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# Plasticisation of amylodextrin by moisture Consequences for drug release from tablets

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**Abstract**

Moisture influences the consolidation behaviour of amylodextrin powders and the porosity and mechanical strength of compacts thereof. The aim of this study is to relate moisture content and compact properties to drug release characteristics of amylodextrin tablets. Therefore, amylodextrin tablets containing theophylline monohydrate were prepared and their release characteristics were studied as a function of moisture content and initial porosity. Drug release from amylodextrin tablets occurs through a leaching mechanism in which cracks are progressively formed in the hydrated part of the matrix leading to almost constant release rates. Small variations in moisture content resulted in large changes of the release rate. A unique relationship between porosity and release rate, which was independent on moisture content and compaction pressure, was observed. Above a critical porosity of 0.075 crack formation was followed by disintegration and fast release. Below this critical porosity, tablets stayed intact despite of the formation of cracks, and sustained release was observed. It is concluded that control over moisture content is essential for the production of amylodextrin tablets with reproducible release characteristics. Using amylodextrin containing 10–17% moisture, tablets with a constant release behaviour can be obtained if sufficient compaction pressure ( > 300 MPa) is applied. Lubrication of amylodextrin powders reduces the effect of porosity significantly and improves the robustness of amylodextrin tablets as a release controlling excipient in tablets largely. 

*Keywords:* Amylodextrin; Moisture; Plasticisation; Porosity; Tablet strength; Percolation threshold; Crack formation; Drug release mechanism

## 1. Introduction

Amylodextrin is a modified starch product with promising controlled release characteristics. Te Wierik et al., (1996, 1993a) reported the application of amylodextrin as a unique excipient for the

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formulation of drug delivery systems with zero-order release. Contrary to pregelatinised (Herman and Remon, 1989; Van Aerde and Remon, 1988) and crosslinked starches (Lenaerts et al., 1998; Shukla et al., 1991), short-chained linear amylodextrins (polymerisation degree 20–35) do not swell or dissolve in water (Te Wierik et al., 1993a). Consequently, amylodextrin tablets do not form a gel-layer, which acts as a barrier to control diffusion of the drug out of the tablet. Instead, release will occur through leaching. A leaching mechanism (Fig. 1) can be characterised by the following steps: water penetrates the tablet through the pores and dissolves the dispersed drug particles. The cavities left by dissolution of dispersed drug particles form, together with the pores initially present, a porous and tortuous network through which the drug diffuses out of the tablet. Obviously, the initial porosity and tortuosity play a decisive role in drug release from leaching-based delivery systems (Baker, 1987; Rowe, 1975). They not only determine the penetration rate of water into the tablet (Desai et al., 1965; Washburn, 1921), but, since the pores form the route along which dissolved drug particles leave the tablet, the porosity and tortuosity of the porous network affect the effective diffusion coefficient of the incorporated drug (Higuchi, 1963). As the diffusional path length for the drug increases with time, the release rate decreases causing the well-known first-order release profiles generally observed for leaching-based drug delivery systems (Desai et al., 1965; Higuchi, 1963).

For amylodextrin tablets compacted at low pressures, first-order release kinetics, as would be expected for a leaching-type release mechanism, were reported (Te Wierik et al., 1993b). However, at high pressures, amylodextrin tablets demonstrated retarded and almost zero-order release kinetics. The strongly retarded drug release and non-disintegration behaviour of amylodextrin tablets was attributed to the excellent binding properties of the polymer (Te Wierik et al., 1993b, 1994). The almost linear drug release from low-porosity amylodextrin tablets was explained by a polymeric relaxation controlled release mechanism (Van der Veen, 1993).

In contrast to drug release from leaching-based drug delivery systems, release from swellable systems (Gao et al., 1995; Hopfenberg and Hsu, 1996; Raymond Davidson and Peppas, 1986; Visavarungroj et al., 1990) is hardly affected by the initial tablet porosity. Consequently, wide tolerances in compaction pressure are permitted since release is governed by diffusion through the swollen gel-layer instead of diffusion through a porous network (Davis, 1985). Robustness with respect to release rate and release profile is one of the most important criteria for the development of a controlled release formulation. Preferably, small changes in the composition of the tablet, the tabletting process or the tablet characteristics (porosity, strength) should not affect the release characteristics of the tablets. Therefore, to develop a robust tablet formulation, a thorough

