Preparation, Characterization, and Pharmaceutical Application of Linear Dextrins. II. Complexation and Dispersion of Drugs with Amylodextrin by Freeze-Drying and Kneading

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The ability of amylodextrin (a linear dextrin) to act as a complexing agent or as a carrier for solid dispersion was evaluated. Blends of amylodextrin with diazepam or prednisolone were freeze-dried and kneaded at elevated temperatures, respectively. The products were analyzed by DSC, X-ray diffractometry, and FTIR spectroscopy. Complex formation with amylodextrin by freeze-drying was found not to occur for diazepam but for prednisolone at a molar ratio of 1 to 1. The freeze-dried product of diazepam with amylodextrin proved to be a solid dispersion. Solid dispersions were formed by both wet (with ethanol) and dry kneading at elevated temperatures of low-melting drugs such as lidocain, diazepam, and methyl-PABA with amylodextrin. No solid dispersions were obtained for high-melting drugs such as prednisolone and salicylic acid. The results point to the formation of solid dispersions by a melting mechanism during the process of kneading at elevated temperatures of low-melting drugs with amylodextrin.

KEY WORDS: amylodextrin; complexation; solid dispersion; freeze-drying; kneading; structural characterization.

INTRODUCTION

Among the methods for improving the release rate of poorly soluble drugs from solid dosage forms (1), complexation of lipophilic drugs by cyclodextrins resulting in hydrophilic complexes is a relatively new possibility (2–4). On the analogy of cyclodextrins, the linear dextrin amylodextrin is expected to be able to form inclusion complexes with drugs. This implies that these complexes can be applied in solid dosage forms to enhance or control drug release. In the preceding paper it was demonstrated that amylodextrin is able to form inclusion complexes of the starch-iodine type with different organic molecules (5). Because these complexes tend to dissociate in water with subsequent precipitation (retrogradation), they may be called metastable amylodextrins. Powder X-ray diffraction studies confirmed that the conformation of amylodextrin is a double helix. Each strand has six glucose units per turn repeating in 21.0 Å. The conformation of all metastable amylodextrins proved to be a single helix with a reduced distance between two turns (8.0 Å) and, depending upon the size of the enclosed molecule, six or seven glucose units per turn. It is consequently assumed that inclusion complexes of drug with amylodextrin will also have a helical conformation with a reduced distance between two turns. The number of glucose units per turn may depend on the structure of the drug.

Amylodextrin had not yet been employed for its capacity to form inclusion complexes with drugs. The present study was therefore performed to explore the potential of amylodextrin to complex or disperse model drugs by freeze-drying or kneading at elevated temperatures, respectively.

MATERIALS AND METHODS

Chemicals

Amylodextrin (DP = 35), prepared from waxy maize by enzymatic hydrolyzation with pullulanase, metastable amylodextrins, prepared with 1-octanol and cyclohexanol, respectively, as complexing agent, and metastable amylose, prepared with 2-methyl-1-butanol as complexing agent, were used as prepared according to the procedure described in the preceding paper (5). Amylose V was obtained from Avebe (Veendam, The Netherlands). Lactose.1aq 100 Mesh was a gift from DMV (Veghel, The Netherlands). Prednisolone, methyl-*p*-aminobenzoate (methyl-PABA), and salicylic acid were supplied by ACF-chemiefarma (Maarssen, The Netherlands), while diazepam and lidocaine were obtained from HPS (Alphen a/d Rijn, The Netherlands). All other products and reagents used were of analytical grade.

Preparation of Physical Mixtures and Freeze-Dried Products

Physical mixtures were prepared by mixing in a Turbula mixer (Bachoven, Basel, Switzerland) at 90 rpm during 15 min.

