Controlled Release of Theophylline Monohydrate from Amylodextrin Tablets: *In Vitro* Observations

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Received February 18, 1993; accepted September 26, 1993

Amylodextrin is a linear dextrin and can be produced by enzymatic hydrolysis of the α-1,6 glycosidic bonds of amylopectin. Tablets compacted from pure amylodextrin showed good binding properties and did not disintegrate in aqueous media. Extended and decreasing drug release rates were found for tablets of 300 mg with a diameter of 9 mm containing 70% amylodextrin and 30% theophylline monohydrate, when compacted at 5 kN. Almost-constant drug release rates were obtained for these tablets when compacted at 10 or 15 kN. Nearly constant drug release rates were also shown for amylodextrin tablets with a drug load up to 75% compacted at 10 kN. Both release rate and release profile could be adjusted by selecting tablet thickness and incorporation of either lactose as a highly soluble excipient or talc as a hydrophobic excipient.

KEY WORDS: amylodextrin; theophylline; controlled release; tablet; porosity; compaction force.

INTRODUCTION

Sustained- or controlled-release delivery systems can achieve predictable and reproducible release rates, extended duration of activity for short-half-life drugs, decreased toxicity, reduction of required dose, optimized therapy, and better patient compliance.

Matrix-type diffusion-controlled delivery systems are popular because of their ease of fabrication. A simple preparation technique involves the compression of a blend of drug and polymer powder by conventional pharmaceutical methods to form disks or tablets (1–3). However, the inherent drawback of matrix systems with conventional geometry such as spheres, cylinders, and slabs is the first-order release pattern (4–6), whereas zero-order drug release is usually desirable. Delivery systems showing constant drug release rates include hydrogel matrices (7), matrices containing porous hydrophobic polymers (8), monolithic matrices (9), and the megaloporous system (10).

Several studies have dealt with the application of modified starches in controlled-release formulations (11–15). Starch consists of two polymers of glucose: amylose and amylopectin (16). Waxy maize is almost completely composed of amylopectin (16). By selective hydrolysis of the 1,6 glycosidic bonds of amylopectin, a linear product, called amylodextrin, can be obtained (17–19). Te Wierik *et al.* (20) prepared amylodextrin from waxy maize by enzymatic hydrolysis with pullulanase.

A recent study showed slow drug release, linear with time, for tablets compressed from amylodextrin and diazepam (21). The present study reports the use of amylodextrin as a new pharmaceutical excipient in the design of solid controlled-release dosage forms. Theophylline monohydrate was chosen as a model drug with a moderate aqueous solubility (1 in 120). The impact of various parameters on drug release was investigated: compaction force, drug load, tablet porosity, tablet thickness, and incorporation of a hydrophilic or a hydrophobic excipient.

MATERIALS AND METHODS

Chemicals

The excipients used were amylodextrin (mean DP = 35), prepared according to the procedure reported by Te Wierik *et al.* (20), microcrystalline cellulose (Avicel PH 101, FMC, Philadelphia, PA), β-cyclodextrin and amylose V [both kindly supplied by Avebe, Foxhol, The Netherlands (NL)], α-lactose monohydrate, 100 mesh (DMV, Veghel, NL), and talc (Centrafarm, Etten-Leur, NL). Theophylline monohydrate Ph. Eur. (Bufa-chemie, Castricum, NL) was used as a model drug. All materials were stored at 20 ± 1°C and 45 ± 5% relative humidity.

Compactibility

Same-sieve fractions (53–300 μm) of the excipients amylodextrin, Avicel PH 101, β-cyclodextrin, and amylose V were each compacted on a hydraulic press (ESH Testing, Brierley Hill, UK) into 300-mg tablets with a diameter of 13 mm. The compaction force was built up in 10 sec and maintained during 0.1 sec. The crushing strength of the tablets was determined, at least 15 min after compaction, on a Schleuniger Model 2E instrument (Dr. K. Schleuniger, Zurich, Switzerland). The data given are the mean values of five measurements.

Preparation of Tablets

Tablets containing amylodextrin and theophylline monohydrate were prepared by blending amylodextrin (<180 μm) and theophylline monohydrate in a Turbula mixer during 30 min with subsequent compaction on a hydraulic press (Paul Weber, Stuttgart Uhlbach, Germany). About 5 g of the powder mix was filled into a die with a diameter of 4.93 cm and compacted with a compaction force of 72 kN. The tablets were crushed using a mortar and pestle and passed subsequently a Frewitt granulator (screens, 2.0 and 1.5 mm). Unless stated otherwise, the tablets were compacted from 300 mg granulate on a hydraulic press (ESH Testing) with flat-faced punches having a diameter of 9 mm. The compaction force was 10 kN, with a load rate of 2 kN/sec. The forces were applied during 0.1 sec.