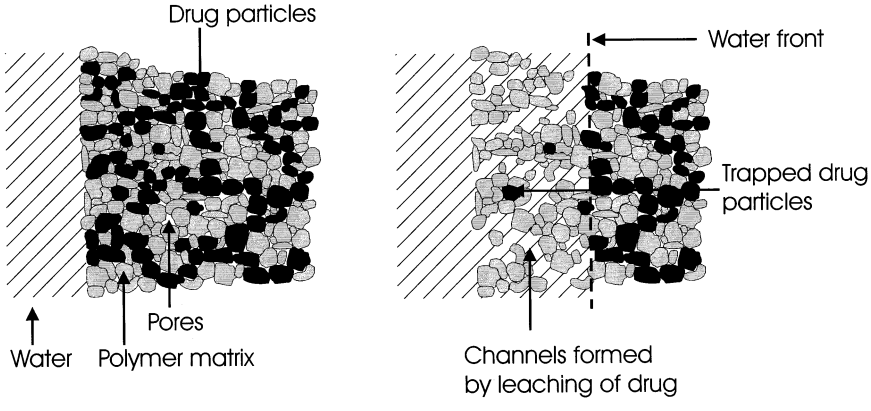


Fig. 1. Schematical representation of drug release from a leaching-based drug delivery system.

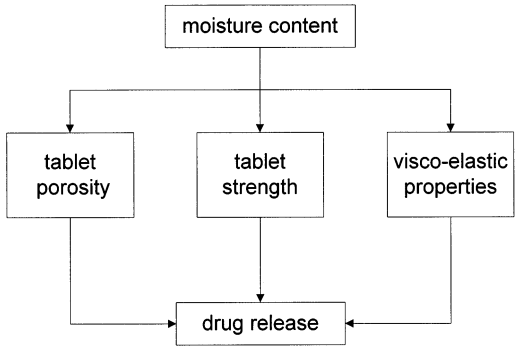


Fig. 2. Schematical representation of the way in which moisture can affect drug release from amylodextrin tablets.

understanding of the critical factors for the release rate and the release mechanism of amylodextrin tablets is required. Previously, we have shown that moisture, in combination with compaction pressure and tabletting speed, largely affects the porosity and tensile strength of amylodextrin compacts (Steendam et al., 2000a). Significant changes in compaction behaviour and tablet porosity or tensile strength were observed when amylodextrin becomes rubbery at high moisture fractions ($x_w > 0.19$). Furthermore, moisture enhances the free volume of the polymer (lowering of the glass transition temperature) which could affect the process of water uptake by the polymer. Therefore, the aim of this paper is to investigate the effect of moisture content on the mechanisms of water penetration and drug release of amylodextrin tablets and elucidate the role of initial porosity and tablet strength (Fig. 2).

## 2. Materials and methods

### 2.1. Materials

Amylodextrin, a linear dextrin with an average DP of 21.5, prepared from potato starch by enzymatic hydrolysis followed by precipitation, filtration and dehydration (Te Wierik et al., 1996), was supplied by AVEBE (Foxhol, The Netherlands). Theophylline monohydrate was supplied by OPG Farma (Utrecht, The Netherlands). Both amylodextrin and theophylline were used as sieve fractions $< 180$ μm. Amylodextrin powders were hydrated over various saturated salt solutions of specified relative humidity (rH). Absolute moisture fractions ($x_w$) were determined with an infrared moisture analyser (Sartorius MA 40 Moisture Analyzer, Göttingen, Germany) by drying the powder at 105°C to constant weight. True densities (22°C) were measured with a helium pycnometer MVP-1 (Quantachrome Corp., Syosset, NY, USA).

### 2.2. Preparation of tablets

Physical mixtures of theophylline monohydrate (10% w/w) and amylodextrin powders (90% w/w) with different $x_w$ were prepared by mixing in a Turbula mixer (Bachoven, Basle, Switzerland) at 90 rpm for 30 min. Lubrication of theophylline/amylodextrin ($x_w = 0.125$) blends was performed by additional blending with 0.5% magnesium stearate for 2 min.

Cylindrically flat-faced amylodextrin compacts (500 mg, diameter 13 mm) were prepared on a hydraulic press (ESH, Brierley, Hill, United Kingdom) at different compaction pressures (load rate 2 kN/s, hold time 0.1 s). Porosities of the tablets were calculated from the weight and dimensions of the tablets and the true densities of the powders.

### 2.3. Dissolution experiments

Release experiments were performed under sink conditions in a USP XXIII dissolution apparatus No II (paddle) (Prolabo, Rhône-Poulenc, Paris, France) at 100 rpm and $37 \pm 0.5$°C in 0.05 M phosphate buffer pH 6.8. Theophylline concentrations were measured spectrophotometrically using an Ultrospec 4052 TDS apparatus (LKB, Zoetermeer, The Netherlands) at 268 nm. All experiments were carried out in duplicate.

