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# Preparation, characterization and pharmaceutical application of linear dextrins: IV. Drug release from capsules and tablets containing amylodextrin

G.H.P. Te Wierik, A.C. Eissens and C.F. Lerk

*Department of Pharmaceutical Technology and Biopharmacy, University of Groningen, Groningen (The Netherlands)*

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## Summary

Linear dextrin (amylodextrin) and its soluble fraction were investigated for their suitability to enhance diazepam release from capsules and tablets. Drug release was analyzed in the USP XXI paddle apparatus and performed in phosphate buffer pH 6.8, with and without α-amylase, and in 0.1 N HCl solution. Diazepam release from capsules was slightly increased on application of amylodextrin, either as a filler in a physical mixture or as a carrier for solid dispersion of the drug, as compared to the release from capsules containing drug only. The limited increase in drug dissolution is caused by the limited solubility of amylodextrin. Application of the soluble fraction of amylodextrin therefore showed faster drug release. In contrast, the limited solubility and non-disintegrating behaviour of amylodextrin appeared to be extremely suitable properties to apply this excipient in the formulation of programmed release systems.

## Introduction

Among the variety of methods to improve the dissolution rate of poorly soluble drugs from solid dosage forms, the use of cyclodextrins is a relatively new possibility. During the past two decades, several papers have been published on improved release of poorly soluble drugs from solid dosage forms containing drug-cyclodextrin complexes (Frömming, 1973; Otagiri et al., 1983; Duchêne and Wouessidjewe, 1990; Szejtli, 1991). Moreover, Nakai (1986) reported improved drug release from solid dispersions of many drugs with α-cyclodextrin, the latter having a cavity which is too small to form complexes with most drugs. During the past 10 years, interest has been increasingly focused on cyclodextrin derivatives. In particular, the methylated cyclodextrins (Uekama, 1985) and hydroxypropyl-β-cyclodextrin (Yoshida et al., 1988) appear to possess promising properties for improving drug release. In contrast, the ethylated cyclodextrins are used for sustained release preparations due to their hydrophobic nature (Uekama et al., 1987).

In contrast to the cyclodextrins, linear dextrins are not known in pharmaceutical practice or liter-

*Correspondence to:* C.F. Lerk, Department of Pharmaceutical Technology and Biopharmacy, University of Groningen, Ant. Deusinglaan 1, 9713 AV Groningen, The Netherlands.

ature. The linear dextrin amylodextrin underwent partial dissolution to an extent of 18% into water at room temperature (Te Wierik et al., 1993a). Freeze-drying and both wet (with ethanol) and dry kneading of a physical mixture of diazepam with amylodextrin at elevated temperature resulted in solid dispersions (Te Wierik et al., 1993b). This paper reports a study on the application of amylodextrin in capsules and tablets as a physical mixture or solid dispersion to enhance or control drug release.

## Materials and Methods

Amylodextrin (DP = 35), prepared from waxy maize by enzymatic hydrolysis with pullulanase, was used as prepared according to the procedure described in a previous paper (Te Wierik et al., 1993a). The soluble fraction of amylodextrin (DP = 24) was isolated by shaking 150 g amylodextrin with 1.5 l water. After centrifugation, the supernatant was filtered through a 0.45 $\mu$m filter (Schleicher & Schuell, Dassel, Germany) followed by freeze-drying in a Lyolab A (Marius instrumenten, Nieuwegein, The Netherlands). The drying conditions were: temperature, $-55$°C; pressure, 0.04 mbar.

Lactose monohydrate 100 Mesh was a gift from DMV (Veghel, The Netherlands). Sodium starch glycolate (Primojel®) was supplied by Avebe (Veendam, The Netherlands). Diazepam was obtained from HPS (Alphen a/d Rijn, The Netherlands), while $\alpha$-amylase was supplied by NOVO (Bagsværd, Denmark). Empty gelatin capsules were obtained from Spruyt Hillen (Utrecht, The Netherlands). The water used throughout the study was deionized and degassed before use. All other products and reagents used were of analytical grade.

Physical mixtures were prepared by mixing in a Turbula mixer (Bachoven, Basle, Switzerland) at 90 rpm for 30 min. Solid dispersions of diazepam in amylodextrin were prepared by freeze-drying and by wet (with ethanol) kneading at elevated temperature (120°C), respectively. Both methods have been described in a previous paper (Te Wierik et al., 1993b). The formation of solid dispersions was checked by differential scanning calorimetry (DSC) and X-ray diffractometry. The former technique was carried out on a Dupont 99 Thermal Analyzer ('s-Hertogenbosch, The Netherlands) with a DSC cell 910 (sample size, 5 mg; scanning rate, 10°C per min). X-ray diffractometry was performed with a Guinier Hagg camera (Jungner instrument, Stockholm, Sweden), which generated X-rays of $\lambda = 1.5406$ Å.

