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Research paper

The effect of powder blend and tablet structure on drug release mechanisms of hydrophobic starch acetate matrix tablets

B. van Veen[a,1], J. Pajander[a], K. Zuurman[b], R. Lappalainen[c], A. Poso[d], H.W. Frijlink[b], J. Ketolainen[a,*]

[a]Department of Pharmaceutics, University of Kuopio, Kuopio, Finland
[b]Department of Pharmaceutical Technology and Biopharmacy, Groningen University Institute for Drug Exploration (GUIDE), Groningen, The Netherlands
[c]BioMater Centre, University of Kuopio, Kuopio, Finland
[d]Department of Pharmaceutical Chemistry, University of Kuopio, Kuopio, Finland

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Abstract

This study investigates the release mechanism of a hydrophilic drug (caffeine) from hydrophobic matrix tablets composed of starch acetate. Different particle size fractions of starch acetate were mixed with caffeine (22% V/V) to obtain various mixture organisations in the powder, as well as in the final tablet. The organisation of powder mixtures was calculated by the carrier payload of starch acetate particles, while the pore size distributions in tablets were measured by mercury intrusion porosimetry. A carrier payload below 1 indicated the existence of a free starch acetate particle surface, while numbers greater than 1 pointed to a complete occupation of the starch acetate particle surface area by caffeine particles. The carrier payload calculations gave a good prediction for the existence of a starch acetate matrix in the tablet structures. Caffeine matrices in tablets compressed from the mixtures could be detected by mercury intrusion porosimetry measurements. The existence of different matrices, as well as different pore networks, determined the physical changes of the tablets and the release mechanism of caffeine during dissolution tests. When a tablet contained only a caffeine matrix, rapid tablet disintegration and immediate release of the total amount of caffeine occurred. A single matrix of starch acetate resulted in tablets that remained intact, although cracks were formed. The co-existence of matrices of both materials created surface erosion of the tablet. The caffeine release profiles of tablets that remained intact or showed erosion were fitted by an equation containing both diffusional and relaxational factors to describe the effect of tablet porosity on drug release.

Keywords: Drug release; Powder blend; Particle size; Hydrophobic matrix tablet; Percolation

1. Introduction

In recent years, a new generation of polymers has been introduced as tablet excipients for purposes of controlled drug release. Different techniques, such as chemical reactions [1], complexation reactions [2] and grafting [3,4] have been applied to alter native biopolymers by process modifications or substitutions with other compounds and on molecular functional groups. Starches are an interesting group of native biopolymers for these objectives. They consist of various ratios of two glucose polymers; linear amylose and branched amylopectine. Native potato starches that are chemically modified with acetylic functional groups are defined as starch acetates (SA) [1]. As a glucose monomer contains three free hydroxyl groups that can be substituted, the average degree of substitution (DS) can range from 0 up to 3.0. The introduction of acetylic functional groups changes the nature of starch (acetate) from hydrophilic to more hydrophobic. This modification consequently inhibits the characteristic swelling and gel layer formation of native starches. This increased hydrophobicity of starch acetate (for degrees of substitution larger than 2.1 [5]), makes the material a suitable controlled drug release excipient for tablets. Drug release rates from starch

* Corresponding author. Department of Pharmaceutics, University of Kuopio, POB 1627, FI-70211 Kuopio, Finland. Tel.: +358 17 162 486; fax: +358 17 162 252.
E-mail address: jarkko.ketolainen@uku.fi (J. Ketolainen).
[1] Present address of B. van Veen: Orion Oyj, Orion Pharma, Pharmaceutical Product Development Department, POB 425, FI-20101 Turku, Finland.

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acetate matrix tablets become slower as the degree of substitution for starch acetate increases. Most other physicochemical and mechanical properties of tablets compressed from starch acetate, such as disintegration time and tablet strength, also depend on the degree of substitution [5,6]. Korhonen et al. [7] recently showed that various drying procedures in the manufacturing process resulted in starch acetate powders with different physical properties. Recent specifications for starch acetates require a degree of substitution between 2.2 and 2.9 [8].

Drug release from tablets compressed from modified starches has been studied widely [9–11]. Besides the characteristic first-order drug release kinetics known for matrix tablets, linear drug releases over time also have been reported [11]. In particular, changes in drug release kinetics were related to changes in the physical appearance of a tablet during drug dissolution testing. The literature on erodible polymeric delivery systems shows that various transport mechanisms simultaneously influence the total drug release rate [e.g. 12]. Basically, for sequential processes the slowest, and for parallel processes the fastest step is of main importance. Furthermore, porosity and pore size describing the initial matrix structure are also factors that have distinctive contributions to these processes of drug release from substituted polymer matrix tablets.

