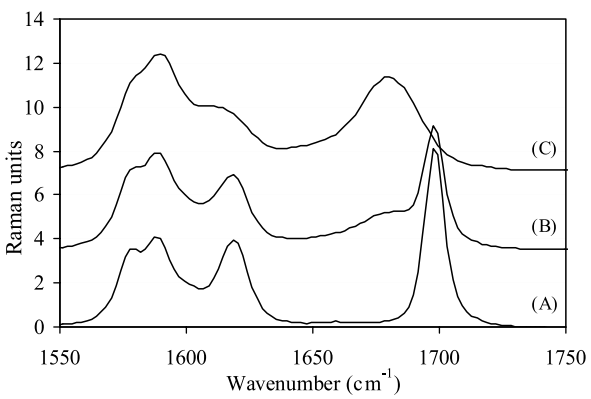

Fig. 4. Raman spectra in the spectral range from 1550 to 1750 cm^{-1}: crystalline (A), mixture of amorphous and crystalline 1:1 (B) and amorphous indomethacin (C).

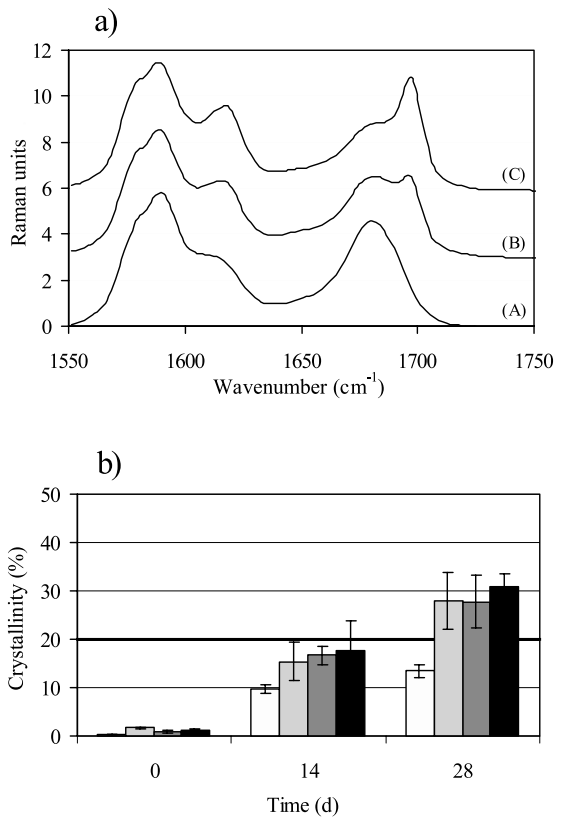

Fig. 5. Recrystallisation of pure indomethacin (a) spectra of tablets at the day of production (A), after 14 days of storage (B), after 28 days of storage (C), (b) calculated crystallinity of the powder (□) and tablets with different relative densities: $\rho_{rel,max} = 0.74/5.3\ MPa$ (▨), $\rho_{rel,max} = 0.83/24.4\ MPa$ (▩), $\rho_{rel,max} = 0.91/58.9 MPa$ (■).

3.4.1. Recrystallisation of amorphous indomethacin in mixtures with excipients

As described for pure indomethacin no recrystallisation at the day of production in all mixtures can be observed. Therefore, Fig. 8 shows only recrystallisation after 14 (Fig. 8(a)) and 28 days (Fig. 8(b)). The effects are not significant due to large standard deviations but tendencies can be noticed. After 14 days of storage most crystalline indomethacin occurs in mixtures with Avicel® PH 101. Slightly lower recrystallisation can be found in mixtures with Avicel® PH 200, DCPD, and HPMC. The values are comparable to pure indomethacin. For MCC, material with a smaller particle size is worse than that with a higher one. The carrageenans show better hindrance than the other materials analysed. ι-Carrageenan seems to be the best since the lowest recrystallisation is observed. Mixtures with one type of excipient show no differences for tablets produced at different relative densities.