## 3. Results and discussion

### 3.1. Effect of moisture on drug release

Fig. 3 shows the release of theophylline mono-

hydrate from amylodextrin tablets with different moisture fractions ($x_w$) compacted at 150 MPa. Release of the incorporated drug slowed down when $x_w$ increased. Tablets with $x_w = 0.049$ and 0.096 disintegrated rapidly after immersion in the aqueous buffer, resulting in fast release of theophylline. For higher $x_w$, no disintegration or erosion was observed and release was increasingly sustained. For the highest moisture fractions, apart from the burst effect, release appeared to be almost linear for 8–10 h.

The effect of moisture content on theophylline release is more clearly depicted by plotting $t_{50\%}$ (the time at which 50% of the drug is released) versus $x_w$ (Fig. 4a) for tablets compacted at 150 MPa). Below $x_w = 0.075$, tablets disintegrated rapidly, resulting in fast dissolution of the drug. For higher moisture fractions, $t_{50\%}$ increased steeply due to decreasing porosities of the tablets and the absence of disintegration. The significant decline of $t_{50\%}$ at $x_w = 0.234$, as compared to $x_w = 0.13$–$0.18$ is explained by the rubbery state of amylodextrin with this moisture content ($T_g = -8.5$°C, Table 1). During the decompression stage of the compaction cycle, extensive elastic relaxation of the rubbery polymer will occur, leading to the formation of relatively porous tablets (Steendam et al., 2000a). Furthermore, the bonding properties of these tablets are relatively low due to a low elastic modulus and multilayer water adsorption. The latter weakens interparticle bonding in the tablet since water now acts as a kind of lubricant. Moreover, these factors lower the tablet strength and facilitate the occurrence of erosion, resulting in faster release.

Increasing of the compaction pressure had a similar effect on drug release as increasing of the moisture content, obviously since they both lower the initial tablet porosity. Drug release from tablets prepared at low compaction pressures was

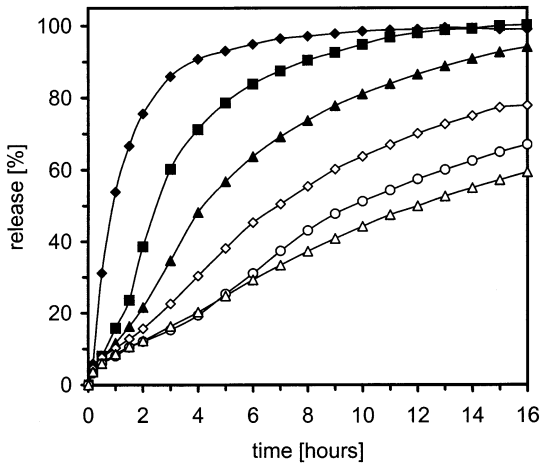


Fig. 3. Theophylline release profiles of amylodextrin tablets with different $x_w$ compacted at 150 MPa. Key: $x_w = 0.049$ (◆), 0.096 (■), 0.108 (▲), 0.117 (◇), 0.137 (○) and 0.152 (△).

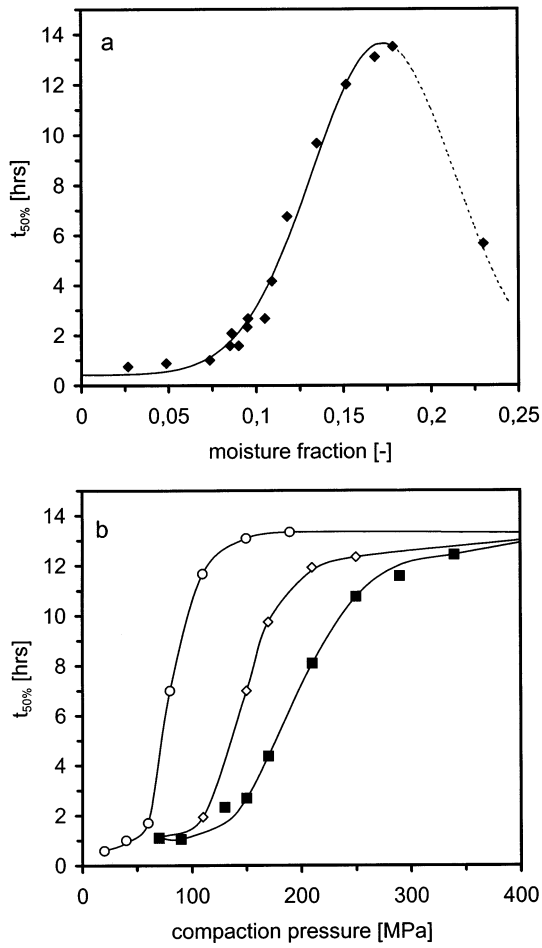


Fig. 4. (a) Effect of moisture content on theophylline release (expressed as $t_{50\%}$.) from amylodextrin tablets compacted at 150 MPa and (b) effect of compaction pressure on theophylline release from amylodextrin compacts with different moisture fractions. Moisture fractions in Fig. 4b are: 0.096 (■), 0.117 (◇) and 0.168 (○).

