Available online at www.sciencedirect.com
ScienceDirect
European Journal of Pharmaceutics and Biopharmaceutics 64 (2006) 167–172
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Liquid boundary movements in cylindrical and convex hydrophobic matrix tablets: Effects on tablet cracking and drug release

Jari Pajander [a,*], Bert van Veen [b], Ossi Korhonen [a], Reijo Lappalainen [c], Jarkko Ketolainen [a]

[a] Department of Pharmaceutics, University of Kuopio, Kuopio, Finland
[b] Orion Pharma, Turku, Finland
[c] BioMater Center, University of Kuopio, Kuopio, Finland

Received 20 December 2005; accepted in revised form 18 May 2006
Available online 2 June 2006

Abstract

The aim of this study was to investigate liquid penetration into both cylindrical and convex hydrophobic matrix tablets and to relate the changes in tablet structure to drug release. Starch acetate with degree of substitution of 2.7 was used as a hydrophobic matrix former and anhydrous caffeine as a freely soluble model drug. Phenolred was used as a colouring agent to enhance the visual detection of the liquid boundary movements, which were examined in axial and radial directions for both types of tablets. The tablets started to expand during the dissolution, resulting in cracking as the liquid boundary penetrated into tablet. The cracking influences drug release by shortening the diffusion path and decreasing the tortuosity. The liquid boundaries proceed differently in cylindrical and convex tablets, this being attributable to differences in pore structure and density distribution. Cylindrical tablets are quite homogeneous in terms of density, but convex tablets have more porous areas at the domes of the tablet.

Keywords: Hydrophobic matrix; Tablet; Starch acetate; Liquid boundary; Tablet cracking; Drug release

1. Introduction

The oral route is the most common and convenient of the current administration routes for the systemic delivery of drugs. The most widely used solid dosage forms for controlled drug release purposes are tablets and these can be divided roughly into matrix and reservoir systems. According to the Higuchi equation [1] for the release of a solid drug from a controlled release matrix tablet structure, the dissolution rate of the drug depends on many factors, including the exposed surface area and porosity of the matrix, and the tortuosity of the capillary system. The dissolution of the drug compound, and furthermore, its release from the dosage form are related to the liquid penetration into the tablet. This is a parameter which is not completely understood.

Starch acetates (SA) are modified starches produced by acetylating native starch [2]. The modification converts starch into a more hydrophobic derivative, as the average degree of substitution (DS) increases from 0 up to 3.0. Starch acetate is a suitable excipient for controlling drug release from tablets when DS is greater than 2.1 [3]. Although several studies [2–5] have been published attempting to establish the drug release from starch acetate matrices, until now the focus has been mainly on tableting and drug release kinetics. Previous studies [2,5] on starch acetate have demonstrated that crack formation takes place in SA matrix tablets during dissolution. Since drug dissolution after the burst of the tablet is initiated by the penetration of bulk liquid into the matrix structure, more focused research is needed to understand the relationships between physical changes which take place during dissolution and the liquid movement in the tablet structure.

* Corresponding author. Department of Pharmaceutics, University of Kuopio, P.O. Box 1627, 70211 Kuopio, Finland. Tel.: +358 17 163 305; fax: +358 17 162 252.
E-mail address: pajander@hytti.uku.fi (J. Pajander).

0939-6411/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejpb.2006.05.011

Many investigators have examined the liquid boundary movement in hydrophilic matrix tablets, and various techniques have been utilized: penetrometer measurements [6], optical microscopy and image analysis [7–9], NMR-imaging [10–12], ultrasound [6] and coloured medium measurements [13,14]. However, hydrophobic matrices differ from hydrophilic polymers in that they do not swell or dissolve during the liquid penetration process. Many of the techniques described above assume that a gel layer is formed. Different or at least modified techniques are needed when the focus is on hydrophobic matrices in order to obtain information from the inside of the matrix during the dissolution phenomena.

The aim of this study was to investigate how the liquid boundaries penetrate into both cylindrical and convex hydrophobic starch acetate (DS 2.7) matrix tablets and relate the observed physical phenomena to drug release. Anhydrous caffeine was chosen as a freely soluble model drug, and phenolred as a pH-sensitive colouring agent. Phenolred changes colour from red to yellow when the pH reaches range from 6.6 up to 8.0 and this indicates where the liquid boundary has been. The procedures described in this study provide information on axially and radially moving liquid boundaries.