For the preparation of equimolar freeze-dried products 5 drops of ethanol was added to 10 mg diazepam or 20 mg prednisolone, followed by dissolution in 50 mL water. Two hundred milligrams (for diazepam) or 316 mg (for prednisolone) amylodextrin was subsequently added, and the mixture was heated to 85°C to dissolve the amylodextrin. The resulting solution was rapidly cooled in fluid nitrogen, followed by freeze-drying in a Lyolab A (Marius instrumenten, Nieuwegein, The Netherlands). The drying conditions were as follows: temperature, −55°C; and pressure, 0.04 mbar. All other freeze-dried products were prepared according to a similar procedure.

Preparation of Products by Kneading

The drug was dissolved in a beaker in a quantity of ethanol sufficient to dissolve the drug completely. The required amount of solid amylodextrin or lactose was subsequently added, and the compounds were blended by means of a magnetic stirring apparatus during 1 min. The blend was subsequently stirred and heated until the ethanol was completely evaporated. During the process a bulk temperature of about 120°C was measured.

Next to this preparation a dry kneading method was

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tested: the above-described method was carried out without the use of ethanol. The solid drug and solid amylodextrin were simultaneously blended and heated by a magnetic stirring apparatus during about 1 hr. A bulk temperature of about 120°C was measured.

Characterization of Products

Complex formation was tested by differential scanning calorimetry (DSC), X-ray diffractometry, and Fourier transform infrared spectroscopy (FTIR). The DSC diagrams were made on a Dupont 99 thermal analyzer ('s-Hertogenbosch, The Netherlands) with a DSC cell 910 (sample size, 5 mg; scanning rate, 10°C/min). A Guinier Hagg camera (XDC-700, Jungner Instrument, Stockholm, Sweden) generated X-rays with a wavelength of 1.5406 Å, which were used for powder diffractometry.

FTIR spectroscopy was carried out as transmission spectroscopy on a Bruker 113v FTIR, operating at 2-cm^{-1} resolution using a TGS detector. The number of scans was 128. The apodization function was Happ Genzel and the zero filling factor was 2. KBr was used as matrix diluter in all measurements.

RESULTS AND DISCUSSION

Freeze-drying of Diazepam and Prednisolone with Amylodextrin

Figure 1 presents the DSC curves of different products of diazepam (mp 128°C) with amylodextrin or lactose. The melting peak of the drug shown by the physical mixture with amylodextrin and by the freeze-dried product with the noncomplexing agent lactose is absent in the plot of the freeze-dried sample with amylodextrin. This indicates that the diazepam molecules may be dispersed throughout a matrix of amylodextrin molecules or enclosed by molecules of amylodextrin, resulting in an inclusion complex of the starch-iodine type. One mole of amylodextrin seems unable to complex or disperse more than 1 mol of diazepam, as supported by the melting peak of the drug shown by the DSC plot of the freeze-dried product of 2 mol drug on 1 mol amylodextrin. Similar results were obtained for the four corresponding products of prednisolone (mp 240°C). This implies, likewise, that prednisolone is also complexed or dispersed by amylodextrin in the equimolar freeze-dried product.

It must, however, be realized that the absence of the melting peak of a substance in the DSC curve does not necessarily imply that there is no free substance present. Moreover, from DSC it cannot be concluded whether a solid dispersion or an inclusion complex has been formed. Therefore, X-ray analysis was performed as a second technique to investigate the products. As expected from the DSC plots, the diffractograms of the equimolar freeze-dried products of both drugs with amylodextrin do not show the diffraction pattern of the drug (Table I). This pattern is present in the diffractograms of the corresponding physical mixtures. This confirms the assumption that freeze-drying results in inclusion or solid dispersion of both drugs by amylodextrin. In the preceding paper (5) it was demonstrated that complexation of amylodextrin with organic molecules, resulting in metastable amylodextrins, reduces the distance between two