fast and rapid disintegration of the tablets was observed. Upon increasing the pressure, $t_{50\%}$ increased steeply at a certain pressure, the value of which was highly dependent on the moisture content (Fig. 4b). Figures 4a and 4b unambiguously show that both $x_w$ and compaction pressure are critical parameters for the release characteristics of amylodextrin tablets. However, the figure also shows that the release rates become constant and more or less equal for all three moisture fractions if sufficient compaction pressure is applied ($x_w = 0.168$: $\sigma > 130$ MPa; $x_w = 0.117$: $\sigma > 190$ MPa; $x_w = 0.096$: $\sigma > 300$ MPa). Consequently, when tablets are prepared at pressures exceeding 300 MPa, the release rate will be independent of moisture content provided that the moisture fraction is between 10 and 17%.

Table 1
Experimentally determined glass transition temperatures ($T_g$), of amylodextrin powders containing different moisture fractions ($x_w$)

| $x_w$ [−] | $T_g$[a] [°C] |
|---|---|
| 0.070 | –[b] |
| 0.114 | 102.3 |
| 0.150 | 46.0 |
| 0.177 | 36.9 |
| 0.230 | −6.6 |
| 0.234 | −8.7 |

[a] Adapted from ref. (Steendam et al., 2000a).
[b] Could not be detected due to degradation of amylodextrin below the glass transition temperature.

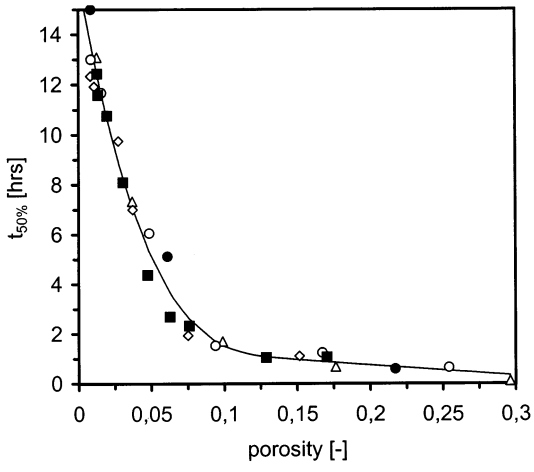


Fig. 5. Effect of initial porosity on theophylline dissolution rate (expressed as $t_{50\%}$) of amylodextrin tablets prepared at different pressures from powders with different moisture fractions. Moisture fractions were 0.096 (■), 0.117 (◇), 0.137 (○) and 0.169 (△) and 0.20 (●).

The interrelationship between moisture content, compaction pressure, tablet porosity and drug release is clearly shown by plotting $t_{50\%}$ versus the initial porosity ($\varepsilon_0$) of the different tablets (Fig. 5). The data shows a unique relationship between $t_{50\%}$ and $\varepsilon_0$, which was independent of both compaction pressure and moisture content. Obviously, tablets with the same porosity, but prepared from powders containing different moisture fractions have the same release characteristics. This implicates that water penetration into the tablets is independent of the moisture content and thus independent of the glass transition temperature and elastic modulus of the amylodextrin matrix. This can be explained by the fact that, irrespective of initial moisture content, the amylodextrin matrix starts to absorb water up to its equilibrium value ($x_w \approx 0.3$), immediately after it has been immersed in water.

### 3.2. Cracking and fracturing of amylodextrin tablets in water

Since amylodextrin does not swell in water but only absorbs approximately 30% w/w water, drug release from porous amylodextrin tablets was expected to occur through a leaching-type mechanism. However, instead of the expected first-order release curves (Higuchi, 1963), release appeared to be close to zero-order over a significant part of the dissolution curve. Furthermore, the release rates even seemed to increase when the fraction theophylline released equalled 20–30%.