2. Materials and methods

2.1. Materials and powder blend preparation

Potato starch acetate with a degree of substitution 2.7 (Polymer Corex Oy Ltd., Kuopio, Finland) was used as the matrix former. Anhydrous caffeine (Sigma–Aldrich, Steinheim, Germany) and starch acetate were both sieved through a 710 μm sieve in order to separate aggregates, while phenolred (Merck, Darmstadt, Germany) was used as received.

The mixture containing 78% starch acetate and 22% caffeine was prepared on a volume basis. The powders were mixed in a mortar in geometric series with a mixing time of 4 min. The homogeneity of the mixture was tested and phenolred 0.5% (m/m) was added to the homogeneous powder mixture in a Turbula mixer (T2C, WAB AG, Basel, Switzerland) with a mixing time of 4 min.

2.2. Tablet compaction and characterisation

Tablets were compacted with a compaction simulator (PCS-1, Puuman Ltd., Kuopio, Finland) to produce cylindrical tablets with a diameter of 13 mm and convex tablets with a diameter of 12 mm, the weights for both types of tablets being 500 mg. A sine wave compaction profile was used for the upper punch, while the lower punch was kept stationary. The amplitude was adjusted to generate compaction pressures of approximately 270 MPa for the cylindrical and 300 MPa for the convex tablets. The die and punches were prelubricated with magnesium stearate powder (Orion Pharma, Espoo, Finland) before each compaction in order to minimize changes in the tablet structures during the ejection. The external lubrication does not affect water uptake and, therefore, drug release as much as the internal lubrication [15]. The procedure was the same for every tablet and it can be assumed that the statistical error of the function of magnesium stearate on water uptake is not significant. The average compaction speed was $4\ \mathrm{mm \cdot s^{-1}}$ and the ejection time was always 1.8 s. After compaction, the tablets were stored over silica for at least 14 h. These procedures yielded tablet porosities of approximately 13% which were calculated by using tablet dimensions, measured densities of SA ($1.624\ \mathrm{g/cm^3}$) and caffeine ($1.404\ \mathrm{g/cm^3}$) (MVP-1, Quantachrome, Syosset, NY, USA) and their respective volume ratio in the prepared mixture. Tablet dimensions were measured with a micrometer (Digitrix, NSK, Japan) and weights were determined on an analytical balance (A200S, Sartorius, Goettingen, Germany).

2.3. Dissolution studies

The dissolution of caffeine from and the liquid penetration into starch acetate tablets were performed with the USP XXVIII (paddle method) dissolution apparatus (AT6, Sotax, Basel, Switzerland) at 75 rpm. The dissolution medium was 0.05 M phosphate buffer solution at pH 6.8. Three tablets were tested individually in 900 ml of buffer solution at 37 °C. Timepoints for sampling were 5, 15, 30, 60, 120, 240, 360, 480 and 1440 min. The concentration of caffeine was determined by UV-spectrophotometry (Genesys 10UV, Thermo Spectronic, Rochester, USA) at a wavelength of 272 nm. The impact of phenolred was taken into consideration by measuring the absorbance of the samples at a wavelength of 430 nm and calculating the indicator's theoretical absorbance at 272 nm in order to correct for the absorbance of caffeine.

2.4. Freeze-drying and picture processing

To be able to measure the liquid boundary movements as a function of time, identical dissolution tests were performed as described in Section 2.3. Three tablets were taken out from the dissolution vessel at each measurement time point, directly frozen at −70 °C and then freeze dried (ModulyoD, Thermo Savant, Rochester, USA) to remove the dissolution liquid by sublimation. It was assumed that freezing of tablets at −70 °C would stop almost immediately the movement of liquid in the tablet structure. The SEM pictures (XL 30 ESEM TMP Microscope, FEI Co, Czech Republic) (results not shown) of the surface and cross-section of both in room temperature stored and freeze-dried tablets after 6 h dissolution confirmed that there are no visible nor measurable changes in morphology. Therefore it was assumed that the formation of ice crystals during freezing would not alter the dimensions of the tablet taken from the dissolution vessel. The dimensions of the freeze-dried tablets were measured before cutting them axially into

two pieces (Isomet Low Speed Saw, Buehler, Lake Bluff, USA) using a 0.3 mm thick blade.