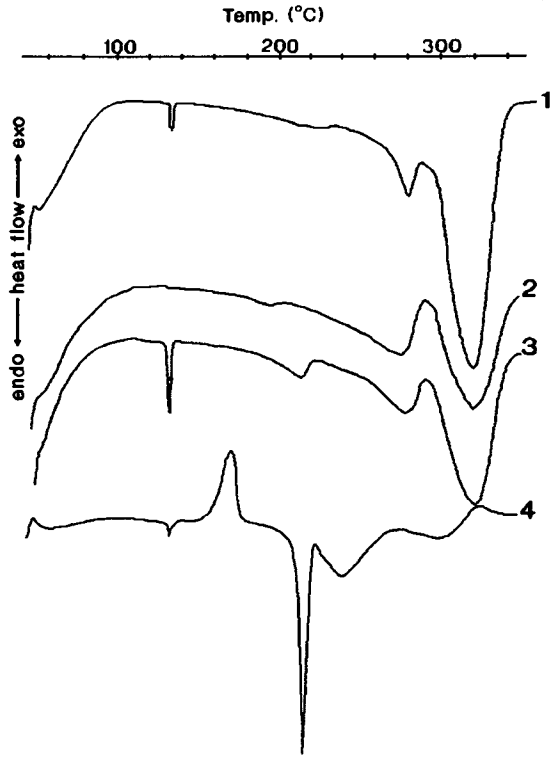

Fig. 1. DSC curves of diazepam–amylodextrin and diazepam–lactose products. (1) Physical mixture of drug with amylodextrin (AD) at a molar ratio of 1:1; (2) freeze-dried product of drug-AD (1:1); (3) freeze-dried product of drug-AD (2:1); (4) freeze-dried product of drug with lactose (1:1).

turns of the amylodextrin helix. The differences in conformation between amylodextrin and the metastable amylodextrins are characterized by different X-ray diffractograms (Table I). The freeze-dried products and the physical mixture of diazepam with amylodextrin showed equal diffraction bands. Therefore, no complex was obtained but, rather, a solid dispersion of diazepam in amylodextrin.

The corresponding products of prednisolone did not show equal patterns. Comparison with the data found for amylodextrin and the metastable amylodextrins showed a similar diffractogram for the freeze-dried product and metastable amylodextrin prepared with cyclohexanol. This result points to complex formation of prednisolone on freeze-drying with amylodextrin. Knowing that the conformation of this metastable amylodextrin is a helix with seven glucose units per turn (5), it is concluded that the freeze-dried prednisolone–amylodextrin complex is also a helix with seven glucose units per turn.

The different affinities of the two drugs tested for amylodextrin agree with the different complex constants as found for these drugs with β-cyclodextrin: 179 M^{-1} for diazepam (6) and 4000 M^{-1} for prednisolone (7).

Comparison of the FTIR spectrum of the physical mixture of diazepam and amylodextrin (Fig. 2a) with the spectrum of the freeze-dried product (Fig. 2b) shows a peak at 1684 cm^{-1} in the former which is absent in the latter spectrum. This peak is probably shifted to a lower wavenumber, thereby being overlapped by the peak at 1653 cm^{-1}. This confirms the formation of a solid dispersion of diazepam by

Table I. X-Ray Diffraction Patterns of Amylodextrin and Metastable Amylodextrins and Experimental Data of Physical Mixtures and Freeze-Dried and Kneaded Products of Amylodextrin with the Drugs Diazepam and Prednisolone, Respectively

Compound	Position of strongest diffraction bands (Å)			Pattern of drug present
Amylodextrin (AD)[a]	6.5	5.3	4.0	
Metastable AD,[a] 1-octanol	7.0	5.2	4.6	
Metastable AD,[a] cyclohexanol		5.0		
Diazepam-AD, 1 to 1 physical mixture	6.5	5.3	4.0	Yes
Diazepam-AD, 1 to 1 freeze-dried	6.5	5.3	4.0	No
Prednisolone-AD, 1 to 1 physical mixture	6.5	5.3	4.0	Yes
Prednisolone-AD, 1 to 1 freeze-dried		5.0		No
Diazepam-AD, 1 to 1 kneaded (dry or wet)	6.5	5.3	4.0	No
Prednisolone-AD, 1 to 1 kneaded (dry or wet)	6.5	5.3	4.0	Yes

[a] Taken from Ref. 5.

freeze-drying. Because the spectrum of the physical mixture of prednisolone and amylodextrin was completely dominated by the excipient, FTIR could not provide information about prednisolone.