The main objective of this study was to investigate the effects of drug-excipient particle interactions in a powder blend and resulting tablet structure on drug release kinetics. The physical behaviour in a liquid medium of tablets with starch acetate (degree of substitution 2.7) as a hydrophobic, inert matrix former was related to drug release mechanisms. Anhydrous caffeine was chosen as a freely soluble model drug. Different SA particle size fractions were employed to establish relationships between mixture organisation, tablet structure, tablet behaviour during dissolution testing and alterations in drug release kinetics.

2. Materials and methods

2.1. Materials and powder blend preparation

Potato starch acetate with a degree of substitution of 2.7 (SA DS 2.7) was kindly donated by Polymer Corex Oy Ltd (Kuopio, Finland). Anhydrous caffeine (Sigma-Aldrich, Steinheim, Germany) was used as supplied, while starch acetate was sieved through vibration sieves (Type 3D, Retsch, Germany) into 5 different fractions: <53 μm, 53–149 μm, 149–297 μm, 297–420 μm and 420–710 μm. All powders were stored over anhydrous silica during the entire process to keep the moisture level constant and as low as possible.

The particle size distributions of the starch acetate sieve fractions and caffeine were analysed by laser diffraction (Mastersizer2000, Malvern Instruments Inc., Southborough, MA, USA) using the dry measurement option (Scirocco2000). The particle densities of starch acetate sieve fractions and caffeine were measured individually by a pycnometrical measuring device (MVP-1, Quantachrome, Syosset, NY, USA). Scanning electron microscopy (SEM)-photographs were taken with a JEOL JSM-35 SEM (JEOL, Tokyo, Japan).

Mixtures containing 78% starch acetate and 22% caffeine were prepared on a volume basis. The powders were mixed in a high shear impeller mixer (MCM1201EU, Bosch, Stuttgart, Germany) at a mixing time of 4 min. The homogeneity of the mixtures was tested prior to tabletting. Measuring the particle size distribution of the mixtures by laser diffraction showed hardly any negative effect from this type of high-shear mixing on the particle sizes of either the starch acetate sieve fractions or caffeine.

2.2. Tablet compaction and characterisation

Tablets were compacted on a compaction simulator (Puuman, Kuopio, Finland). Tablet geometry was cylindrical, with a diameter of 13 mm and tablet weights were 500 mg. Compaction profiles were sinusoidal waves for the upper punch, while the lower punch was stationary. Different amplitudes were applied to achieve compaction pressures of 81, 91, 110, 180 and 290 MPa. Die and punches were prelubricated with magnesium stearate before each compaction to assure both complete force distribution throughout the powder bed and homogenous tablet structures after ejection from the die. The average compaction speed was 4 mm s^{-1} and the ejection time was 1.8 s. After compaction, the tablets were stored over anhydrous silica for at least 14 h. Tablet dimensions were measured with a micrometer (Digitrix, NSK, Japan) and weights were determined by an analytical balance (A200S, Sartorius, Goettingen, Germany). Tablets of pure materials were compacted and treated in a similar way. The fracture/yield strength of the single materials and sieve fractions were analysed from their densification profiles according to Heckel [13].

To obtain tablets with porosities lower than 10%, single tablets were separately compressed with a hand press at a compaction pressure of 220 MPa with a dwell time of 30 min. Tablets were kept overnight in the die and removed from the die the following day. Tablets were further processed as described above.

The pore size distributions of tablets were analysed by mercury intrusion porosimetry measurements (Micromeritics, Model Autopore 9220, Norcross, GA, USA). Sufficient amounts of tablets were used for each particle size distribution and porosity to obtain a sufficient change of mercury in the penetrometers, and thus an accurate measurement. The pressures applied in the low-pressure and high-pressure domains were from 7 to 171 kPa and 0.2–370 MPa, respectively. These pressures correspond to pore sizes ranging from 220 to 0.004 μm. The contact angle of mercury with starch acetate and caffeine was assumed to be 140° and the surface tension of mercury 480 mN m^{-1}.