The liquid boundary was photographed with a digital camera (Camedia C-3030, Olympus, Tokyo, Japan) using a light microscope (SZ-PT, Olympus, Tokyo, Japan). In order to attach scale to the pictures, they were processed digitally (Photoshop Elements 2.0, Adobe, USA).

2.5. Tablet structure analysis by micro computed tomography

The micro computed tomography measurements (Skyscan 1072 X-ray Micrograph, Skyscan n.v., Aartselaar, Belgium) were carried out in order to establish the differences in pore structure for both the cylindrical and convex tablets before the dissolution tests were performed. The tablets were placed on a rotary turntable with their axes in the horizontal direction. The data were collected using 90 kV voltages, 1 mm thick aluminium filter and by rotating the tablet 0–360°. The angular increment used in these scans was 0.68° and at each angle, three radiographic images were averaged. The pixel size achieved with this setup was approximately 14.5 μm. The obtained data were converted into 3D images using 3D-Creator Format Converter (SkyScan version 1.1, Aartselaar, Belgium).

3. Results and discussion

3.1. Tablet structure properties

The 3D images generated on the basis of raw micro computed tomography data are shown in Fig. 1. The micro computed tomography image of cylindrical tablets' cross-section confirmed that there were no great variations in the pore distribution (Fig. 1a). These findings support earlier studies claiming that cylindrical tablets are rather homogeneous in terms of their density [16].

In contrast to cylindrical tablets, there were differences in the pore distribution in convex tablets. Visible pores could be seen at the dome and in the middle of the convex tablet (Fig. 1b). It can be estimated that the density of the tablets was at its lowest where there are more pores. Earlier studies support this conclusion for convex tablets [17,18].

3.2. Liquid boundary movement

The liquid boundary movement in both the cylindrical and convex tablets is shown in Fig. 2a and b, respectively. The equations for description of liquid boundary movement for both cylindrical and convex tablets are presented in Table 1. Data points for cylindrical tablets are shown only up to 360 min, because the tablets had become completely wetted at 480 min. For the same reason, the data points for convex tablets are only shown up to 480 min. The radial movement in the cylindrical tablets followed first order kinetics up to 120 min, after which there was an abrupt, but constant, increase in the movement and then

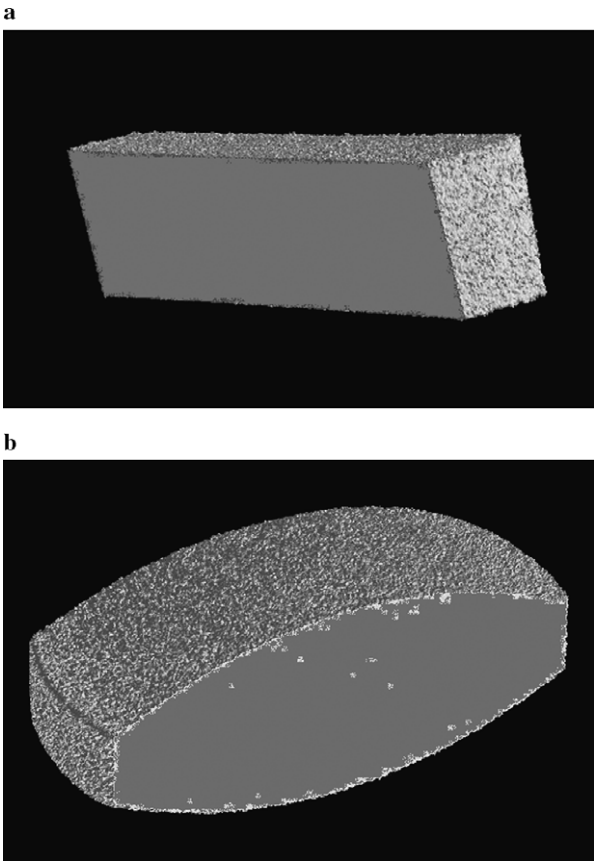

Fig. 1. The computer generated 3D cross-section images of (a) cylindrical and (b) convex tablet. The pores at the dome and in the middle of the convex tablet (b) stand out from the grey background as light grey dots.

it started to proceed linearly as a function of time (Fig. 2a). The axial liquid boundary movement followed also first order kinetics up to 120 min and from then on it also started to proceed linearly as a function of time (Fig. 2a).