Fig. 6a shows photographs of the surface (top view) of an amylodextrin tablet ($x_w = 0.137$, $\varepsilon_0 = 0.02$) after different periods in water. The photographs clearly show the movement of the waterfront originating from radial penetration. Although fracturing was observed near the edge, the appearance of the cylindrical face of the tablet did not change within the first hours of immersion. However, microscopic examination showed that small fractures formed immediately at the

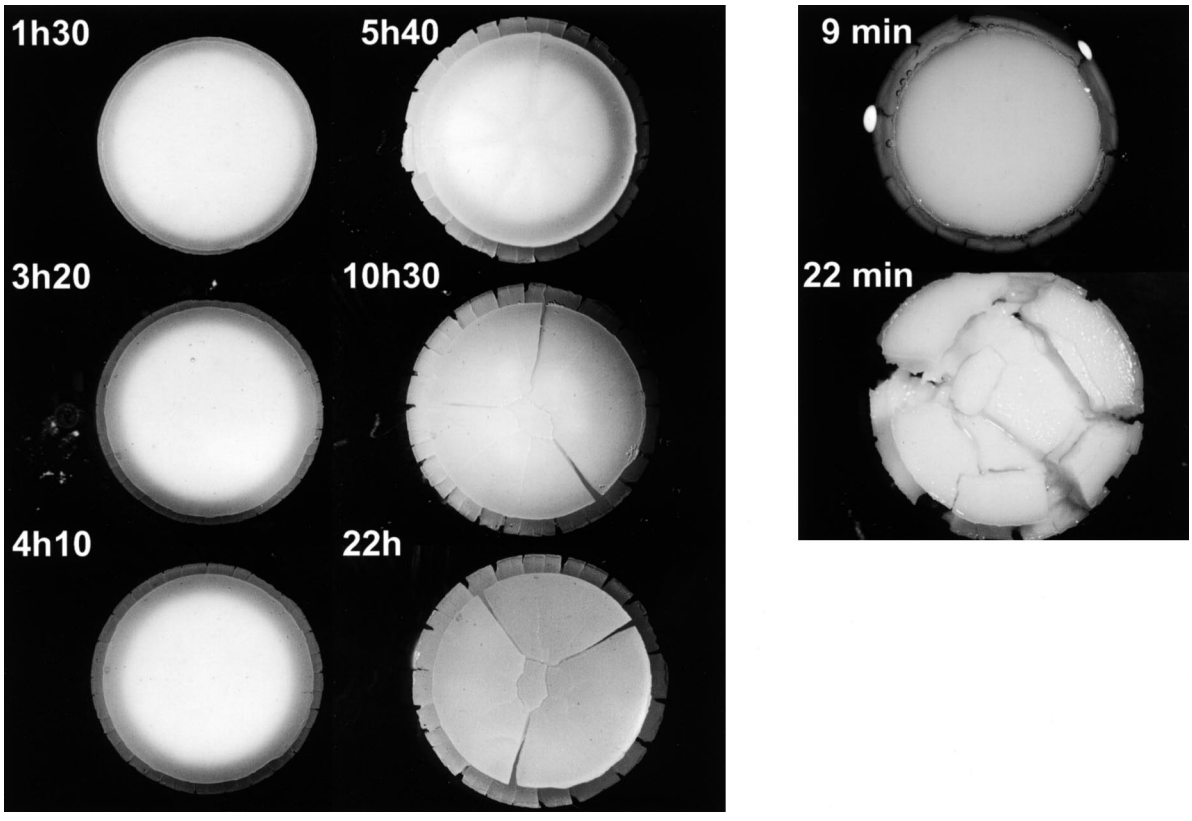


Fig. 6. Photographs of upper surface of amylodextrin tablets ($x_w = 0.136$) after several periods of immersion (no stirring). The tablets (500 mg, 13 mm diameter) were compacted at (a) 160 MPa ($\varepsilon_0 = 0.020$) and (b) 40 MPa ($\varepsilon_0 = 0.15$).

cylindrical surface after immersion of the tablets in water. Furthermore, at the edges of the upper tablet face, large cracks were formed which propagated into the centre of the tablet, thereby nearly separating the upper part from the lower part of the tablet (Fig. 7). The cracks in the cylindrical face of the tablet showed a difference in size between top and bottom of the tablet. This difference is explained by the non-uniform distribution of the compaction pressure over the powder bed during consolidation. Only after about 5 h, the fractures in the two circular faces increased rapidly in size and could macroscopically be observed, as is clearly shown by the photographs taken after 10 and 22 h. From the photographs and the position of the penetration front in the tablets (after breaking the tablets into two halves), it was concluded that large macroscopic cracks did not form until the penetration fronts met in the centre of the tablet and the tablet was completely hydrated (Fig. 7d). Fracturing is caused by restriction of volume expansion of the rubbery region by the rigid glassy core to which it is attached (Alfrey et al., 1966). When the penetration fronts meet in the centre of the tablet, the glassy core disappears. Volume expansion of the now completely rubbery tablet is not restricted anymore and the cracks increase rapidly in size. Crack formation contributes to the creation of the porous network through which dissolved drug molecules diffuse out of the tablet. The effect of this process on the release rate ($dM/dt$) can be understood by application of the following relationship which relates the release rate of a drug to the porosity ($\varepsilon$) and the tortuosity ($\tau$) of the matrix in which the drug is incorporated (Higuchi, 1963):

