International Journal of Pharmaceutics, 102 (1994) 81–90

© 1994 Elsevier Science Publishers B.V. All rights reserved 0378-5173/94/$07.00

IJP 03351

Preparation, characterization and pharmaceutical application of linear dextrins: V. Study on the binding properties of amylodextrin, metastable amylodextrin and metastable amylose

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

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

(Received 27 April 1993)
(Accepted 16 June 1993)

Key words: Amylodextrin; Binding properties; Lubrication; Metastable amylose; Moisture content; Plastic deformation; Scanning electron microscopy

Summary

Amylodextrin, metastable amylodextrins, Amylose V and metastable amylose were investigated on their dry binding properties. Amylose V showed poor binding properties. Both amylodextrin and metastable amylodextrin produced tablets showing crushing strengths comparable with microcrystalline cellulose, whereas tablets compressed from metastable amylose even showed crushing strengths which were more than 2-fold greater. Both amylodextrin and metastable amylose showed a granular structure composed of very small primary particles (mean diameter 1–2 μm). During compression the granulates disaggregated into the primary particles. The latter deformed plastically followed by the formation of hydrogen bonds. Plastic deformation was confirmed by force-displacement curves and formation of hydrogen bonds was supported by the observation of increasing binding on increasing moisture content. Neither amylodextrin nor metastable amylose showed susceptibility for magnesium stearate, while Amylose V did show sensitivity for this lubricant. The difference is explained by the higher specific surface area and poorer flowing properties of amylodextrin and metastable amylose, as compared to Amylose V.

Introduction

Amylodextrin is a mainly linear dextrin with a mean DP (degree of polymerization) of 35. The conformation of amylodextrin proved to be a double helix (Te Wierik et al., 1993a), each strand containing six glucose units per turn. Complexation of amylodextrin changed the conformation into a single helix with six glucose units per turn when prepared with 1-octanol or 2-methyl-1-butanol, but in a single helix with seven glucose units per turn when prepared with cyclohexanol or 3-methylcyclohexanol. The complexes of amylodextrin are designated as metastable amylodextrins, because they dissociate in the presence of water (Te Wierik et al., 1993a). Amylodextrin and the metastable amylodextrins prepared with 1-octanol or 2-methyl-1-butanol demonstrated the phenomenon of partial dissolution of 18% in water at room temperature, whereas the metastable amylodextrins prepared with cyclohex-

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

anol or 3-methylcyclohexanol exhibited 35% dissolution. The fraction dissolved consisting of shorter chain molecules (mean DP = 24) could be isolated from solution by freeze-drying. In addition to the metastable amylodextrins, metastable amylose was prepared from Amylose V by complexation with 2-methyl-1-butanol. Metastable amylose proved to have a single helical conformation with six glucose units per turn, whereas Amylose V has the same double helical conformation as amylodextrin. The double helix of Amylose V, however, is folded due to intramolecular hydrogen bonds. These bonds are absent in the helices of amylodextrin, metastable amylodextrins and metastable amylose (Te Wierik et al., 1993a).

Continued research (Te Wierik et al., 1993b) showed that tablets containing diazepam and amylodextrin as physical mixture disintegrated neither in phosphate buffer pH 6.8 with or without α-amylase nor in 0.1 N HCl solution. The drug release rate from these tablets was demonstrated to be not only strongly retarded but in particular remarkably constant. Amylodextrin, which is not known from pharmaceutical practice or literature, thus appeared to be a unique excipient in the formulation of programmed release matrix tablets. This study reports the dry binding properties of both amylodextrin, metastable amylodextrin and metastable amylose as compared to Amylose V.

Materials and Methods

Amylodextrin (DP = 35), prepared from waxy maize by enzymatic hydrolysis with pullulanase, metastable amylodextrins, prepared with 1-octanol, 2-methyl-1-butanol, cyclohexanol and 3-methylcyclohexanol, 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 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 μm 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. Freeze-dried amylodextrin (DP = 35) was prepared by dissolving 4% w/v amylodextrin in water at a temperature of 80°C, followed by freeze-drying according to the above-described conditions.