In conclusion, freeze-drying is not generally applicable for forming inclusion complexes of drugs with amylodextrin. Moreover, freeze-dried products are less suitable for application in tablets because of their low bulk densities. Therefore, the method of kneading at elevated temperatures with ethanol, applied to prepare complexes of drugs with cyclodextrins (8,9), was explored for its ability to incorporate drugs in amylodextrin.

Kneading of Diazepam and Prednisolone with Amylodextrin

DSC showed similar results for the kneaded products of diazepam with amylodextrin as for the freeze-dried products (Fig. 3a). Both the kneaded product with amylodextrin at a molar ratio of 2 to 1 and the kneaded product with lactose showed the melting peak of the drug, as observed for the physical blend. This peak was not shown by the equimolar kneaded product with amylodextrin, which points to complexation or solid dispersion of diazepam in amylodextrin by "wet kneading" at elevated temperatures with ethanol.

Most interesting is the observation of a similar result obtained by simply heating and blending or "dry kneading" diazepam with amylodextrin (Fig. 3b). The dry kneaded equimolar product showed no melting peak of the drug. This points to complexation or solid dispersion of diazepam by simply heating and blending the drug with amylodextrin. This peak is present for products prepared by blending without heating (physical mixture) or by dry kneading the drug with amylodextrin at a molar ratio of 2 to 1.

Formation of a solid dispersion or complex was confirmed by FTIR, which showed, for both the wet and the dry kneaded equimolar product, a spectrum similar to that obtained for the freeze-dried product (Fig. 2b). The X-ray diffraction pattern of both kneaded products did not show the pattern of the drug (Table I). The strongest diffraction bands were equal for the two kneaded products and the physical mixture. A solid dispersion of diazepam in amylodextrin was thus formed by both the wet and the dry kneading method at elevated temperatures.

Kneading was also tested on prednisolone. Although the DSC curves of the kneaded equimolar products showed no melting peak of the drug, the diffraction bands of the drug were present in the X-ray diffractogram (Table I). Thus, in contrast to diazepam, kneading of prednisolone with amylodextrin does not result in a complex or solid dispersion.

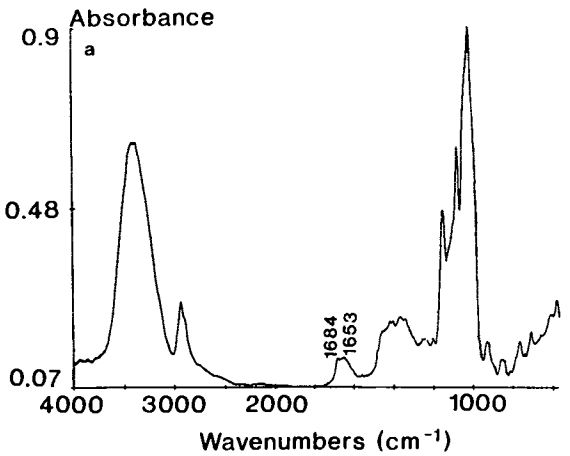

Fig. 2a. FTIR spectrum of a physical mixture of diazepam and amylodextrin at a molar ratio of 1:1.