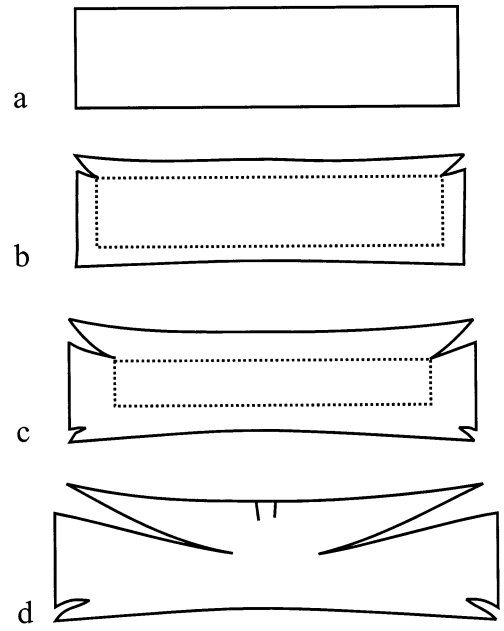


Fig. 7. Cross sectional representation of crack formation in an amylodextrin tablet in water (the dotted line represents the position of the water front): dry tablet (a); partly hydrated tablet (b) and (c) and completely hydrated tablet (d) in which the water fronts have met in the centre. The upper side faced the upper punch during compaction.

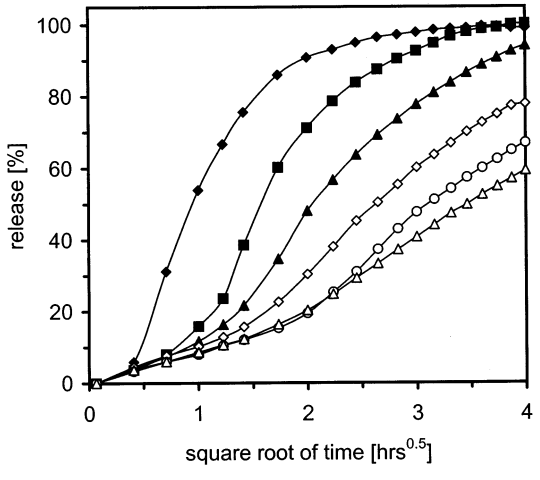


Fig. 8. Percentage theophylline released versus square root of time for amylodextrin tablets with different moisture fractions and compacted at 150 MPa. Moisture fractions (and porosities) were: 0.049 ($\varepsilon = 0.17$) (◆), 0.096 ($\varepsilon = 0.078$) (■), 0.108 ($\varepsilon = 0.057$) (▲), 0.117 ($\varepsilon = 0.038$) (◇), 0.137 ($\varepsilon = 0.026$) (○) and 0.152 ($\varepsilon = 0.014$) (△).

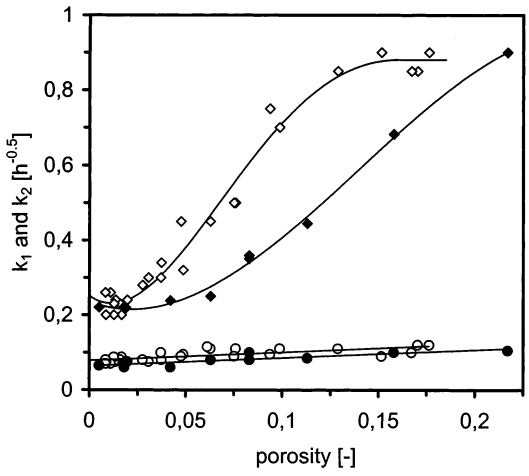


Fig. 9. Effect of initial tablet porosity on the release rate constant before ($k_1$, ●, ○) and after ($k_2$, ◆, ◇) the inflection point in the release curves. Open symbols represent unlubricated tablets (different moisture contents), closed symbols represent lubricated tablets (0.5% w/w magnesium stearate, moisture fraction 0.125)

$$\frac{\mathrm{d}\,M}{\mathrm{d}\,t} \div \sqrt{\frac{ID \cdot \varepsilon}{\tau \cdot t}} = \sqrt{\frac{ID_{eff}}{t}} \tag{1}$$