All tablet and capsule formulations contained 5 mg diazepam. Sodium starch glycolate (4%) was added as a disintegrant to some tablet formulations. Tablets with a diameter of 9 mm were compacted on an instrumented hydraulic press (ESH Testing, Brierley Hill, U.K.) in a die having flat-faced punches. The compaction force was 15 kN, with a load rate of 2 kN/s. The force was applied for 0.1 s. The freeze-dried product of diazepam with amylodextrin was filled into capsules no. 0, the other products being filled into capsules no. 1.

The release profiles, expressed as percentage dissolved, of the tablets were measured in a USP XXI paddle apparatus (Rhône-Poulenc, Paris, France) at 100 rpm. Drug release from capsules was measured in the paddle apparatus at 100 rpm according to the method described by Proost (1987). Drug release studies were performed in 0.05 M phosphate buffer pH 6.8 (with or without 50 mg/l $\alpha$-amylase) and 0.1 N HCl. Drug concentrations were measured spectrophotometrically at 231 nm for tablets, 250 nm for capsules and 242 nm for release profiles in 0.1 N HCl solution, using an Ultrospec 4052 TDS apparatus (LKB, Zoetermeer, The Netherlands). All experiments were carried out in triplicate.

## Results and Discussion

Fig. 1a presents the release profiles in phosphate buffer pH 6.8 of diazepam from capsules containing drug only and different products of drug with an excipient in a molar ratio of 1:1, respectively. All release profiles demonstrate an initial delay of about 2 min, corresponding to the time required to dissolve the capsule wall. As anticipated, the extent of diazepam release from

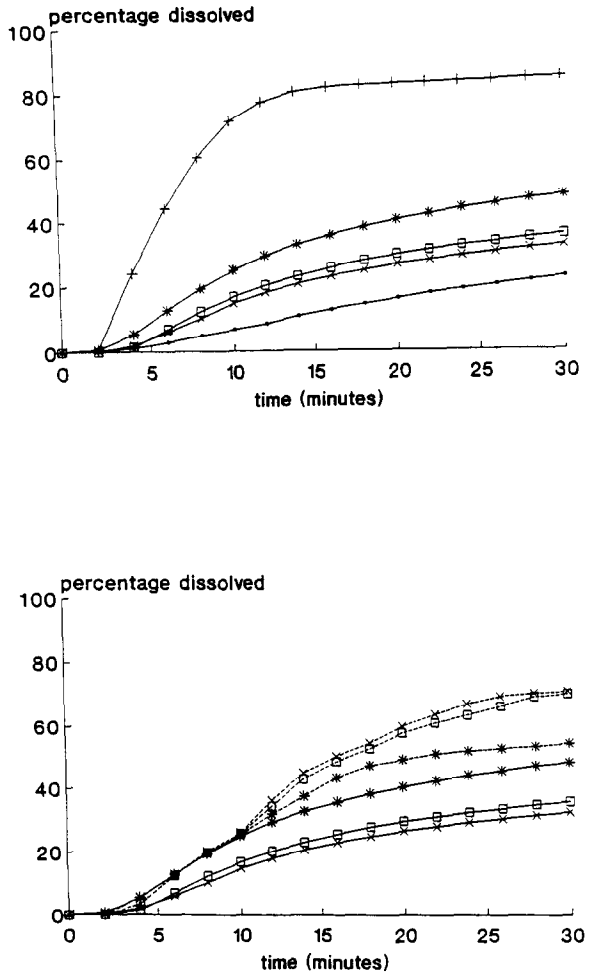


Fig. 1. (a, top) Release of diazepam (5 mg) from capsules in phosphate buffer pH 6.8. (●) Drug only, (+) physical mixture of drug with lactose, (∗) physical mixture of drug with amylodextrin (AD), (□) freeze-dried product of drug-AD, (×) kneaded product of drug-AD. (b, bottom) Release of diazepam (5 mg) from capsules in phosphate buffer pH 6.8 without (continuous line) and with α-amylase in solution (dashed line), respectively. (∗) Physical mixture of drug with amylodextrin (AD), (□) freeze-dried product of drug-AD, (×) kneaded product of drug-AD