The radial movement in convex tablets moved linearly as a function of time up to 240 min, and after that time there was another linear movement (Fig. 2b). However, the axial movement in convex tablets followed first order kinetics throughout the measured data points (Fig. 2b).

The difference in the liquid boundary movement rates can be explained by the differences in the internal density distributions and the pore structure of the cylindrical and convex tablets. The fact that the convex tablets were less dense at the domes of the tablet can be seen from the 3D images generated from the raw micro computed tomography data (Fig. 1). Pores can be seen at the domes and in the middle of the tablet but not at the edges of cylinder. These findings support earlier studies [17,18] and, thus, it can be concluded that the density of convex tablets is lowest where the number of pores is greatest. The liquid boundary moves faster in a more porous and less dense matrix, i.e. at the domes of the convex tablet. The radial movement in convex tablets was very similar to the liquid boundary movement in cylindrical tablets. The slightly slower axial liquid boundary movement as a function of time and the sudden acceleration after four hours in the

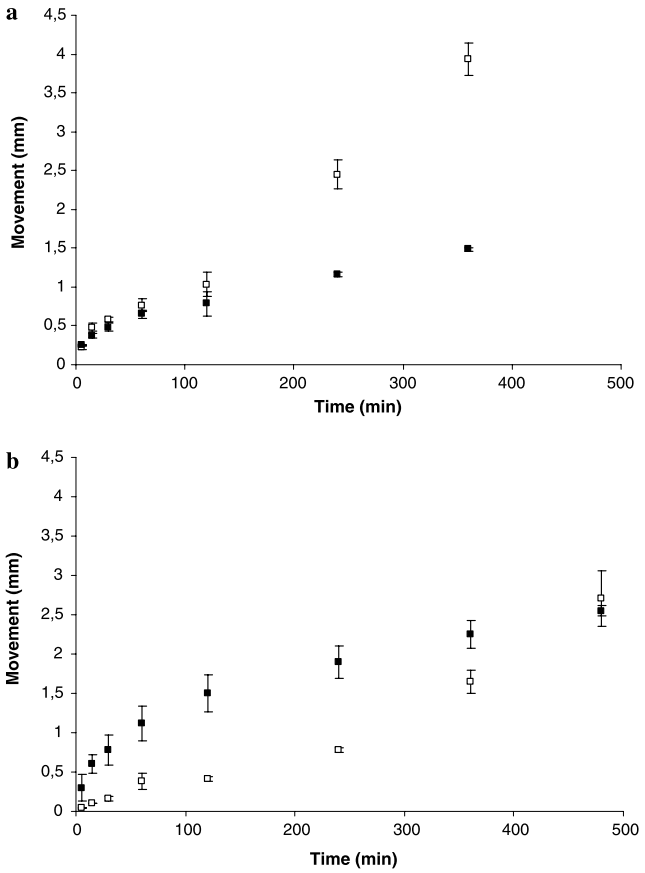

Fig. 2. The axial (■) and radial (□) liquid boundary movements in both cylindrical (a) and convex (b) tablets as a function of time.

Table 1
The equations used to describe axial and radial liquid boundary movements in both the cylindrical and convex tablets as a function of time

Tablet geometry	Movement direction	Timescale (min)	Equation	R^2
Cylindrical	Axial	0–120	$y = 0.1716\ln(x) - 0.063$	0.9743
		120–360	$y = 0.0029x + 0.444$	0.9970
	Radial	0–120	$y = 0.246\ln(x) - 0.2$	0.9778
		120–360	$y = 0.0121x - 0.4278$	0.9998
Convex	Axial	0–480	$y = 0.4915\ln(x) - 0.7225$	0.9574
	Radial	0–240	$y = 0.003x + 0.0834$	0.9499
		240–480	$y = 0.008x - 1.1639$	0.9970

convex tablets is likely to be attributable to their more dense edges compared to cylindrical tablets. The sudden acceleration in radial liquid boundary movement may well be associated with the changes occurring in the tablet structure in the radial direction.