Obviously, crack formation results in an increase of the porosity and a reduction of the tortuosity. Consequently, progressive crack formation leads to an increase of the effective diffusion coefficient of the drug ($ID_{\mathrm{eff}}$) with time (Eq. (1)), resulting in an apparent constant release rate (Fig. 3) for an extended period of time. The increase of the effective diffusion coefficient due to crack formation is clearly illustrated by plotting the fraction released versus $\sqrt{t}$ (Fig. 8). Up to 10–20% released, theophylline release followed first order kinetics, after which a more or less gradual increase of the release rate was observed. Above the inflection point, release was again linear with $\sqrt{t}$ for a significant further part of the curve. Fig. 9 shows the first order release rate constants of drug release before ($k_1$, up to point of inflection) and after ($k_2$, point of inflection up to 60% released) the point of inflection, as calculated from the slopes of the curves in Fig. 8. The figure shows that $k_1$ is hardly affected by $\varepsilon_0$, whereas $k_2$ was highly dependent on $\varepsilon_0$. Below $\varepsilon_0 = 0.02$ $k_2$ appears to be constant, but it increased steeply between $0.02 < \varepsilon_0 < 0.17$.

From visual examination of the surface characteristics of the tablets, it was observed that the point of inflection of the release curves of Fig. 8 coincided with the time at which macroscopically observable cracks started to form in the tablet surface (cracking time, $t_{crack}$). Moreover, examination of the interior of the tablets after breaking the tablets into two halves, showed that the cracking time coincided with the time at which the axial penetration fronts met in the center of the tablets. Plotting of the visually determined cracking time versus the initial porosity (Fig. 10), shows that $t_{crack}$ exhibits a similar dependence on initial porosity as does $t_{50\%}$ (Fig. 5). The linear relationship between $t_{crack}$ and $t_{50\%}$ (inset Fig. 10) suggests that release is directly related to the process of crack formation in the tablet.

The porosity of 0.075 was found to be a threshold value for the occurrence of erosion and disintegration, as was concluded from visual examination of the tablets during dissolution. At porosities exceeding 0.075, cracking occurred almost immediately and was followed by disintegration of the tablets, as is illustrated by the photographs of Fig. 6b, which shows an amylodextrin tablet with $\varepsilon_0 = 0.15$ after 9 and 22 min of immersion, respectively. Tablets with $\varepsilon_0 <$ 0.075, however, stayed intact, despite the fact that large cracks were formed when the penetration fronts met in the centre of the tablet. The effect of compaction pressure, and consequently porosity, on the strength of hydrated amylodextrin compacts can be understood by a closer examination of the process of powder consolidation.

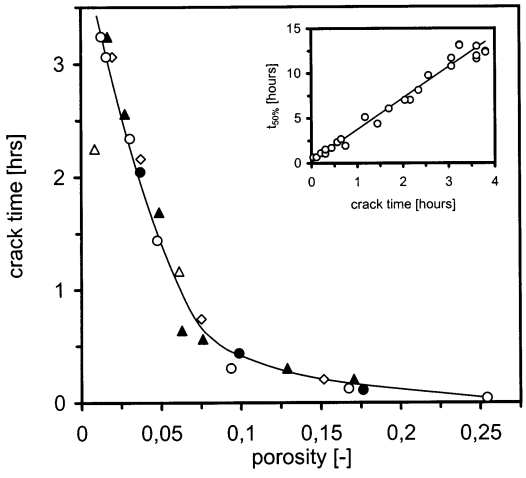


Fig. 10. Effect of porosity and moisture fraction on cracking time of amylodextrin tablet. The inset shows the relationship between $t_{50\%}$ and the time at which cracking. Moisture fractions were 0.096 (■), 0.117 (◇), 0.137 (○) and 0.169 (△) and 0.20 (●).

### 3.3. Powder consolidation

During compaction of a ductile powder, several steps can be distinguished. Initially, particles undergo rearrangement without deformation, but already at relatively low pressures, high pressures may be generated at interparticulate contact points leading to local plastic deformation. In terms of percolation theory, at this stage, the powder consists of isolated clusters of bonded particles. When clusters of bonded particles start to span the whole tablet (percolating network) a compact with a minimum strength is first formed. Upon further increasing the pressure, more and more particles join the percolating network leading to an increase of the rigidity and further lowering of the porosity. At high porosity, the pores form a percolating network spanning the three-dimensional structure of the compact. Upon reducing the porosity, finite isolated pore clusters, randomly distributed in the polymer matrix start to form below the so-called pore percolation threshold ($p_c$). Holman, (1991) stated that in order to create a discontinuous pore network, extensive plastic deformation of the particles should occur. From compaction experiments, Holman determined a value of approximately 0.09 for the pore percolation threshold of Starch 1500, which gets near the percolation threshold for the occurrence of erosion and disintegration ($p_{dis}$) of 0.075 as determined for our amylodextrin tablets. In a previous study we showed that the pore percolation threshold of amylodextrin tablets was approximately 0.037, as determined from mercury porosimetry and water penetration experiments (Steendam et al., 2000b). This value agreed very well with the results of some Monte Carlo simulation studies which reported pore percolation threshold in the range 0.03–0.04 (Elam et al., 1984; Kertész, 1981). Therefore we believe that