Amylose V was obtained from Avebe (Veendam, The Netherlands). Microcrystalline cellulose (Avicel PH 101®) was delivered by FMC (Philadelphia, PA, U.S.A.), while magnesium stearate was supplied by Centrachemie (Etten-Leur, The Netherlands). Lubrication with 0.5% magnesium stearate was carried out by blending with the lubricant in a Turbula mixer (Bachoven, Basle, Switzerland) at 90 rpm for 2 min. All products were stored at a temperature of 20 ± 1°C and a relative humidity of 45 ± 5%.

Tablets with a weight of 300 mg and a diameter of 13 mm were compacted from sieve fractions, ranging from 53 to 300 μm, on an instrumented hydraulic press (ESH testing, Brierley Hill, U.K.) in a die having flat-faced punches. The compaction load was built up in 10 s and applied during a period of 0.1 s. Crushing strength of the tablets was determined, at least 15 min after compaction, on a Schleuninger Instrument Model 2E (Dr K. Schleuninger, Zürich, Switzerland). The data presented are the mean values of five measurements.

Electron micrographs were recorded using a scanning electron microscope (Jeol JSM-U3, Japan). Prior to investigation, the samples were coated with gold, using a direct current sputter technique. The water content of the materials was determined by drying at 120°C until constant weight. The specific surface area of powders and tablets was determined by nitrogen adsorption in a Quantasorp gas adsorption apparatus (Quantachrome Corp., Syosset, NY, U.S.A.). The porosity of the tablets was calculated from the tablet dimensions, tablet weight and true density of the powders, the latter determined with a (He)-pycnometer model MVP-1 (Quantachrome Corp., Syosset, NY, U.S.A.). Porosities were determined in 5-fold.

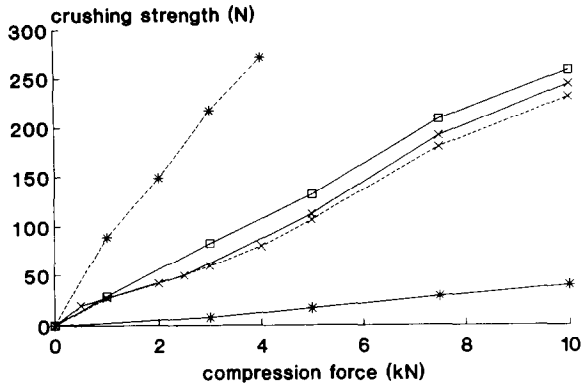

Fig. 1. Relationship between the crushing strength and the compression force of different pharmaceutical excipients. (× ——— ×) Amylodextrin, (×------×) metastable amylodextrin, (* ——— *) Amylose V, (*------*) metastable amylose, (□ ——— □) microcrystalline cellulose.

Amylodextrin and metastable amylose were compressed into tablets at different compaction loads on an excenter press (Indola, Rijswijk, The Netherlands). Force-displacement curves of each compression were recorded by an HDM apparatus (Darmstadt, Germany).

Results and Discussion

Fig. 1 presents the crushing strength of tablets compressed from amylodextrin, metastable amylodextrin prepared with 1-octanol, metastable amylose and Amylose V, respectively, as a function of the compaction load. For the purpose of comparison, Fig. 1 also includes the strengths as