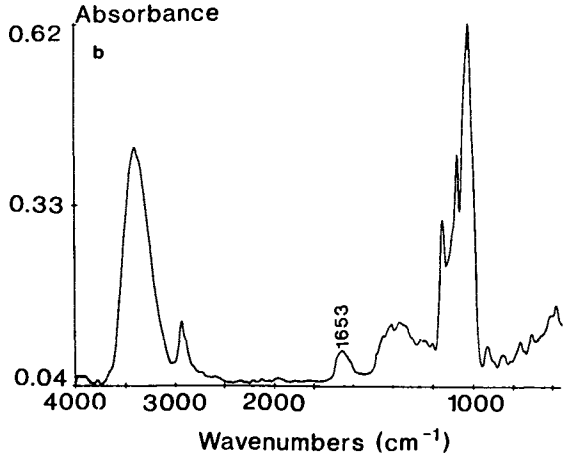

Fig. 2b. FTIR spectrum of a freeze-dried product of diazepam and amylodextrin at a molar ratio of 1:1.

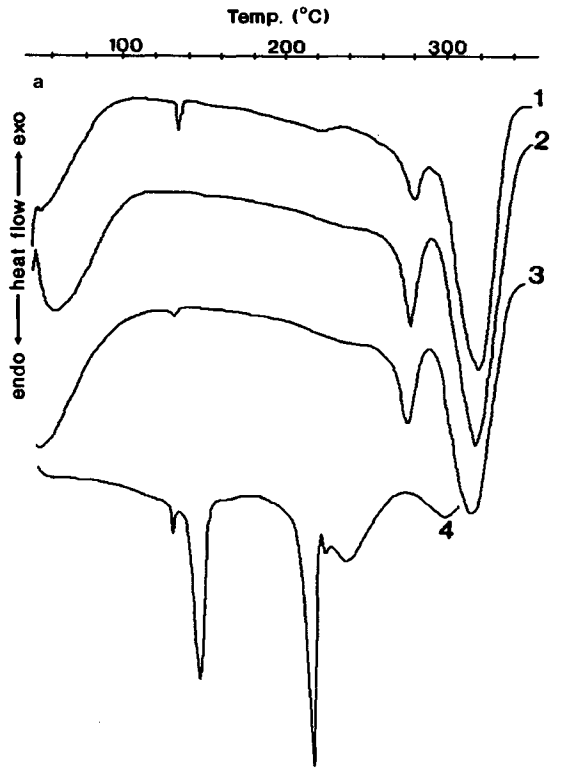

Fig. 3a. DSC curves of diazepam–amylodextrin and diazepam–lactose products. (1) Physical mixture of drug with amylodextrin (AD) at a molar ratio of 1:1; (2) wet kneaded product of drug-AD (1:1); (3) wet kneaded product of drug-AD (2:1); (4) wet kneaded product of drug with lactose (1:1).

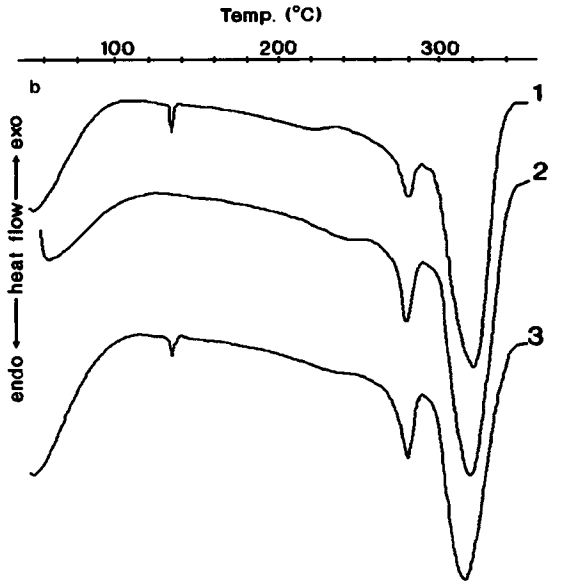

Fig. 3b. DSC curves of diazepam–amylodextrin products. (1) Physical mixture of drug with amylodextrin (AD) at a molar ratio of 1:1; (2) dry kneaded product of drug-AD (1:1); (3) dry kneaded product of drug-AD (2:1).