0.075 is not the pore percolation threshold of amylodextrin tablets but a critical threshold for the strength of hydrated amylodextrin compacts and for the transformation from disintegration based release to sustained release through leaching. Upon increasing the compaction pressure, around $p_{dis}$, interparticulate bonding is strongly enhanced due to extensive plastic deformation of powder particles. Obviously, below $p_{dis}$ the interparticulate bond strength is sufficient to withstand the weakening effect of absorbed water and the generated disruptive forces of the penetrating water (crack formation), whereas above $p_{dis}$ this is not the case and the tablets will disintegrate. The dependence of the drug release rate on the initial porosity of amylodextrin tablets make it necessary to control the moisture content of the powder (control over storage conditions!) and the compaction process (pressure and rate of compaction) to obtain a robust process.

### 3.4. Effect of lubrication

Fig. 9 also shows the relationship between $k_2$ and $\varepsilon_0$ for amylodextrin tablets containing magnesium stearate as a lubricant. Disintegration of lubricated tablets was only observed for the tablets with initial porosities of 0.16 and 0.22, whereas the tablets with $\varepsilon_0 = 0.12$ eroded slightly. The effect of a lubricant is that the compressive force is distributed more homogeneously over the compact during compaction, resulting in tablets with a more homogeneous porosity and pore structure. Consequently, the residual stress in the tablet is lower, resulting in a lower extent of stress relaxation induced fracturing. The porosity above which erosion and disintegration occurred was significantly higher, as compared to tablets without a lubricant. Theophylline release from lubricated amylodextrin tablets was significantly slower than release from tablets without the lubricant, as can be concluded from the lower $k_2$ values in Fig. 9. Obviously, the use of a lubricant makes the pore surfaces more hydrophobic which lowers the capillary water penetration rate. Water penetration into amylodextrin tablets is a combination of capillary water uptake through the pores and diffusion through the polymer phase (Steendam et al., 2000b). Since the latter is hardly dependent on porosity, the porosity dependency of capillary water uptake and drug release of lubricated amylodextrin tablets is lower compared to that of unlubricated amylodextrin tablets. Furthermore, Fig. 9 shows that the drug release rate of lubricated tablets is constant up to a porosity of nearly 0.07, since both $k_1$ and $k_2$ remain constant in this region. Consequently, the robustness of amylodextrin tablets is significantly enhanced by the use of a lubricant. Therefore, it can be concluded that lubricated amylodextrin is a suitable excipient for the preparation of controlled release tablets with reproducible release rates.

## 4. Conclusion

The results in this study clearly show that moisture can have a significant effect on drug release characteristics of amylodextrin tablets. Due to its plasticising effect, moisture changes the compression characteristics of amylodextrin powders and the porosity of tablets prepared thereof. However, once the pore structure is formed, the moisture fraction does not affect the release characteristics. Release studies showed a critical porosity of 0.075, above which crack formation was followed by disintegration and fast release. Below this critical porosity, the tablets stayed intact despite of the formation of cracks, and sustained release was observed. It can be concluded that control over moisture content and compaction pressure is essential to produce amylodextrin tablets with reproducible and constant release rates. For amylodextrin powders with moisture contents between 10 and 17%, a compaction pressure exceeding 300 MPa was found to be sufficient to obtain linear release curves independent of moisture content and compaction pressure. The application of a lubricant, however, reduces the influence of tablet porosity on the release rate and improves the applicability and robustness of amylodextrin as a release controlling excipient in tablets.

## Acknowledgements

The authors would like to thank AVEBE (Foxhol, The Netherlands) for kindly supplying amylodextrin.

## Appendix A. Symbols

| | |
|---|---|
| $x_w$ | moisture fraction |
| rH | relative humidity |
| $T_g$ | glass transition temperature |
| $E$ | elastic modulus |
| $p_c$ | pore percolation threshold |
| $p_{dis}$ | percolation threshold for disintegration |
| $ID$, $ID_{eff}$ | diffusion coefficient and effective diffusion coefficient |
| $t_{50\%}$ | time at which 50% theophylline is released |
| $t_{crack}$ | time at which penetration fronts meet in the centre of the tablet and macroscopically observable cracks are formed |
| $k_1$, $k_2$ | release rate constants of drug release before and after crack formation ($t_{crack}$) |
| $\sigma$ | compaction pressure |
| $\varepsilon$, $\varepsilon_0$ | tablet porosity, and initial tablet porosity |
| $\tau$, $\tau_0$ | tortuosity and initial tortuosity |

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