2.3. Dissolution studies

The dissolution testing of caffeine release from starch acetate tablets was performed in a USP II (paddle method) dissolution apparatus (AT6, Sotax, Basel, Switzerland) at 75 rpm. The dissolution medium was a 0.05 M phosphate buffer solution at pH 6.8. Three tablets were tested individually in 900 ml buffer solution at 37 °C for each tablet porosity and particle size fraction of starch acetate. Aliquots of 2 ml were manually taken from the dissolution vessels, and the same volume was replaced by fresh dissolution medium. Sampling times were 5, 10, 15, 20, 30, 45, 60, 120, 240, 360, 480 and 1440 min. Additional samples at 600, 720, 840 and 960 min in place of 1440 min were taken for caffeine release from tablets with an initial porosity lower than 10%. The concentrations of caffeine in the samples were measured by UV-spectrophotometry (Cary50 Bio, Varian Inc., Palo Alto, CA, USA) at a wavelength of 272 nm.

3. Results and discussion

3.1. Powder and mixture characterisation

The starch acetate particle size fractions consisted of particles having fairly round shapes and smooth surfaces (e.g. 297–420 μm fraction, (Fig. 1a). The powder characteristics, such as pycnometric particle density, mean particle size and fracture/yield strength of the starch acetate particle size fractions and caffeine are given in Table 1. The starch acetate particle density determined by pycnometry decreased with increasing particle size. Besides the partially brittle behaviour, a cross-section of a starch acetate particle (Fig. 1b) also shows large holes inside the particle. In case these encapsulations are impermeable to helium gas intrusion during pycnometry measurements, the holes are responsible for lower measured particle densities compared to that of milled starch acetate (Table 1). Hence, unsieved starch acetate was milled firmly and the milled starch acetate consequently consisted mainly from the shells of the starch acetate particles. The measured density of milled starch acetate can be regarded as a more accurate estimation of the real material density, and is used in further calculations. As for most drugs, the particle size of caffeine is small compared to most SA particle size fractions.

Depending on differences in particle size, surface morphology and surface energy, powder mixtures can have different organisations. Although the surface energies have not been calculated, it can be assumed that the micronised drug particles adhere to the larger SA particles (a so-called ordered mixture) [14]. Only for the smallest SA fraction, a random mixture type is obtained. Barra et al. [14,15] described the interaction frequency between drug and carrier, and pointed out that the larger the difference in particle size, the more frequent the interaction. However, the interaction frequency cannot take into account the total amount of drug

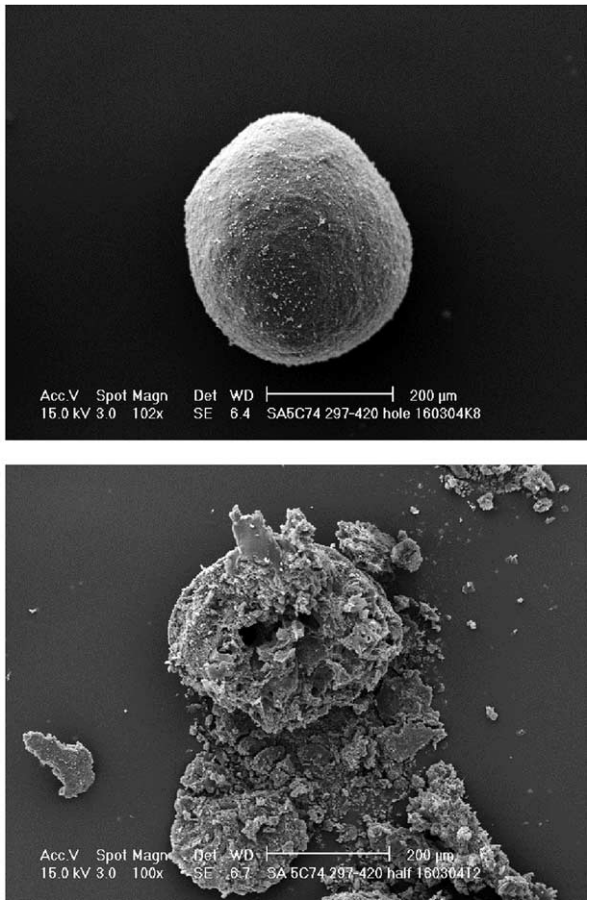

Fig. 1. Representative scanning electron microscopy photographs of starch acetate; (a) an intact 297–420 μm SA particle; (b) cross-section of a 297–420 μm SA particle.

and carrier particles in a blend, especially when all carrier surfaces are completely occupied. For a calculation of the coverage of carrier particles by all drug particles, the following assumptions made by Dickhoff et al. [16] were applied:

- All particles of each compound are spherical and monodisperse with a diameter that equals the volume mean particle size obtained by laser diffraction measurements.
- Projection of each drug particle on the carrier surface is a square with a side that has the same length as the diameter of the particle.

