Preparation, Characterization, and Pharmaceutical Application of Linear Dextrins. III. Drug Release from Fatty Suppository Bases Containing Amylodextrin

Gerrit H. P. Te Wierik,[1] Anko C. Eissens,[1] and Coenraad F. Lerk[1,2]

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Drug release from fatty suppository bases containing a solid dispersion of diazepam with amylodextrin or a complex of prednisolone with amylodextrin was analyzed in a flow-through model. Being present as a suspension in the fatty base, particles of complex or solid dispersion are transported to the lipid–water interface by sedimentation. After entering the aqueous phase they partially dissolve. The suppositories showed increased drug release compared with the corresponding suppositories containing drug only. Because of the partial solubility of amylodextrin, drug release was lower than the release from drug–cyclodextrin complexes. Use of the soluble fraction of amylodextrin for both the solid dispersion and the complex further enhanced drug release, but it was still below that of drug–cyclodextrin complexes.

KEY WORDS: amylodextrin; complex; release mechanism; solid dispersion; solubility; suppository.

INTRODUCTION

Dextrins are oligosaccharides (1) with a linear, branched, or cyclic structure. The latter, called cyclodextrins, are able to form hydrophilic inclusion complexes with many lipophilic drugs (2). Frijlink *et al.* (3) investigated drug release from fatty suppositories containing drug–cyclodextrin complexes. Upon melting of the fatty base, the lipid-insoluble complex particles are transported to the lipid–water interface by sedimentation and enter the dissolution medium, where they dissolve. The dissolved complex partially dissociates. Drugs with a high octanol/water (o/w) partition coefficient diffuse back into the lipid layer, which lowers drug release. This effect was pronounced for complexes of low stability, and it was suppressed by complexation with hydroxypropyl-β-cyclodextrin, yielding complexes with increased drug dissolution and stability constants (4,5).

In analogy to cyclodextrins, the linear dextrin amylodextrin was expected to influence drug release from suppositories. A previous study (6) showed the formation of an inclusion complex with prednisolone on freeze-drying and of a solid dispersion of diazepam on kneading at elevated temperature. This paper reports the effect of amylodextrin in suppositories on diazepam and prednisolone release.

[1] Department of Pharmaceutical Technology and Biopharmacy, University of Groningen, Ant. Deusinglaan 1, 9713 AV Groningen, The Netherlands.

[2] To whom correspondence should be addressed.

MATERIALS AND METHODS

Chemicals

Amylodextrin (DP = 35), prepared from waxy maize by enzymatic hydrolysis with pullulanase, was used and prepared as described previously (7). The soluble fraction of amylodextrin (DP = 24) was isolated by shaking 150 g amylodextrin with 1.5 L water. After centrifugation, the supernatant was filtrated through a 0.45-μm filter (Schleicher & Schuell, Dassel, Germany) followed by freeze-drying in a Lyolab A (Marius Instrumenten, Nieuwegein, The Netherlands). The drying conditions were a temperature of −55°C and a pressure of 0.04 mbar.

Diazepam was obtained from HPS (Alphen a/d Rijn, The Netherlands), while prednisolone was supplied by ACF-Chemiefarma (Maarssen, The Netherlands). Witepsol H15 was obtained from Centrachemie (Etten-Leur, The Netherlands). The water used throughout the study was deionized and degassed before use. All other products and reagents used were of analytical grade.

Preparation of Complexes and Solid Dispersions

Solid dispersions of diazepam with amylodextrin at a molar ratio of 1:1 were prepared by kneading with ethanol at elevated temperature (120°C). Complexes of prednisolone with amylodextrin at a molar ratio of 1:1 were prepared by freeze-drying. Both methods have been described in a previous paper (6). The formation of solid dispersions and complexes was confirmed 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/min). X-ray diffractometry was performed with a Guinier Hagg camera (Jungner Instrument, Stockholm, Sweden), which generated X rays with $\lambda = 1.5406$ Å.