3.3. Tablet expansion and crack formation

As the liquid boundary proceeds inside the tablet, it starts to expand due to water absorption. This phenomenon is recognized as tablet expansion. As the expansion proceeds, the solid structure of the tablet starts to disintegrate and visible cracks are generated in the radial side of the tablet. This phenomenon is known as cracking.

Cylindrical and convex tablets both showed expansion and cracking during the dissolution process. The expansion of matrix in the radial direction in both the cylindrical and convex tablets and at the domes of the convex tablets was insignificant. Since the tablet expansion and cracking are closely connected phenomena, the extent of the expansion and consequently, crack formation can be measured using the percentage of expansion ($E_t\%$) which is calculated as follows:

$$E_t\% = \frac{H_t}{H_{before}} \times 100\%, \quad (1)$$

where H_t is the height of the cylinder of the tablet after the dissolution test and freeze drying and H_{before} is the height of the cylinder of the tablet before the dissolution test. The percentage of expansion for the cylindrical and convex tablets as a function of time is shown in Fig. 3.

The first visible cracks in the middle of the faces of the cylinder of the tablets became apparent after 2 h with the cylindrical tablets and at 4 h with the convex tablets as the $E_t\%$ reached approximately 110%. However, it can be seen from Fig. 3 that the matrix started to expand almost immediately when the tablets were immersed into the dissolution medium. It can be concluded that the structure of the tablet changes dramatically as the expansion proceeds up to an $E_t\%$ of 110 %. This phenomenon can also be seen in the liquid boundary movement: there was an abrupt change in the radial liquid boundary movement speed at 2 h for cylindrical tablets and at 4 h for convex tablets (Fig. 2a and b). The expansion had reached its maximum within 8 h with cylindrical tablets but with convex tablets the percentage of expansion changed only 7% from 8 to 24 h (results not shown). The difference between expansion behaviour of tablets was most probably due to differences in internal density and stress distribution in tablets.

Tablets are complex systems, which consist of inter (between drug and matrix compound particles) and intra (between two matrix compound particles) particulate bonds, where the energy generated during the compression

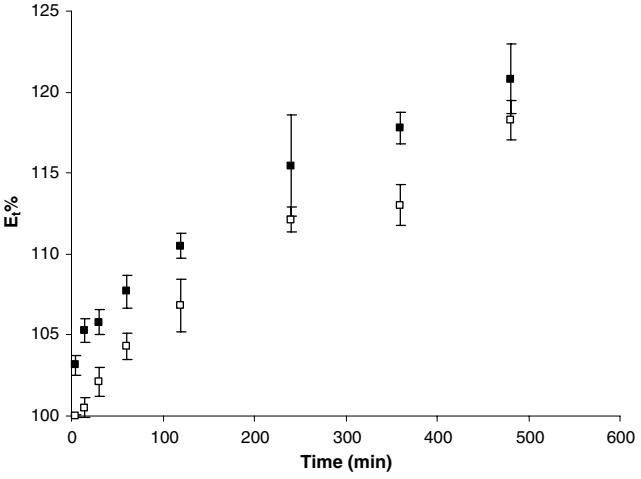

Fig. 3. The percentage of expansion for cylindrical (■) and convex (□) tablets as a function of time.

is stored [19]. SA that has DS value as high as 2.7 is virtually in an amorphous and glassy state [3] and during the dissolution process, it starts to expand due to the penetration of the solvent. The solvent molecules occupy positions among the polymer molecules and reduce the secondary inter and intra molecular bonding forces [20,21]. In the case of a drug containing non-dissolving hydrophobic polymer matrix, this results in cracking. It can be concluded that the densest areas of the tablets contain substantial amounts of inter and intra molecular, and particle bonds and, therefore, stored energy. This energy is then released due to relaxation as the solvent penetrates between the molecules and particles, and is reflected as expansion, which ultimately leads to cracking [21]. This phenomenon has been observed earlier with SA [2,5] and confirms also findings made with another hydrophobic polymer, amylodextrin [22,23].