Since the particles of SA particle size fractions have round shapes and smooth surfaces, these assumptions are considered to be valid. Thus, the carrier payload can be defined as the ratio between the total projection surface area of caffeine particles and the total outer particle surface area of SA, which is expressed by the following equation:

$$\frac{d^2_{\text{mean,Caffeine}} N_{\text{Caffeine}}}{\pi d^2_{\text{mean,SA}} N_{\text{SA}}} \quad (1)$$

Table 1
Physical characteristics of starch acetate sieve fractions, caffeine and their mixtures

Material	Sieve fraction (μm)	Pycnometric particle density (g/cm^3)	Volume mean particle size (μm)	Fracture strength[a] (MPa)	Carrier payload (−) 78/22% SA/Caffeine
Starch acetate	<53	1.341	11	63[b]	0.06
	53–149	1.341	110	48	0.59
	149–297	1.367	265	47	1.44
	297–420	1.324	396	50	2.09
	420–710	1.311	542	53	2.83
	Milled	1.425	13		
Caffeine	–	1.404	11	90[b]	

[a] Fracture strength was calculated as an average value in the range of compaction pressures used.
[b] Viscoelastic densification.

where d_{mean} is the mean particle size of a compound and N is the number of particles in the mixture. Table 1 gives the calculated carrier payloads for the different SA particle size fractions in the studied blends with 22% caffeine. Although a mixture containing the smallest particle size fraction of SA is to be considered as a non-interactive mixture, the carrier payload is still a good indicator of SA surface occupation within this mixture. A carrier payload exceeding 1 indicates for round and smooth particles, such as SA, that the complete outer particle surface area is covered by caffeine particles with no free SA outer particle surface area available. Theoretically, all SA particles in the mixture are occupied by caffeine particles for the three largest SA particle size fractions with even more than one layer of drug particle.

In agreement with earlier reports, which state that SA particles partially fragment and plastically deform during powder compaction [5,6], the densification profiles of the SA particle size fractions calculated according to Heckel [13] depicted typical curves known for particle fragmentation. Instead, the caffeine particles behaved viscoelastically during the compaction experiments. Due to the low fracture strengths of SA particle size fractions compared to the yield strength of caffeine (Table 1), SA particles fracture at an earlier stage during compaction of the blend [17]. When the carrier payload of SA is lower than 1, SA particles will establish a continuous (percolating) network in tablets compressed from the mixtures more easily than caffeine particles. It is expected that tablets compressed from blends with <53 μm and 53–149 μm SA particle size fractions contain a percolating SA matrix, irrespective of tablet porosity. However, it can be assumed for mixtures with a carrier payload larger than 1 that complete occupation of the SA particle surface area will reduce the opportunity for starch acetate particles to form interparticle SA-SA bindings. Higher densification is necessary to overcome this barrier of drug particles towards bond and matrix formation of SA-particles in the tablet structure.

3.2. Pore size distribution in tablets compressed from blends

Tablets compressed from binary mixtures can be regarded as three-component heterogeneous particulate systems. The air fraction (porosity) consisting of different pore size distributions between the particles is the third component. Porosity is a very important factor, as the first phase of drug dissolution from a porous system is penetration of the dissolution medium into the pores of the tablet. The application of equal compaction pressures resulted in comparable tablet porosities of 12, 15, 20, 22 and 25% for tablets compressed from the SA particle size fractions. Because the SA/caffeine tablets expanded by 10% after compaction, lower tablet porosities could not be obtained under the used process conditions. Similar tablet porosities were found by mercury intrusion measurements, as calculated by tablet volume, weight and the density of milled starch acetate (Table 1), indicating that all pores are interconnected and form a percolating network inside the tablet structure. The critical transition porosity from a continuous porous network to discontinuous clusters is normally defined as the percolation threshold of air. This percolation threshold of air is reported to be at approximately 10% tablet porosity [10,18].

The initial particle size distribution of a blend determines the pore size distribution between the particles in a tablet structure. For brittle materials, particle fragmentation will partially eliminate the effect of particle size over a certain particle size range. Porosity and pore size distribution will be less dependent on the initial particle size fraction [19]. Also, for the tablets containing 78% brittle SA particles, no large differences were found between pore size distributions of different SA particle size fractions at equal tablet porosity. This implies that initial differences in pore size distribution cannot be the predominant reason for differences in drug release during dissolution tests, as was also described by Barra et al. [20].

The walls of pores in tablets compressed from mixtures of a drug and excipient can consist of different materials: only drug, excipient as well as drug, or only excipient. The pore wall construction depends on the particle packing in the tablet structure. Percolation theory describes the existence of particles in separate clusters or in a continuous matrix. A percolating pore network with walls entirely covered by drug particles can only exist when the drug particles form a percolating matrix throughout the tablet.