Tablets containing amylodextrin, theophylline monohydrate, and lactose or talc were prepared by blending the components, having a particle size <180 μm, in a Turbula mixer during 30 min. The tablets were compacted without

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0724-8741/94/0400-0499$07.00/0

the granulation step on a hydraulic press (ESH Testing) from the blend as described above.

Determination of Tablet Porosity

The porosities of the tablets were calculated from the tablet dimensions, tablet weights, and true densities of the components, the latter determined with a (He)-pycnometer Model MVP-1 (Quantachrome Corp., Syosset, NY). The true densities of the components are shown in Table I. Porosities were determined sixfold.

In Vitro Drug Release

The *in vitro* dissolution testing was performed in a paddle apparatus (Prolabo, Rhône-Poulenc, Paris, France) under conditions specified in the USP XXII. The dissolution medium, 1000 ml 0.05 *M* phosphate buffer, pH 6.8, was deaerated and maintained at 37 ± 1°C. The rotation speed of the paddle was 100 rpm. The samples were analyzed for the drug content at λ 268 nm, using a Biochrom spectrophotometer (LKB, Cambridge, England). Each tablet formulation was tested in duplicate.

RESULTS AND DISCUSSION

To evaluate its dry binding properties, pure amylodextrin was compacted with increasing compaction force in tablets and tested for crushing strength. The data obtained were compared with the crushing strength of tablets compacted from pure microcrystalline cellulose (Avicel PH 101), amylose V, and β-cyclodextrin, respectively. Avicel was chosen as a reference because of its excellent binding capacity (22). Amylose V is a spray-dried product of amylose, whereas β-cyclodextrin has a cyclic structure composed of 7 glucose units. The latter two excipients were chosen because of their chemical similarity to amylodextrin. The results of the comparative evaluation are illustrated in Fig. 1 by the profiles of crushing strength versus compaction force. Both amylodextrin and Avicel PH 101 demonstrate excellent binding capacities, whereas Amylose V and β-cyclodextrin show relatively inferior binding properties. Therefore, amylodextrin exhibits sufficient binding capacity to serve as a candidate matrix former in solid dosage forms. Further, amylodextrin tablets do not disintegrate in aqueous media, whereas tablets of Avicel PH 101, amylose V, or β-cyclodextrin all disintegrate in aqueous media.

Amylodextrin was subsequently investigated for its properties to sustain drug release by compacting physical mixtures of amylodextrin and theophylline monohydrate at 5, 10, and 15 kN, respectively, in tablets containing 30% of the drug. The tablets were tested for drug release in 0.05 *M* buffer, pH 6.8, during 24 hr. The results are presented in Fig.

Table I. Densities (g/cm³) of the Tablet Components

Compound	Density (g/cm³)
Amylodextrin	1.53
Theophylline monohydrate	1.46
Lactose monohydrate	1.54
Talc	2.82

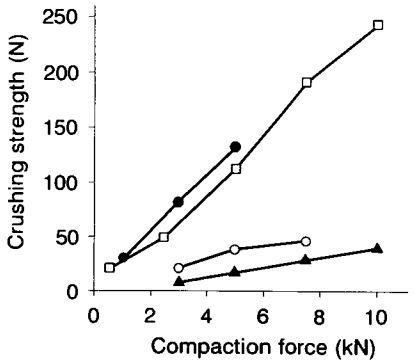

Fig. 1. Crushing strength of tablets (300 mg, 13 mm) compacted from various excipients as a function of compaction force. (▲) amylose V; (○) β-cyclodextrin; (□) amylodextrin; (●) microcrystalline cellulose (Avicel PH 101).

2 and show complete drug release within 24 hr for the tablets compacted at 5 kN. Drug release is relatively fast during the first hours, but then it slows down. In contrast, a small burst effect in the first half-hour is followed by almost-constant drug release up to 15 hr for the tablets compacted at 10 and 15 kN compaction force. Moreover, both the 10- and the 15-kN tablets show similar release profiles, with an overall drug release of 75% within 24 hr. Thus, different compaction pressures produce different release profiles. These results can be attributed to solvent penetration into the tablet as the rate-determining step (23).