3.4. Effect of tablet expansion and crack formation on drug release

The crack formation could have a great impact on drug release behaviour. The porosity and the effective surface area both increase and tortuosity decreases because of the structural changes occurring in the tablet during the dissolution process. According to the Higuchi equation [1]

$$Q = \sqrt{\frac{D\varepsilon}{\tau}(2A - \varepsilon C_s)C_s t}, \quad (2)$$

where Q is the amount of drug released after time t per unit exposed area, D the diffusivity of the drug in the permeating fluid, τ the tortuosity factor of the capillary system, A the total amount of drug present in the matrix per unit volume, C_s the solubility of the drug in the permeating fluid and ε the porosity of the matrix. All these factors control the drug release. The effect of cracking on surface area in both the cylindrical and convex tablets can be seen in Fig. 4. Cracking enlarges the surface area of the solid exposed to the liquid. As can be seen from Fig. 4, the interface of the undissolved matrix and the liquid boundary is a single unit, but it has been divided into two sections after six hours because of cracking.

The equations for describing the fraction of released caffeine as a function of the percentage of expansion are presented in Table 2 and the corresponding plot is shown in Fig. 5. A linear correlation was obtained between the cracking and the release of caffeine with both cylindrical and convex tablets over the experiment i.e. up to 8 h (time points are not shown in Fig. 5). The linearity could be due to continual crack formation promoting the drug release. The rate of drug release decreases as the cracking reaches its maximum, this being reflected in lack of correlation at 24 h (time point is not shown in Fig. 5). The diffusion path for the drug compound does not shorten any longer after the crack formation has reached its maximum. In Table 2, the high value of the slope describing the magnitude of the impact of the percentage of expansion on the rate of drug release in cylindrical tablets might be due to findings which have effect also on the cracking formation discussed in chapter 3.3. The cylindrical tablets are more dense than the convex ones and, therefore, the percentage of

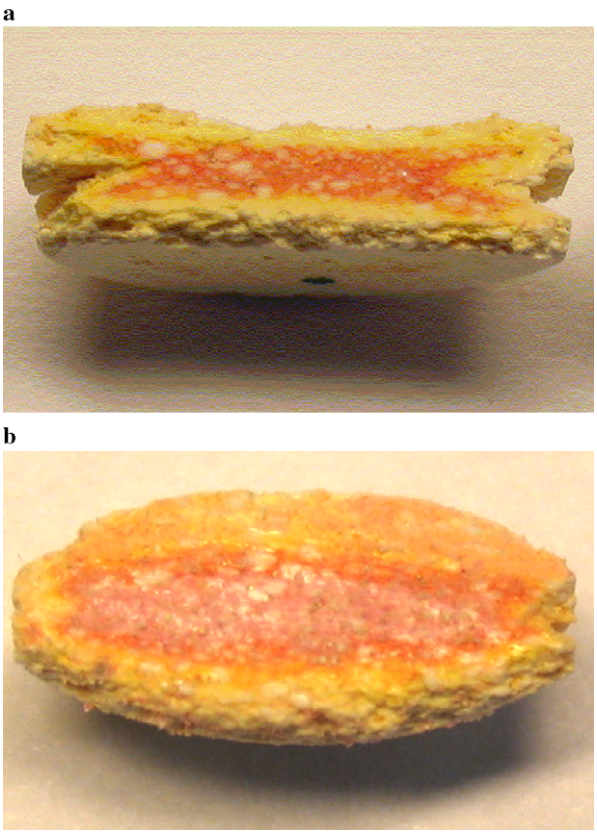

Fig. 4. An axial cross-section of a cylindrical (a) and a convex (b) tablet after 360 min in the dissolution bath.