capsules containing drug only was found to be low due to the hydrophobic nature of the drug. The capsules containing a physical mixture of diazepam with lactose showed very rapid drug release up to about 80% within 15 min, as expected from the hydrophilic nature and considerable aqueous solubility of the excipient. Much slower drug release was obtained for the capsules containing a physical mixture of diazepam with amylodextrin, resulting in only 40% release within 30 min. This result is explained by the rather hydrophilic nature but limited solubility of the excipient amylodextrin. Even poorer release profiles were shown by the capsules containing the freeze-dried or kneaded product of drug with amylodextrin. As reported earlier (Te Wierik et al., 1993b), both the processes of freeze-drying and kneading at elevated temperature of diazepam with amylodextrin led to a product that was identified as a solid dispersion. Incorporation of a drug in amylodextrin as a solid dispersion implies that the excipient must dissolve before dispersed drug is accessible for dissolution. Since amylodextrin demonstrated partial dissolution into water (Te Wierik et al., 1993a), release of diazepam from the solid dispersions with amylodextrin was indeed expected to be worse than the release from capsules filled with a physical mixture of the drug with amylodextrin. In the latter case, dissolution of drug is not dependent on dissolution of the soluble fraction of the amylodextrin. The high intrinsic solubility of β-cyclodextrin, as reported in the literature (Bootsma et al., 1989), explains the superior release of diazepam from capsules containing the drug as a complex with β-cyclodextrin.

Since starch and starch-related compounds are hydrolysed by amylases, which are present in the intestine, capsules containing amylodextrin as excipient are expected to show greater drug release in a dissolution medium containing the enzyme α-amylase. Therefore, the release rates of diazepam from capsules containing the drug and amylodextrin as a physical mixture and freeze-dried and kneaded product, respectively, all in a molar ratio of 1 : 1, were subsequently determined in phosphate buffer pH 6.8 containing α-amylase. The release profiles are presented in Fig. 1b. For purposes of comparison, Fig. 1b also depicts the release patterns from the same capsule formulations analyzed in phosphate buffer pH 6.8 containing no α-amylase. For the capsules containing a physical mixture of drug with amylodextrin, the plot shows only a slight improvement in drug release on addition of α-amylase to the dissolu-

tion medium. The capsules containing either the freeze-dried or kneaded product, exhibiting almost equal release profiles, both demonstrated markedly increased release rates when evaluated in the medium containing $\alpha$-amylase. This result confirms the hydrolytic action exerted on amylodextrin by $\alpha$-amylase, giving faster dissolution of amylodextrin with subsequent more rapid release of the drug from the solid dispersion with amylodextrin. However, drug release remains inferior as compared with that for the capsules filled with a physical mixture of diazepam with very rapidly dissolving lactose (Fig. 1a).

The soluble fraction of amylodextrin, consisting of shorter chain molecules (Te Wierik et al., 1993a), was subsequently investigated with respect to its suitability as a release-enhancing excipient in capsules. Fig. 2 presents the release profiles in phosphate buffer pH 6.8 of diazepam from capsules containing drug and the soluble fraction of amylodextrin in a molar ratio of 1:1, as a physical mixture or as a solid dispersion. The latter was prepared by wet kneading at elevated temperature. To facilitate comparison, Fig. 2 includes the drug release profiles as obtained from the capsules containing the same formulations but produced with the partially water soluble amylodextrin. As expected from the increased aqueous solubility of the excipient, the capsules

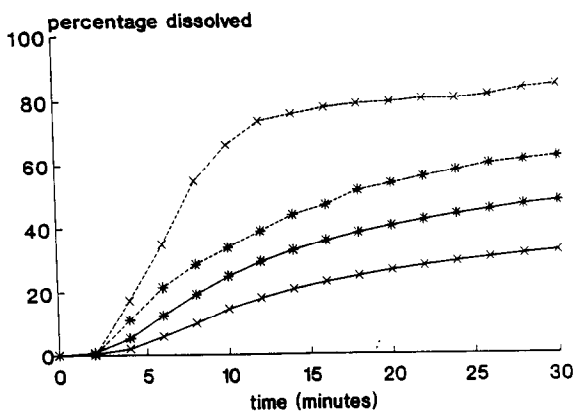


Fig. 2. Release of diazepam (5 mg) from capsules containing the drug as product with amylodextrin (AD) (continuous line) or with the soluble fraction of AD (dashed line), in phosphate buffer pH 6.8. (*) Physical mixture of drug with AD, (×) kneaded product of drug-AD.