After 28 days of storage a slightly different picture can be

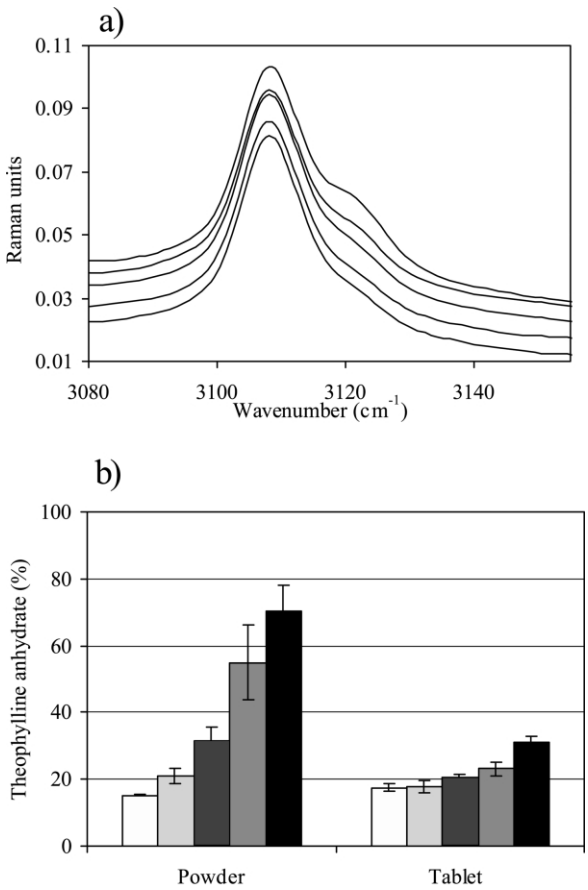

Fig. 6. Dehydration of pure theophylline monohydrate (a) from the bottom to the top: Raman spectra of tablets at the day of production, after one day, four days, eight days and after 16 days of storage, (b) calculated ratio of theophylline anhydrate at day of production (□), after one day (▨), four days (▨) eight days (▨) and 16 days of storage (■).

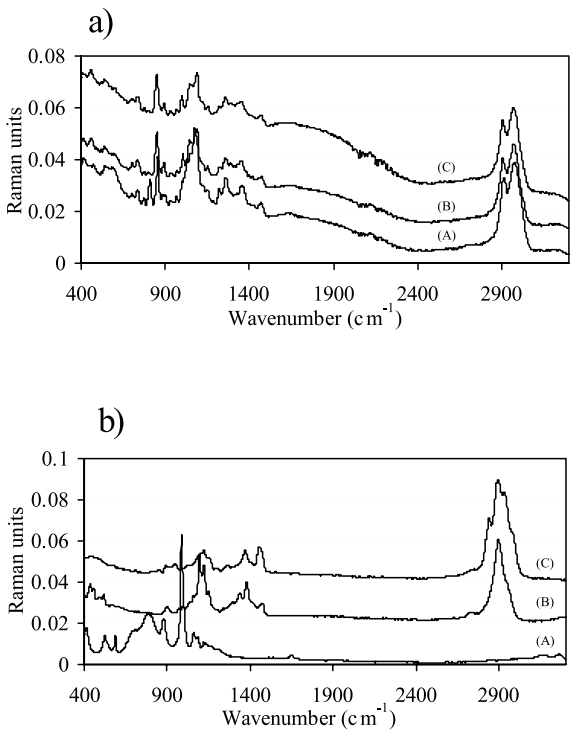

Fig. 7. Raman spectra of the excipients (a) carrageenans: Gelcarin GP-379 NF (A), Gelcarin GP-812 NF (B), Gelcarin GP-911 NF (C), b) DCPD (A), Avicel PH 200 (B), HPMC (C).

seen. Recrystallisation has continued in all mixtures. Most crystalline indomethacin is found in mixtures with MCC, especially Avicel® PH 200, and DCPD, even more than in tablets made of pure indomethacin (see Fig. 5). A reason can be the much higher punch pressure which is necessary for reaching a similar porosity in these tablets compared to that necessary for tablets made of mixtures with the other excipients (Table 2). However, Fig. 8(b) also shows that recrystallisation for both these mixtures is lower in tablets produced at high relative density. This behaviour can be attributed to a transgression of the glass transition temperature of amorphous indomethacin during tableting caused by high pressure. As described, the glass transition temperature is at 36°C. Due to cooling down, indomethacin transforms back to the glassy state which is stable as a compact mass [20]. This effect is visible at the edges of tablets of pure indomethacin. At these contact areas with the punches and the die, partially glassy mass can be found. However, for these tablets it has no influence on the values of crystallinity since the process is different inside the tablets, where the measurements are performed.