Table 2
The equations used to describe the fraction of drug release as a function of the percentage of expansion

Tablet geometry	Timescale (min)	Equation	R^2
Cylindrical	0–480	$y = 2.4104x - 244.95$	0.9945
Convex	0–480	$y = 1.5117x - 145.49$	0.9918

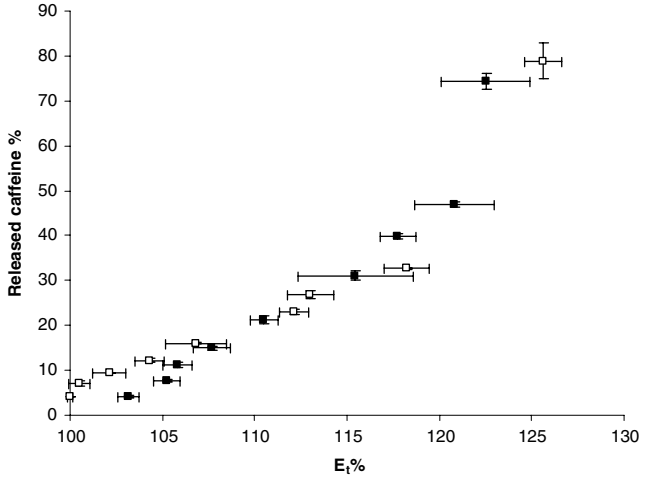

Fig. 5. The fraction of released caffeine for cylindrical (■) and convex (□) tablets as a function of the percentage of expansion.

expansion and cracking has a greater impact on geometry changes and, consequently, drug release.

The effect of expansion and crack formation on drug release is a chain reaction. The tablets start to expand due to polymer relaxation as the liquid penetrates into matrix. Cracks continue to be generated until the expansion proceeds up to the point where E_t% is 110%. Crack formation shortens the length of the diffusion path and decreases the tortuosity. This promotes drug release and the liquid can penetrate deeper into the matrix. It seems that the structure of both cylindrical and convex tablets changes drastically as the cracking proceeds.

4. Conclusions

The liquid penetration into the tablet is a prerequisite for the dissolution of the drug compound and its consequent release. This study showed that our method is suitable for investigating the liquid penetration into hydrophobic matrix tablets. However, the liquid boundary penetrated into cylindrical and convex tablets differently due to their different internal pore structures. The penetrating liquid weakened internal bonds and initially this caused tablet expansion which was then transformed as a function of time into cracking. The cracking increased the drug release rate by shortening the length of the diffusion path, increasing the effective surface area and lowering the degree of tortuosity.

Acknowledgements

This research was performed as part of the VARMA-project in the COMBIO-program, financially supported by The National Technology Agency (Tekes) of Finland. The authors thank Polymer Corex Oy Ltd. for the generous gift of starch acetate. The technical assistance of Mrs. Päivi Tiihonen, Mr. Esa Miettinen and Mr. Juhani Hakala is kindly acknowledged. The authors also thank Prof. Kalervo Väänänen, Ms. Johanna Tuomela (MSc) and Ms. Maija Vainiomäki (MSc) in the Department of Anatomy, University of Turku, for their collaboration in micro computed tomography analysis. This study was also supported by grant from Association of Finnish Pharmacies (AFP), Finland.