To continue the investigation of prolonged release from amylodextrin tablets, the release of theophylline monohydrate from amylodextrin tablets with various drug loading was determined. Figure 3 reflects the percentages of drug released from the tablets as a function of time. All tablets were compacted at 10 kN. The results show identical release profiles for the tablets with a drug loading of 20 and 30%. The profiles demonstrate a relatively high initial drug release, followed by an almost-constant drug release rate up to about 15 hr. Drug release continues with a slightly slower constant rate, resulting in 70% drug release within 24 hr. The tablets containing 50% theophylline monohydrate show slightly faster but similar drug release profiles, resulting in a total drug release of about 80% in 24 hr. Incorporation of 75% of theophylline monohydrate in amylodextrin tablets shows the

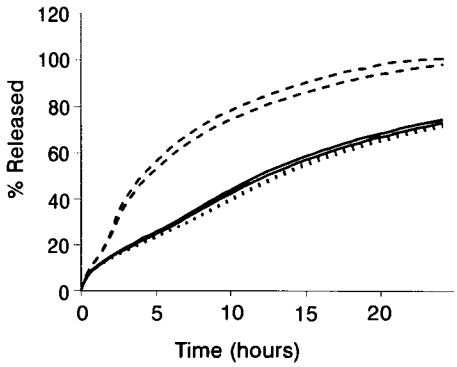

Fig. 2. Effect of compaction force on the release profile of theophylline from amylodextrin tablets (300 mg) with a drug load of 30%: (----) 5 kN; (——) 10 kN; (····) 15 kN.

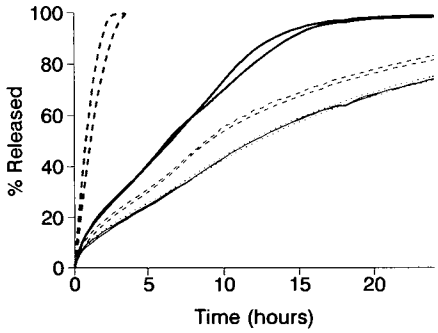

Fig. 3. Effect of drug load on the release profile of theophylline from amylodextrin tablets (300 mg) containing various percentages of theophylline monohydrate: (——) 20%; (····) 30%; (---) 50%; (——) 75%; (---) 100%.

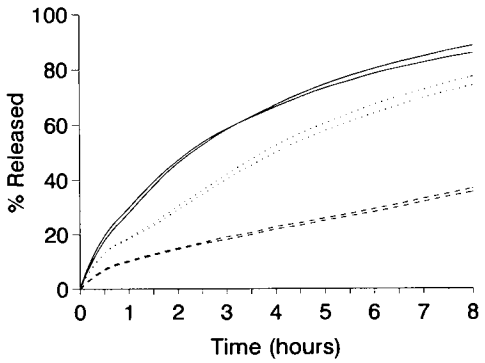

Fig. 4. Effect of tablet thickness on the release profiles of theophylline from amylodextrin tablets with a drug load of 30%: (----) 3.4 mm (300 mg); (····) 1.7 mm (150 mg); (——) 1.1 mm (100 mg).

highest, but still almost-constant, drug release up to about 90% of total drug release. Total drug release has been accomplished within 18 hr. For comparison, the dissolution profiles obtained for nondisintegrating tablets compacted from pure theophylline monohydrate are included in Fig. 3. The presented release profiles clearly reflect the favorable extended-release properties of amylodextrin tablets. Tablets compacted from binary powder mixtures of amylodextrin and drug demonstrate sustained and almost-constant drug release.

The porosities of amylodextrin tablets of 300 mg, containing 30% of theophylline monohydrate, were determined at three compaction forces. Increasing compaction forces resulted in strongly decreasing porosities. A porosity of 16.4% was found for the tablets compacted at 5 kN, but very low porosities, 6.6 and 3.3%, for the tablets compacted at 10 and 15 kN, respectively. It is noted that the high-porosity tablets demonstrate decreasing drug release rates with time, changing into almost-constant drug release for the low-porosity tablets. Table II depicts the porosities of 300-mg amylodextrin tablets, compacted at 10 kN, with various drug loadings. Tablets compacted of either pure amylodextrin or pure theophylline monohydrate both show a low porosity, about 7.7%. Tablets compacted from the binary blends show even lower porosities, ranging from approximately 6 to 7%. Both the amylodextrin and the theophylline monohydrate powders are well compressible. Moreover, it is concluded that drug load has only a minor impact on tablet porosity.