HPMC and the carrageenans show a higher protection potential against transformation. The κ-carrageenans Gelcarin® GP-812 NF and Gelcarin® GP-911 NF can be compared with HPMC whilst in mixtures with the

Table 2
Upper punch pressure used for production of tablets with defined relative density in mixture with amorphous indomethacin

	$\rho_{rel,max}$ = 0.73 MPa	$\rho_{rel,max}$ = 0.81 MPa	$\rho_{rel,max}$ = 0.89 MPa
Indomethacin	5.3	24.4	58.9
Avicel PH 101	35.9	60.6	94.1
Avicel PH 200	44.1	71.4	115.3
DCPD	40.0	89.4	173.6
HPMC	21.0	40.0	71.6
Gelcarin GP-379 NF	26.3	50.5	90.5
Gelcarin GP-812 NF	27.4	49.5	87.3
Gelcarin GP-911 NF	34.7	58.9	98.9

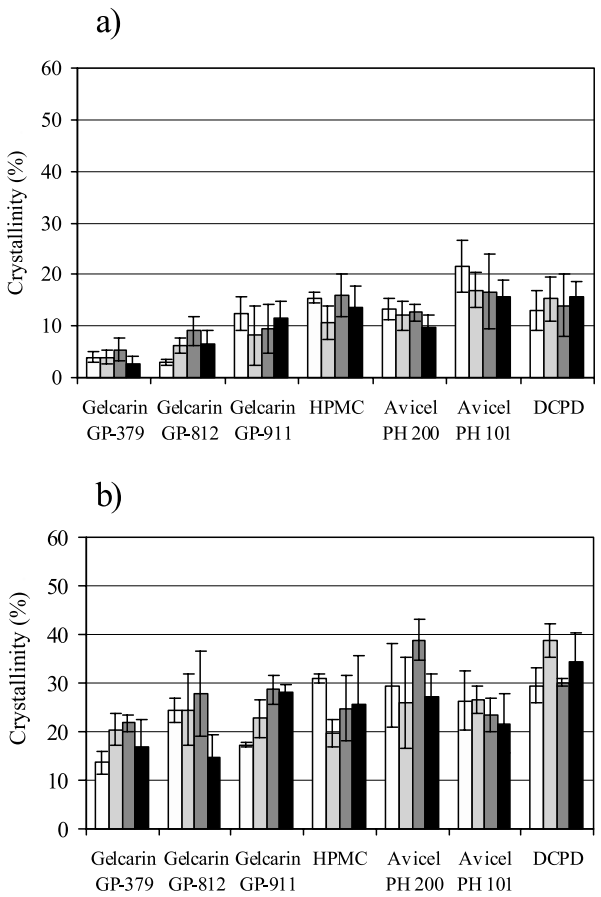

Fig. 8. Recrystallization of amorphous indomethacin in mixture with different excipients: physical mixtures (□) and tablets tableted to different relative densities: $\rho_{rel,max} = 0.73$ (▨), $\rho_{rel,max} = 0.81$ (▩), $\rho_{rel,max} = 0.89$ (■) (a) after 14 days of storage and (b) after 28 days of storage.

ι-carrageenan Gelcarin® GP-379 NF the lowest recrystallisation takes place. The upper punch pressure necessary for mixtures made of indomethacin and the carrageenans for reaching similar relative densities is between DCPD or MCCs and HPMC (see Table 2). For the carrageenans it is also possible that the glass transition temperature of amorphous indomethacin was exceeded at the highest relative density. The recrystallisation is lower, as it is visible for Gelcarin® GP-379 NF and Gelcarin® GP-812 NF.