References

[1] T. Higuchi, Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices, J. Pharm. Sci. 52 (1963) 1145–1149.
[2] S. Pohja, E. Suihko, M. Vidgren, P. Paronen, J. Ketolainen, Starch acetate as a tablet matrix for sustained drug release, J. Control. Release 94 (2004) 293–302.
[3] O. Korhonen, P. Raatikainen, P. Harjunen, J. Nakari, E. Suihko, M. Vidgren, P. Paronen, Starch acetates – multifunctional direct compression excipients, Pharm. Res. 17 (2000) 1138–1143.
[4] O. Korhonen, S. Pohja, S. Peltonen, E. Suihko, M. Vidgren, P. Paronen, J. Ketolainen, Effects of physical properties for starch acetate powders on tableting, AAPS Pharm. Sci. Tech. 3 (2002) 1–9.
[5] B. van Veen, J. Pajander, K. Zuurman, R. Lappalainen, A. Poso, H.W. Frijlink, J. Ketolainen, The effect of powder blend and tablet structure on drug release mechanisms of hydrophobic starch acetate matrix tablets, Eur. J. Pharm. Biopharm. 63 (2005) 149–157.
[6] R. Konrad, A. Christ, G. Zessin, U. Gobet, The use of ultrasound and penetrometer to characterize the advancement of swelling and eroding fronts in HPMC matrices, Int. J. Pharm. 163 (1998) 123–131.
[7] I.S. Moussa, L.H. Cartilier, Characterization of moving fronts in cross-linked amylose matrices by image analysis, J. Control. Release 42 (1996) 41–55.
[8] I.S. Moussa, V. Lenaerts, L.H. Cartilier, Image analysis studies of water transport and dimensional changes occurring in the early stages of hydration in cross-linked amylose matrices, J. Control. Release 52 (1998) 63–70.
[9] P. Colombo, R. Bettini, P. Santi, A. De Ascentiis, N.A. Peppas, Analysis of the swelling and release mechanisms from drug delivery systems with emphasis on drug solubility and water transport, J. Control. Release 39 (1996) 231–237.
[10] A.R. Rajabi-Siahboomi, R.W. Bowtell, P. Mansfield, A. Henderson, M.C. Davies, C.D. Melia, Structure and behaviour in hydrophilic matrix sustained release dosage forms: 2. NMR-imaging studies of dimensional changes in the gel layer and core of HPMC tablets undergoing hydration, J. Control. Release 31 (1994) 121–128.
[11] W.E. Baille, C. Malveau, X. Zhu, R.H. Marchessault, NMR imaging of high-amylose starch tablets. 1. Swelling and water uptake, Biomacromolecules 3 (2002) 214–218.
[12] C. Malveau, W.E. Baille, X. Zhu, R.H. Marchessault, NMR imaging of high-amylose starch tablets. 2. Effect of tablet size, Biomacromolecules 3 (2002) 1249–1254.
[13] C. Ferrero, A. Muñoz-Ruiz, M.R. Jiménez-Castellanos, Fronts movement as a useful tool for hydrophilic matrix release mechanism elucidation, Int. J. Pharm. 202 (2000) 21–28.
[14] C. Ferrero, I. Bravo, M.R. Jiménez-Castellanos, Drug release kinetics and fronts movement studies from methyl methacrylate (MMA) copolymer matrix tablets: effect of copolymer type and matrix porosity, J. Control. Release 92 (2003) 69–82.
[15] M. Otsuka, M. Sato, Y. Matsuda, Comparative evaluation of tableting compression behaviors by methods of internal and external lubricant addition: inhibition of enzymatic activity of trypsin preparation by using external addition during the tableting compression process, AAPS Pharm. Sci. 3 (2001) 1–11.
[16] R. Charlton, J.M. Newton, Application of gamma-ray attenuation to the determination of density distributions within compacted powders, Powder Technol. 41 (1985) 123–134.
[17] I.C. Sinka, J.C. Cunningham, A. Zavaliangos, Analysis of tablet compaction. II. Finite element analysis of density distributions in convex tablets, J. Pharm. Sci. 93 (2004) 2040–2053.
[18] J.C. Cunningham, I.C. Sinka, A. Zavaliangos, Analysis of tablet compaction. I. Characterization of mechanical behavior of powder and powder/tooling friction, J. Pharm. Sci. 93 (2004) 2022–2039.
[19] K. van der Voort Maarschalk, K. Zuurman, H. Vromans, G.K. Bolhuis, C.F. Lerk, Porosity expansion of tablets as a result of bonding and deformation of particulate solids, Int. J. Pharm. 140 (1996) 185–193.
[20] B. Narasimhan, Mathematical models describing polymer dissolution: consequences for drug delivery, Adv. Drug Deliv. Rev. 48 (2001) 195–210.
[21] W.D. Callister Jr., Degradation of polymers, in: W.D. CallisterJr. (Ed.), Materials Science and Engineering An Introduction, John Wiley, New York, 2000, pp. 596–600.
[22] G.H.P. Te Wierik, J. Van der Veen, A.C. Eissens, C.F. Lerk, Preparation, characterization and application of linear dextrins. Part IV. General applicability and mechanism of programmed release from amylodextrin tablets, J. Control. Release 27 (1993) 9–17.
[23] R. Steendam, A.C.E. Einssens, H.W. Frijlink, C.F. Lerk, Plasticisation of amylodextrin by moisture consequences for drug release from tablets, Int. J. Pharm. 204 (2000) 23–33.