Preparation of Suppositories

The powders, all having a particle size of <180 μm, were mixed with molten Witepsol H15 and poured into plastic molds (3 mL). All suppositories were stored for at least 24 hr. Four suppositories were prepared, containing

- 210 mg diazepam–amylodextrin solid dispersion (=10 mg diazepam),
- 147 mg diazepam–amylodextrin (soluble fraction) solid dispersion (=10 mg diazepam),
- 84 mg prednisolone–amylodextrin complex (=5 mg prednisolone), and
- 59 mg prednisolone–amylodextrin (soluble fraction) complex (=5 mg prednisolone)

Solubility of Drug Products in the Suppository Base

To determine the amount of drug dissolved in the lipid suppository, the suppositories were melted (40°C) and subsequently filtered over a 0.2-μm filter. To 500 mg filtered base, 5.0 mL methanol (40°C) was added. After cooling of the methanolic solution, 2.0 mL of this liquid was evaporated. The residue was dissolved in 5.0 mL of distilled water. In the aqueous solution the amount of drug was determined

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spectrophotometrically at 231 nm for diazepam and at 247 nm for prednisolone.

Suppository Release Study

To determine the release rates of the drugs from the suppositories, expressed as percentage dissolved, a flow-through model was used, as described previously by Frijlink *et al.* (3). The release vessel contained 60 mL 0.05 *M* phosphate buffer, pH 7.4. Release rates were determined by measuring drug concentrations in the phosphate buffer, leaving the vessel, spectrophotometrically at 231 nm for diazepam and at 247 nm for prednisolone. The amylodextrin concentrations were determined spectrophotometrically at 625 nm after reaction with anthrone (8). All experiments were carried out in triplicate.

RESULTS AND DISCUSSION

Release of Diazepam from Suppositories with Amylodextrin

Figure 1 illustrates the release profiles, expressed as percentage dissolved, of diazepam from different suppositories. Because of the lipophilic nature of diazepam (o/w partition coefficient, 473), the suppositories containing drug only showed almost no diazepam release. An improved drug release in 180 min, of about 7% of the total amount present in the suppositories, was demonstrated by the suppositories containing the equimolar solid dispersion of drug with amylodextrin. Further, amylodextrin release from these suppositories (18%) was higher than diazepam release.

As expected from the release mechanism of drug–cyclodextrin complexes (3), the hydrophilic solid dispersion was found to be present in the suppository as a suspension of solid particles, which moved within 20 min to the lipid–water interface by sedimentation. On entering the aqueous phase the amylodextrin is assumed to dissolve up to the previously reported constant percentage of 18% (7), which indeed agrees with the release profile of amylodextrin (Fig. 1). However, because of a stoichiometry of the solid dispersion of 1:1, the amount dissolved, ≈7%, for diazepam appears too low. This discrepancy is explained by back diffusion of the drug into the fatty base (3). Moreover, the solid dispersion could have been decomposed during preparation of the suppositories, resulting in dissolution of free drug molecules in the lipid base. The latter suggestion was confirmed by the observation that 15% of the diazepam was dissolved in the lipid base.

The release of diazepam from the suppositories containing a solid dispersion in amylodextrin was lower than that reported for complexes with γ-cyclodextrin (3) and hydroxypropyl-β-cyclodextrin (5) (Fig. 1). Amylodextrin thus seems to be less suitable as excipient to enhance the release of poorly water-soluble drugs with a high o/w partition coefficient, such as diazepam, from fatty suppositories. Back diffusion was expected to be insignificant for drugs with a low o/w partition coefficient, such as prednisolone (o/w partition coefficient, 39).