To examine the influence of the thickness of the tablets on drug release, tablets were compacted with a drug load of 30%, having weights of 300, 150, and 100 mg, respectively, corresponding to tablet thicknesses of 3.4, 1.7, and 1.1 mm, respectively. Figure 4 illustrates the release profiles obtained for the 300-, 150-, and 100-mg tablets. Expressed as a percentage of the total drug present in the tablet, the results demonstrate higher release rates for the thinner tablets. Next to the initial burst for all tablets, it is noted that the thinner tablets show a change in release profile from constant release to decreasing drug release rates with time, over a period of 8 hr. The period of constant release is shorter the thinner the tablets. This behavior is explained by a change in release mechanism from a (constant) solvent penetration rate-controlled release to a diffusion rate-controlled release as soon as the tablet is completely wetted, which happens sooner with thinner tablets (23). Both the percentage of drug released with the time and the shape of the release profile can thus be adjusted by changing the geometry of the tablet.

The influence of the presence of a highly soluble excipient in theophylline monohydrate-containing amylodextrin tablets was investigated by the incorporation of lactose. Figure 5 illustrates the drug release profiles obtained for tablets, compacted at 15 kN, containing 30% theophylline monohydrate and 0, 10, and 20% lactose monohydrate, respectively. Incorporation of lactose monohydrate demonstrates slightly increasing drug dissolution rates with increasing lactose contents. The porosities of these tablets are 3.3% for tablets

Table II. Porosities (%) of 300-mg Amylodextrin Tablets, Compacted at 10 kN, with Various Percentages of Theophylline Monohydrate Incorporated

Drug load (%)	Porosity (%)
0	7.8
10	6.9
20	6.1
30	6.6
50	6.2
75	6.1
100	7.7

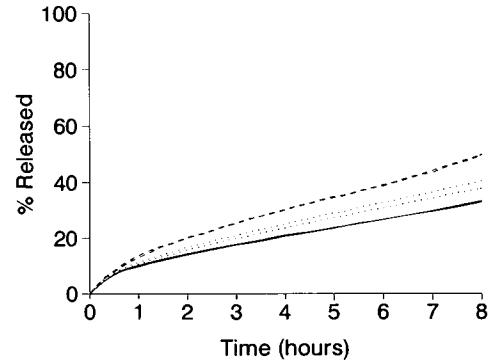

Fig. 5. Drug release profiles from 300-mg amylodextrin tablets containing 30% theophylline monohydrate and various percentages of lactose monohydrate, compacted at 15 kN: (——) 0%, (····) 10%, and (----) 20% lactose monohydrate.

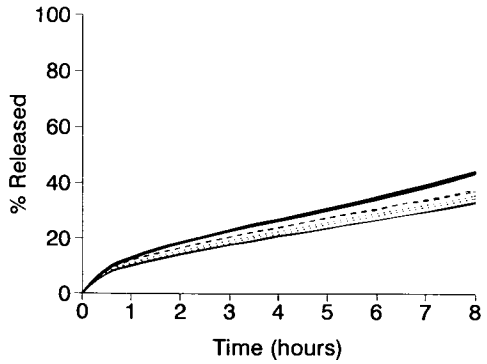

Fig. 6. Drug release profiles from 300-mg amylodextrin tablets containing 30% theophylline monohydrate and various percentages of talc, compacted at 15 kN: (——) 0%, (····) 10%, (----) 20%, and (——) 30% talc.

containing no or 10% lactose and 3.8% for tablets containing 20% lactose. Incorporation of up to 20% lactose in theophylline monohydrate-containing amylodextrin tablets therefore hardly changes the tablet porosity. The slightly increasing release rates with increasing lactose loads may be attributed to the faster water penetration into the tablets, caused by the hydrophilicity of the incorporated lactose monohydrate.

The impact of the presence of an insoluble pharmaceutical excipient on the drug release from amylodextrin tablets was studied by incorporation of talc. Talc is insoluble and hydrophobic, implying a poor wettability. The drug release profiles from 300-mg amylodextrin tablets containing 30% theophylline monohydrate and various percentages of talc are shown in Fig. 6. The tablets contained 0, 10, 20, and 30% talc, respectively, and were compacted at 15 kN. The profiles show very small increases in release rates with increasing talc loads. Porosities of talc containing amylodextrin tablets were also determined. Porosities of 3.3, 6.6, 9.5, and 11.6% were found for the tablets containing 0, 10, 20, and 30% talc, respectively. Whereas lactose monohydrate hardly changed the porosity of the tablets, incorporation of talc resulted in increasing porosities of the theophylline monohydrate-containing amylodextrin tablets. These increased tablet porosities could have increased drug release rates, but the hydrophobic character of talc inhibits liquid penetration of the pores and thus dissolution of drug from the tablet. Hence, the effect of increased tablet porosity on incorporation of talc is suppressed by poor wetting of the system.

Incorporation of either lactose monohydrate or talc in theophylline monohydrate-containing amylodextrin tablets emphasizes, next to their solubility and wettability properties, the importance of tablet porosity on drug release.

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