To determine whether or not a drug percolating matrix existed in a tablet structure, the pore size distributions of tablets compressed from SA/caffeine blends were compared with the pore size distribution of tablets compressed from pure SA and caffeine at equal tablet porosities. Tablets compressed from pure caffeine showed particular pore sizes between the caffeine particles for each tablet porosity. These pore sizes are indicators of the packing of caffeine particles in a matrix, and no similar pore sizes were found in tablets compressed from pure SA particles (Fig. 2a). When caffeine particles are not able to form pores between themselves, especially when the carrier payload of SA is smaller than 1, no extra pores of similar size were measured in the pore size distribution of tablets compressed from blends (Fig. 2a). In other tablets, mostly with carrier payload greater than 1, extra pores were found with the same size as those in the caffeine tablets, demonstrating the existence of a caffeine matrix in the mixture tablets (Fig. 2b). Caffeine matrices could be distinguished in tablets compressed from SA particle size fraction 53–149 μm with tablet porosities of 20% and higher, and in tablets prepared from the three highest SA particle size fractions with tablet porosities of 15% and higher. As no distinctive pore size could be detected in the pore size distribution of pure SA tablets, it was impossible to establish by mercury intrusion porosimetry measurements whether SA matrices existed or not in the different tablets. The material (drug or excipient) covering the walls of the pores is highly relevant, because the capillary forces in a pore determine the uptake of dissolution medium by the pore. Since the magnitude of the capillary force is related to the contact angle between medium and pore wall material, the pore wall material determines the medium penetration rate, and is as important as the size of the pores.

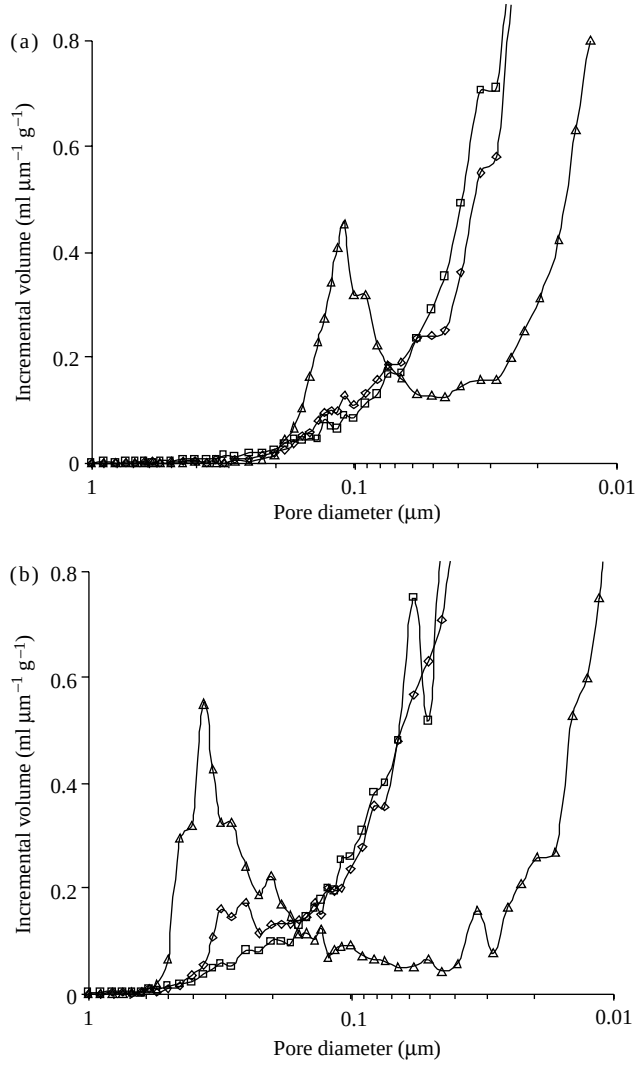

Fig. 2. Pore size distributions of tablets, measured with mercury intrusion porosimetry, consisting of (◇) 78% 149–297 μm SA and 22% caffeine, (□) 100% 149–297 μm SA and (Δ) 100% caffeine with equal tablet porosities of (a) 12% and (b) 22%.

3.3. Relation between tablet dissolution behaviour and drug release

Tablets compressed from the different mixtures showed variable behaviours during drug dissolution tests. Fig. 3a shows the physical appearances of tablets that were strong enough to be removed from the vessels after 24 h dissolution tests. A scheme classifying the physical occurrences during the dissolution test is given in Fig. 3b. The characteristic changes in physical appearance during dissolution could be classified into three different groups:

- Tablets maintained more or less their appearance, but cracks appeared in the tablets.
- Surface erosion of the tablets.
- Rapid tablet disintegration during dissolution.