Following that, the recrystallisation of amorphous indomethacin decreases in mixture with the analysed excipients in the following order ι-carrageenan < κ-carrageenans = HPMC < MCC (50 μm) < MCC (200 μm) = DCPD. Thus, the ι-carrageenan Gelcarin® GP-379 NF shows best protection potential against recrystallisation of amorphous drug but it is only able to delay transformation, not to prevent it. The favourable properties of carrageenans have to be seen in combination with the tableting behaviour. As described, they show the largest part of elastic deformation of the excipients investigated. Most elastically deforming is ι-carrageenan Gelcarin® GP-379 NF. For it, a soft embedding of amorphous drug is given.

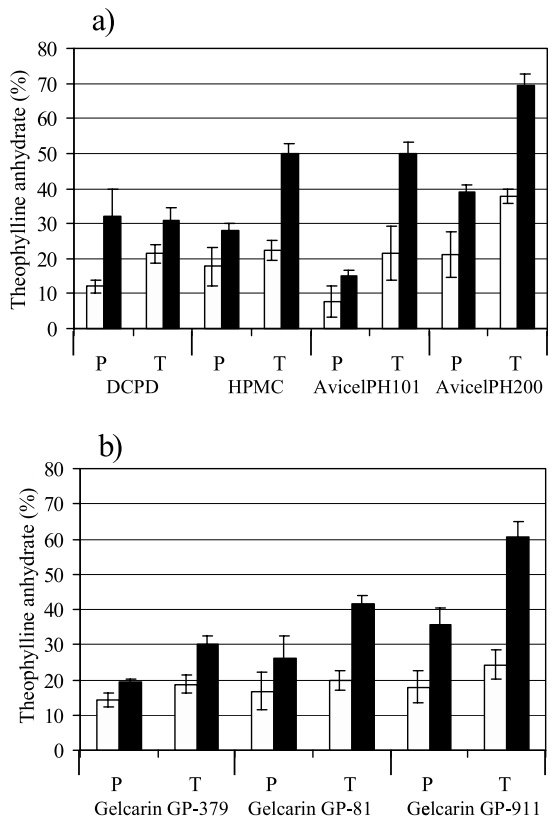

Fig. 9. Dehydration of theophylline monohydrate in mixtures with different excipients: physical mixtures (P) and tablets tableted to a maximum relative density $\rho_{rel,max} = 0.90$ (T) at the day of production (□) and after one day of storage (■).

3.4.2. Dehydration of theophylline monohydrate in mixtures with excipients

Fig. 9 shows dehydration of theophylline monohydrate in physical mixtures and in tablets with excipients. As already described dehydration is influenced by environmental conditions, thus partial dehydration is faster in powder mixtures than in tablets. To minimise these influences only the results of the day of production and after one day of storage were chosen for interpretation. With exception of DCPD, Fig. 9 shows for each mixture with excipients a higher dehydration of theophylline monohydrate in tablets than in the physical mixture. The highest portion of theophylline anhydrate occurs in mixture with Avicel® PH 200. In this case Avicel® PH 101 and HPMC seem to have a better protection potential than Gelcarin® GP-911 NF. Lowest transformation takes place in mixture with Gelcarin® GP-379 NF. These observations support the results obtained with amorphous indomethacin.

4. Conclusions

The recrystallisation of amorphous indomethacin in mixtures with frequently used excipients MCC and DCPD is slightly stronger in tablets than in pure indomethacin

tablets. Carrageenans could prevent transformation of the drug partially. This is especially the case for the ι-carrageenan Gelcarin® GP-379 NF. This behaviour can be attributed to the larger portion of elastic deformation during tableting which is the highest for the ι-carrageenan. The energy induced by the tableting process, which could induce recrystallisation is the lowest. For HPMC similar properties were found as for the κ-carrageenans, the deformation is more plastic during tableting. However, processes after tableting may be important as well. The carrageenans show high elasticity also after tableting [14]. Study of tablets made from mixtures with theophylline monohydrate verify these results. The order for the potential of tested excipients to protect the embedded drug from polymorphic transformation during tableting is ι-carrageenan < κ-carrageenans = HPMC < MCC = DCPD.

Following that, carrageenans are not only able to prevent inactivation of α-amylase during tableting, they can also reduce the transformation of polymorphic and pseudopolymorphic modifications due to tableting. This could be an approach for further investigations.

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