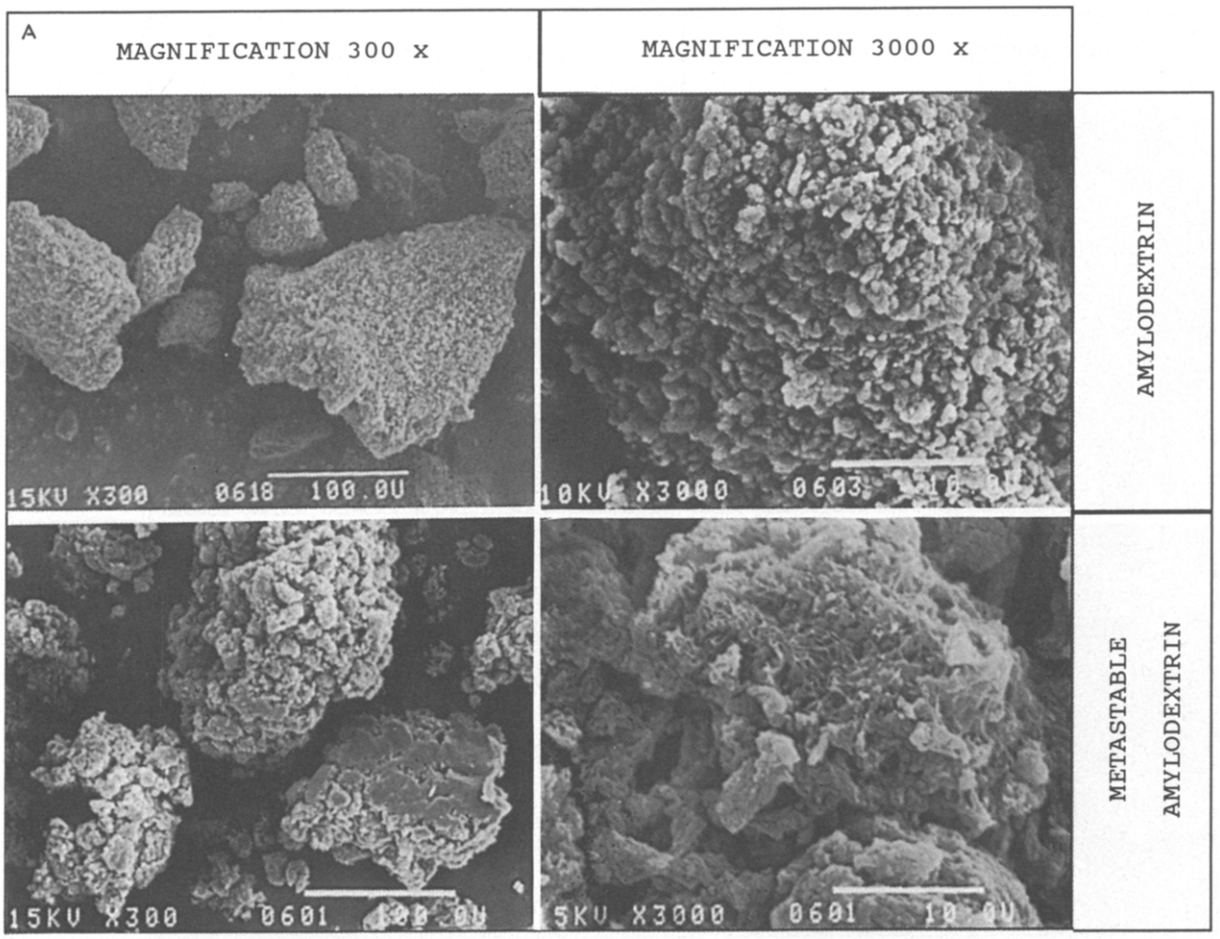

Fig. 2. Scanning electron micrographs: (a) amylodextrin and metastable amylodextrin prepared with 1-octanol; (b) Amylose V and metastable amylose; (c) freeze-dried amylodextrin and the soluble fraction of amylodextrin.

obtained for tablets compressed from the excellent dry binder microcrystalline cellulose (Bolhuis and Lerk, 1973). As expected, the latter excipient produced tablets with high crushing strength up to 250 N at a compaction load of 10 kN. In contrast, Amylose V tablets showed very poor crushing strength, namely, 30 N at a compaction load of 10 kN. Surprisingly, both amylodextrin and metastable amylodextrin prepared with 1-octanol demonstrated binding properties which were almost as good as those shown by microcrystalline cellulose. Both the amylodextrin and metastable amylodextrin tablets exhibited a crushing strength of 250 N at a compression force of 10 kN. The results as obtained for the three other metastable amylodextrins, which are not included in Fig. 1, were comparable with amylodextrin and metastable amylodextrin prepared with 1-octanol. Even better binding properties were found for metastable amylose, whose crushing strength was more than 2-fold greater as compared to microcrystalline cellulose. The difference in compactibility between the product metastable amylose and its raw material Amylose V is striking.

In conclusion, amylodextrin, the metastable amylodextrins and metastable amylose proved to be unique candidates as direct compression filler-binders, in addition to their suitability as excipients in programmed release tablets. The high binding properties are explained by a lack of crystallinity, the texture of the particles and the molecular structure.