Tablets that maintain their shape and showed only cracks are typically those that contain only a SA matrix in the tablet structure. Tablets are energetic systems with internal elastic energy, which is counteracted by interparticle bonding strength [21]. Although SA with a degree of substitution 2.7 can be considered as a hydrophobic material by the substitution of most hydroxyl groups by acetylic functional groups, the esters and remaining hydroxyl groups still contribute to a small hydrophilic affinity. The interaction of a liquid with similar dielectric constant (like water) lowers the total bonding energy between the particles [22,23]. A slow interaction with water could lower the glass transition temperature of the substituted starch acetate and transform the polymer from a glassy, rigid configuration into a rubbery state with an increase in elastic energy. All phenomenon combined results in a release of the internal elastic energy, and subsequent a relaxational expansion of the tablet volume. The effects of this elastic energy release on the physical changes of the tablets depend on weakened particle interactions in the continuous network present in the tablet structure. This typical crack formation was previously

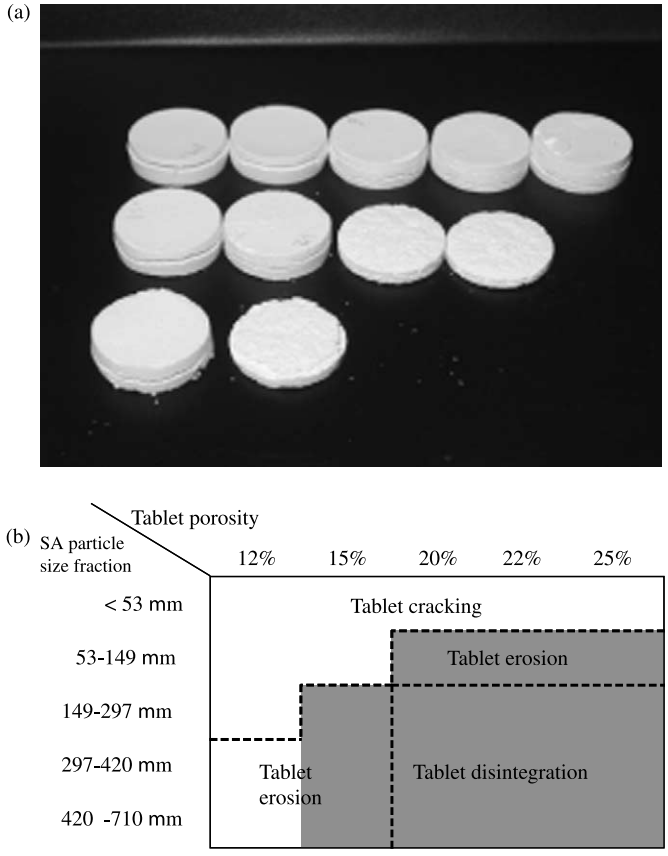

Fig. 3. (a) Tablet shapes after 24 h dissolution test. SA particle size fractions: upper row <53 μm, middle row 53–149 μm and lower row 149–297 μm. Other tablets were too weak to be recovered from the dissolution vessels. (b) Schematic representation of different tablet behaviours during drug dissolution tests: tablet cracking, tablet erosion and tablet disintegration. Variables are the initial tablet porosity (*x*-axis) and SA particle size fraction (*y*-axis). The grey background indicates the presence of a caffeine matrix in the tablet, as detected by mercury intrusion porosimetry.

described by Pohja et al. [6] and Steendam et al. [10] for starch acetate and amylodextrin tablets, respectively.

The range of tablet compositions that have a caffeine matrix (according to mercury porosimetry) is indicated by the grey area in Fig. 3b. The caffeine-covered pore network in these tablets allows for a rapid penetration of water into the tablet. In the case where only a caffeine matrix exists, this results in rapid disintegration of the tablet. When a caffeine matrix coexists with a percolating SA matrix, surface erosion is observed. Surface erosion occurs when water penetration is slower than the polymer matrix degradation [12]. The absence of a percolating caffeine matrix through which a pore network runs will considerably slow down water uptake.

Results from the range of tablets, where mercury porosimetry detected the existence of a caffeine matrix, are in a good agreement with the observed tablet behaviour during dissolution tests. The SA matrix prediction by carrier payload calculation (Section 3.1) is strengthened by the absence of tablet disintegration, i.e. tablets stay intact and crack or show slow erosion.