Release of Prednisolone from Suppositories with Amylodextrin

Figure 2 illustrates the release profiles, expressed as percentage dissolved, of prednisolone from different suppositories. Incorporation of pure drug showed a prednisolone release from the suppositories of ≈30% in 180 min. The release of both prednisolone and amylodextrin from suppositories containing the equimolar drug–amylodextrin complex was ≈40%. Being insoluble in the fatty base, both prednisolone and its complex with amylodextrin were released from the molten suppository base by the sedimentation and dissolution mechanism, as described for diazepam. Sedimentation again appeared complete within 20 min. The increased drug dissolution rate from the suppositories containing the complex is explained by its higher solubility. The almost-equal release profiles for prednisolone and amylodextrin from the suppositories containing the complex endorse the insignificance of back diffusion for a drug with a low o/w partition coefficient. Complexes of amylodextrin with large molecules proved to have a helical conformation with seven glucose units per turn, exhibiting partial dissolution of 35% in water (7). Moreover, the conformation of the complex of amylodextrin with prednisolone was also found to be a helix

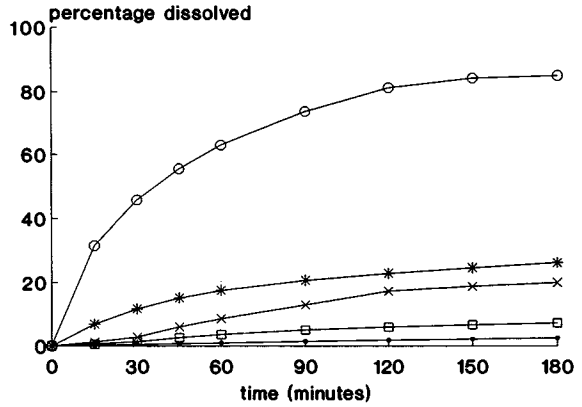

Fig. 1. Release of diazepam and of amylodextrin, expressed as percentage dissolved, from fatty suppositories containing 10 mg diazepam. (●) Diazepam release from suppositories containing drug only; (□) diazepam release and (x) amylodextrin release from suppositories containing a solid dispersion of diazepam in amylodextrin; diazepam release from suppositories containing complex with (*) γ-CD (3) and (○) HPBCD (5), respectively.

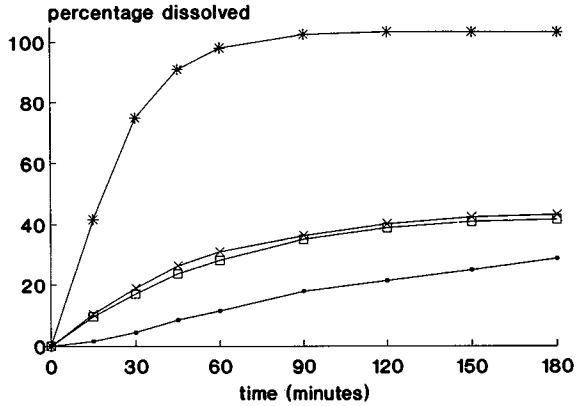

Fig. 2. Release of prednisolone and of amylodextrin, expressed as percentage dissolved, from fatty suppositories containing 5 mg prednisolone. (●) Prednisolone release from suppositories containing drug only; (□) prednisolone and (x) amylodextrin release from suppositories containing a complex of prednisolone with amylodextrin; (*) prednisolone release from suppositories containing complex with β-CD (3).

with seven glucose units per turn (6). Consequently, the prednisolone–amylodextrin complex was expected to show 35% amylodextrin dissolution, which agrees with the observation of ≈40% dissolution of amylodextrin from the suppositories containing the complex (Fig. 2).

Drug release from the suppositories containing prednisolone–amylodextrin complex was lower than that reported for the complex with β-cyclodextrin (3) (Fig. 2). This is ascribed to the limited aqueous solubility of amylodextrin. Therefore, the soluble fraction of amylodextrin, consisting of shorter-chain molecules (7), was subsequently tested for its suitability to enhance drug release from fatty suppositories.