Mechanism of the Formation of Solid Dispersions by Kneading at Elevated Temperatures

Nakai (10) reported the formation of solid dispersions by grinding various drugs, such as diazepam, with microcrystalline cellulose or α-cyclodextrin. Previous to the formation of a solid dispersion, the carrier became amorphous. The drug molecules were included in a matrix of carrier molecules by means of hydrogen bonds. Because α-cyclodextrin and amylodextrin have comparable chemical structures, this process might also occur during kneading of diazepam with amylodextrin at elevated temperatures. Except for the evaporation of ethanol during wet kneading, resulting in solid diazepam again, the process of formation of a solid dispersion is supposed to be similar for both kneading methods. In contrast to Nakai (10), the mixtures of drug and amylodextrin were not ground, but simultaneously blended and heated. Knowing that the bulk temperature of the blend during kneading was measured to be about 120°C, the solid dispersion of diazepam (mp 128°C) by amylodextrin may be ascribed to a melting mechanism. This hypothesis agrees with the observation of no formation of a dispersion by kneading prednisolone (mp 240°C) at elevated temperatures with amylodextrin. To verify this hypothesis, a series of drugs was tested with increasing melting points.

For Lidocaine (mp 69°C) and methyl-PABA (mp 131°C), similar results were obtained as for diazepam. The wet and dry kneaded equimolar products with amylodextrin showed DSC curves without the melting peaks of the drugs, whereas their X-ray diffractograms showed no diffraction pattern of the drug (Table II). The positions of the strongest diffraction bands are similar to those observed for the corresponding physical mixtures. Thus, solid dispersions in amylodextrin are formed by kneading drugs with a lower (Lidocaine) or an almost-equal (diazepam, methyl-PABA) melting point, compared to the bulk temperature of about 120°C during kneading. In contrast, the X-ray diffraction pattern of the kneaded

Table II. X-Ray Diffraction Patterns of Physical Mixtures and Kneaded Products of Amylodextrin with the Drugs Lidocaine, Methyl-PABA, and Salicylic Acid, Respectively

Compound	Position strongest diffraction bands (Å)			Pattern of drug present
Lidocaine-AD, 1 to 1 physical mixture	6.5	5.3	4.0	Yes
Lidoacine-AD, 1 to 1 kneaded (dry or wet)	6.5	5.3	4.0	No
Methyl-PABA-AD, 1 to 1 physical mixture	6.5	5.3	4.0	Yes
Methyl-PABA-AD, 1 to 1 kneaded (dry or wet)	6.5	5.3	4.0	No
Salicylic acid-AD, 1 to 1 physical mixture	6.5	5.3	4.0	Yes
Salicylic acid-AD, 1 to 1 kneaded (dry or wet)	6.5	5.3	4.0	Yes

products of salicylic acid (mp 158°C) with amylodextrin shows the pattern of the drug (Table II). No solid dispersion is formed for the high-melting drugs prednisolone and salicylic acid by kneading at elevated temperatures. Melting of the drug seems to be a prerequisite for the formation of a solid dispersion.

Finally, the wet kneading method was tested on Amylose V and metastable amylose as carrier. Eighty moles of diazepam was kneaded at an elevated temperature with 1 mol of metastable amylose and Amylose V, respectively. This ratio corresponds to an equimolar ratio of drug and amylodextrin. DSC showed absence of the melting peak of diazepam for the product with metastable amylose and presence of the melting peak for the product with Amylose V. It seems possible to prepare a solid dispersion of diazepam in metastable amylose, but not in Amylose V, by wet kneading.

In conclusion, freeze-drying of drug with amylodextrin results in an inclusion complex for prednisolone and a solid dispersion for diazepam. Solid dispersions are also obtained on wet or dry kneading drug with amylodextrin at elevated temperatures. Melting of the drug is a prerequisite for the formation of a solid dispersion.

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