Fig. 4 illustrates the drug release from tablets produced from the 149–297 μm SA particle size fraction, with different initial tablet porosities, as an example. The transitions found between the release profiles coincide with observed tablet behaviours in a liquid environment. Disintegrating SA tablets released the total drug content rapidly, whereas tablets that showed only cracking or erosion displayed sustained release of the drug. Tablets that maintained their shape and showed only cracking had a low variation in drug

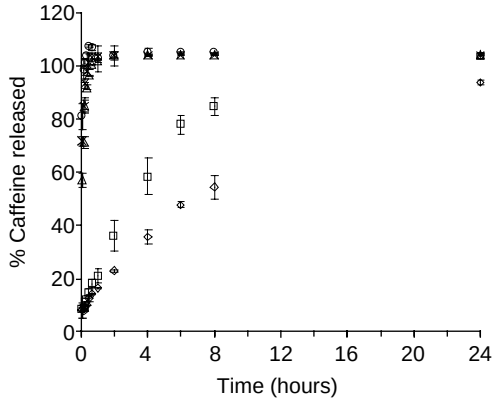

Fig. 4. Percentage of caffeine released from tablets compressed from 149–297 μm SA as a function of time. Initial tablet porosities are 12% (◇), 15% (□), 20% (Δ), 22% (×) and 25% (○). Standard deviations are given as error bars ($n=3$).

release rates. Erodible tablets displayed larger variations between individual tablets. At lower porosities (12 and 15%) where water penetration into and drug diffusion out of the matrix through the continuous pore system and newly formed pores became more obstructed, the drug profile changed from the diffusion profile (first-order) to a more linear (zero-order) drug release in time.

3.4. Drug release from tablets with a discontinuous pore system

To elucidate the contribution of tablet appearance changes on drug release kinetics without the influences of Fickian diffusion through a continuous network of initially present pores in the tablet structure, low-porous SA tablets (average 8% tablet porosity) were specially produced (dwell time 30 min) and drug release was examined (Fig. 5). Initially, a burst of 10–20% indicated a fast diffusional release of drug, which was mostly probably located on the surface of the tablets. After this initial stage, the release profiles showed all near linear release kinetics. All tablets remained intact during the dissolution tests and only cracking was observed with exception of the tablets containing the largest SA fraction, which displayed signs of erosion. The large variation in release rate of tablets consisting of this largest SA particle size fraction is the result of the poor reproducibility of the erosion process.

The dissolution rate in the linear phase was related to the SA particle size (Fig. 5). Small particle sizes result in the absence of a percolating caffeine network, through which pores run, which may facilitate rapid medium penetration into the tablet. The absence of a continuous pore matrix results in a significant reduction in the liquid penetration rate, which is now controlled by penetration along SA particles. Tablet containing SA particle size fractions with lower carrier payloads have more unoccupied SA particle surface and hydrophobic barriers for the penetrating liquid to overcome. In addition, the tortuosity of the dense SA matrix also increases with decreasing SA particle size. Therefore, it can be concluded that drug release by tablet cracking as a relaxational Case II mechanism results in a nearly zero-order release rate of the drug compound.

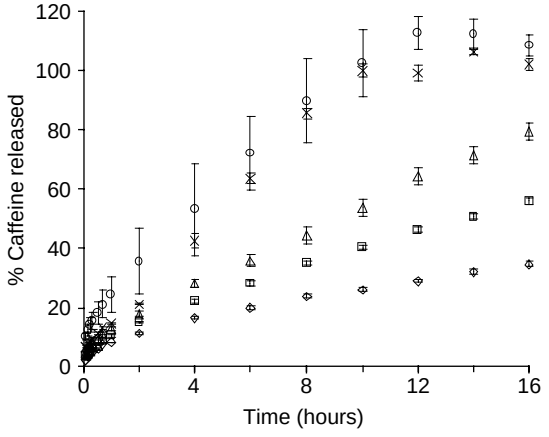

Fig. 5. Percentage of caffeine released from tablets compressed from different SA particle size fractions with an initial tablet porosity of 8% as a function of time. SA particle size fractions are <53 μm (◇), 53–149 μm (□), 149–297 μm (Δ), 297–420 μm (×) and 420–710 μm (○). Standard deviations are given as error bars ($n=3$).