Application of the Soluble Fraction of Amylodextrin in Fatty Suppositories

As expected, the equimolar solid dispersion of diazepam with the soluble fraction of amylodextrin was found to be present in the fatty suppositories as a suspension of particles, inducing the earlier-described release mechanism. The release profiles indeed show an amylodextrin dissolution of 100% within 60 min, but a diazepam release of only 10% within 180 min (Fig. 3). The latter is again attributed to back diffusion (3) and to decomposition of the solid dispersion, with subsequent dissolution of diazepam molecules into the lipid base during preparation of the suppositories. Indeed, ≈35% diazepam was recovered in the fatty base. Diazepam release from suppositories containing the drug as a solid dispersion in the soluble fraction of amylodextrin was again inferior to that reported for the complexes with γ-cyclodextrin (γ-CD) (3) and hydroxypropyl-β-cyclodextrin (HPBCD) (5) (Fig. 3).

Application of the soluble fraction of amylodextrin as excipient in fatty suppositories was also evaluated for prednisolone. In contrast to the expectation of 100% release, the suppositories containing the complex demonstrated an amylodextrin release of only 80% (Fig. 4). This incomplete release may be caused by the large bulk volume of the freeze-dried drug–amylodextrin complex, which resulted in poor spreading of the molten suppository and incomplete sedimentation of the solid particles. Further, the drug demonstrated a dissolution profile which significantly differs from the amylodextrin release (Fig. 4). This observation, which was not expected from the stoichiometry (1:1) of the complex, might be due to low stability of the prednisolone–amylodextrin complex, as reported for starch–iodine and amylose–*n*-butanol complexes (9). The dissolved complex might dissociate, possibly resulting in a supersaturated solution of prednisolone near the dissolving solid. Consequently, drug molecules might partially precipitate. Drug release from suppositories containing drug–amylodextrin (soluble fraction) complex was still inferior to the release profile obtained for β-cyclodextrin complex (3) (Fig. 4).

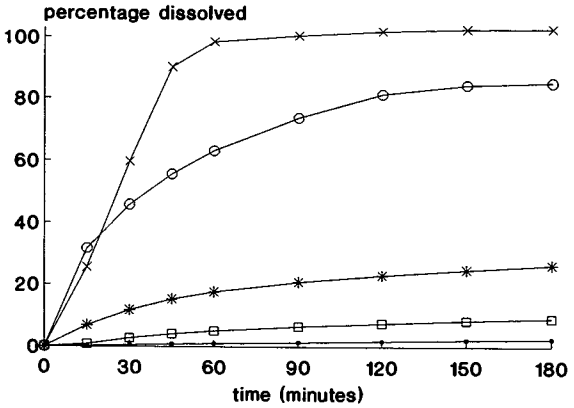

Fig. 3. Release of diazepam and of amylodextrin, expressed as percentage dissolved, from fatty suppositories containing 10 mg diazepam. The soluble fraction of amylodextrin was used. For symbols, see the legend to Fig. 1.

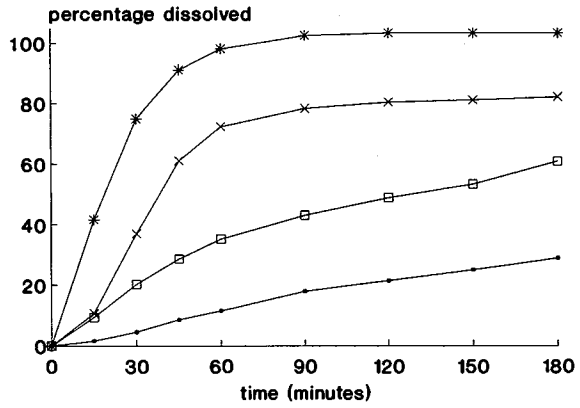

Fig. 4. Release of prednisolone and of amylodextrin, expressed as percentage dissolved, from fatty suppositories containing 5 mg prednisolone. The soluble fraction of amylodextrin was used. For symbols, see the legend to Fig. 2.

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