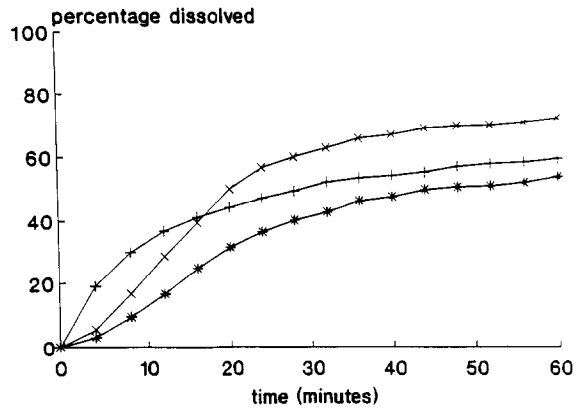


Fig. 3. Release of diazepam (5 mg) from tablets in phosphate buffer pH 6.8. (+) Physical mixture of drug with lactose, (*) physical mixture of drug with the soluble fraction of amylodextrin (soluble AD), (×) kneaded product of drug-soluble AD.

containing a physical mixture of diazepam with the soluble fraction of amylodextrin showed improved drug release. A very rapid rate of dissolution was demonstrated by the capsules filled with the kneaded product of drug with the soluble fraction of amylodextrin.

Fig. 3 presents the release profiles of diazepam in phosphate buffer pH 6.8 from tablets compressed from a physical mixture of the drug with lactose or with the soluble fraction of amylodextrin and from a kneaded product of the drug with the soluble fraction of amylodextrin, respectively, all in a molar ratio of 1:1. Since neither amylodextrin nor lactose possesses disintegrating properties, resulting in poor drug release, 4% sodium starch glycolate was incorporated in all tablet formulations as a super-disintegrant. The tablet formulations containing the soluble fraction of amylodextrin, either as a physical mixture or as a kneaded product, both showed a delayed initial drug release. This feature is attributed to the process of tablet disintegration being inhibited. In spite of the presence of a super-disintegrant, these tablets disintegrated gradually over a period of about 10 min, while those containing lactose and super-disintegrant as excipients disintegrated immediately. Indeed, the latter tablets showed the fastest initial drug release but a lower final total amount dissolved after 60 min, as com-

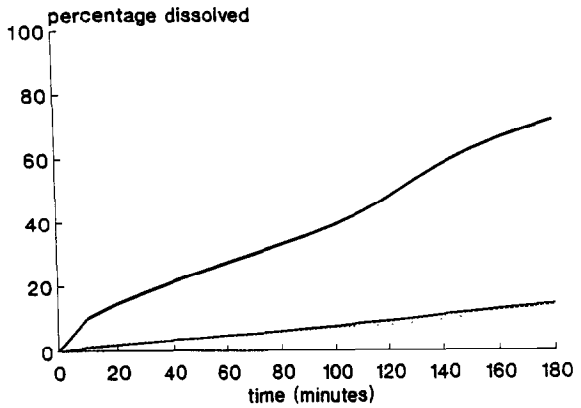


Fig. 4. Release of diazepam (5 mg) from tablets containing the drug as product with amylodextrin, determined in different dissolution media: (continuous line) physical mixture and (dotted line) kneaded product in phosphate buffer pH 6.8 without $\alpha$-amylase; physical mixture in (dashed line) buffer pH 6.8 with $\alpha$-amylase and in (bold line) 0.1 N HCl.

pared with those compressed from the kneaded product of diazepam with soluble fraction of amylodextrin, formulated with super-disintegrant. As evaluated from the moment of complete disintegration, the greatest rate of drug release is displayed by the tablets compressed from the kneaded product.

The expected characteristics of non-disintegration and limited solubility of amylodextrin were the factors motivating us to determine whether this product would be suitable as an excipient for the formulation of programmed release systems. A physical mixture and a solid dispersion, prepared by wet kneading at elevated temperature, respectively, of diazepam with amylodextrin, both in a molar ratio of 1:1, were compressed into tablets and evaluated with respect to drug release in phosphate buffer pH 6.8. The tablets indeed exhibited no disintegration and both exhibited not only an identical and very low release profile but also a remarkably constant dissolution rate (Fig. 4). Following the observation of the increased dissolution rate of diazepam from capsules containing amylodextrin when examined in a medium containing $\alpha$-amylase, the behaviour of tablets compressed from the physical mixture was also analyzed in phosphate buffer pH 6.8 containing $\alpha$-amylase. The recorded profile showed no difference from that obtained in the dissolution medium without $\alpha$-amylase. From this result it is concluded that the non-disintegrating tablet is not attacked by the enzyme. However, it is suggested that disintegration with correspondingly changing release profiles can be adjusted by incorporation of $\alpha$-amylase in the solid dosage form.

In 0.1 N HCl solution the tablets again did not disintegrate but displayed enhanced drug release as compared to the dissolution rate in buffer pH 6.8. Taking into account the fact that diazepam is readily soluble in acidic media, the release profile characteristic of the tablets can still be assessed as being retarded. It is therefore expected that drug-amylodextrin tablets will disintegrate neither in the stomach nor in the intestine, resulting in controlled drug delivery.

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