3.5. Drug release kinetics from tablets with continuous porous networks

To describe the release behaviour of tablets showing a combination of Fickian diffusion and Case II relaxation, Ritger and Peppas [24] and Peppas and Sahlin [25] derived an equation depicting diffusion and relaxation mechanics as limits of controlled drug release:

$$M_t/M_\infty = k_1 t^n + k_2 t^{2n} \quad (2)$$

where the first term on the right-hand side of the expression represents the Fickian contribution and the second term the Case II relaxation contribution to the fractional drug release. The purely Fickian diffusion exponent n and the relaxation exponent, which is two times the factor n, depend on the aspect ratio between tablet diameter and height. These exponents for tablets used in this study with average aspect ratios of 4 were derived from studies by Ritger and Peppas [24] and reported to have values of 0.45 and 0.89 for the diffusional and relaxational exponent, respectively. These values were used in the present study. A factor of 0.89 for relaxational release confirms the concept that release of a hydrophilic drug from cylindrical hydrophobic matrix tablets cannot reach full zero-order kinetics as seen in Section 3.4.

The caffeine release profiles up to 60% from porous SA tablets depicting cracking and erosion with porosities higher than 10% were fitted by Eq. (2). The diffusional and relaxational drug release rate coefficients are represented in Fig. 6a and b, respectively, as a function of the initial tablet porosity. Although the diffusional and relaxational coefficients cannot be compared directly due to the different exponents of the units, the comparison between Fig. 6a and b depicts some pronounced alterations. For tablet porosities lower than 20%, the difference in caffeine release is primarily the result of changes in $k_{\text{relaxation}}$ (Fig. 6b). When the tablet porosity exceeds 20%, $k_{\text{diffusion}}$ plays a more important role in changes of the caffeine release rate (Fig. 6a). For parallel processes, water penetration and drug diffusion at higher tablet porosities are dominant over the contribution made by the relaxational release mechanism.

4. Conclusion

The relevance of powder blend organisation for the tablet structure, and eventual drug release kinetics from matrix tablets is often underestimated. The carrier payload

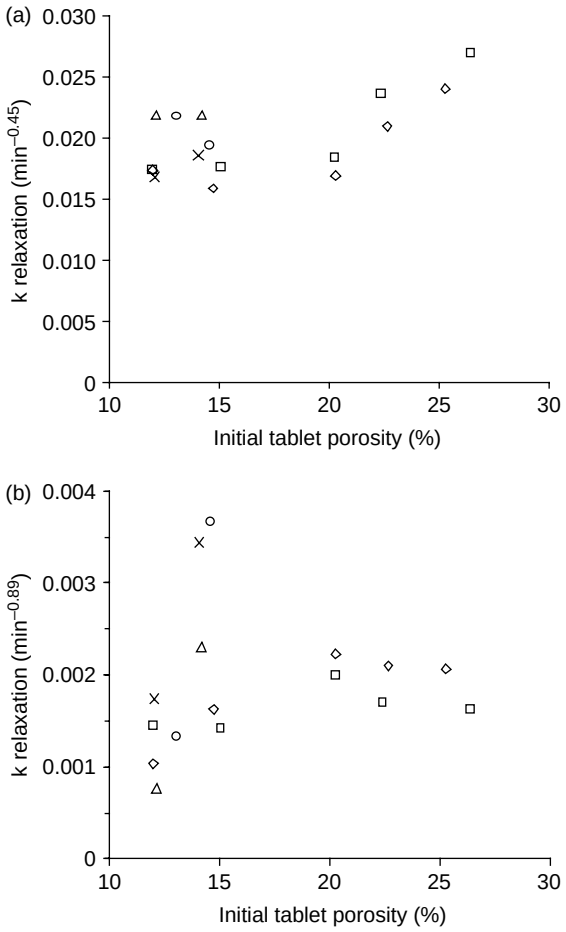

Fig. 6. (a) $k_{diffusion}$ and (b) $k_{relaxation}$ of caffeine released from SA tablets as a function of initial tablet porosity. SA particle size fractions as given in Fig. 5.

calculation in combination with the difference in fracture/yield strength enables the prediction of tablet structure; more specifically, in relation to the existence of an excipient matrix. Matrices of drug particles in tablets compressed from the studied mixtures were identified by mercury intrusion porosimetry measurements. Because most drugs are available as micronised powder, this combined approach of carrier payload calculations and mercury intrusion porosimetry measurements offers an improved understanding of the particulate tablet structure and resulting drug release mechanism. When the hydrophobic excipient is percolating, tablets maintain their shape and only crack during dissolution tests. This results in a slow release of the drug. Co-existing percolating networks of drug and excipient create surface erosion of the tablet and highly variable drug release. Finally, a matrix of hydrophilic drug alone leads to immediate tablet disintegration and rapid drug release.

Drug release kinetics are zero-order over time in case the tablet porosity is lower than the percolation threshold of air (i.e. $<10\%$). At tablet porosities higher than 10%, drug release can be described by a diffusional and relaxational component.

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