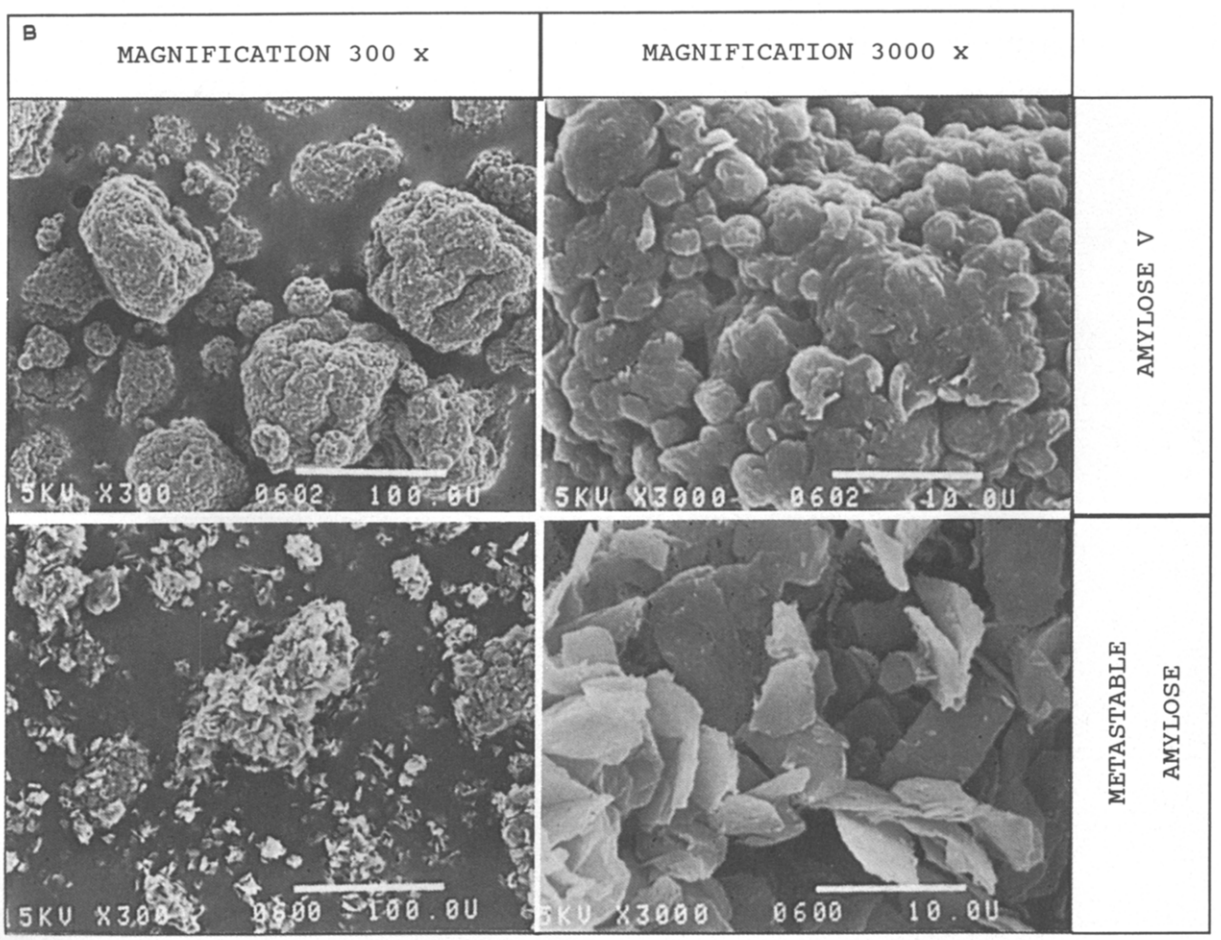

Fig. 2 (continued).

In a previous paper, it has been demonstrated by X-ray diffraction that amylodextrin, the metastable amylodextrins, metastable amylose and Amylose V are highly amorphous materials (Te Wierik et al., 1993a). Compounds with a lack of crystallinity generally demonstrate a good dry binding tendency (Hüttenrauch, 1983). This phenomenon is consistent with strong dry binding properties observed for amorphous lactose (Vromans et al., 1987).

Fig. 2a and b presents scanning electron micrographs of amylodextrin and metastable amylodextrin prepared with 1-octanol and of Amylose V and metastable amylose, respectively. Fig. 2a illustrates that the amylodextrin produced in this study is a granular product composed of very small primary particles; the latter have a diameter of 1–2 μm. The corresponding pictures of metastable amylodextrin illustrate granulates with an irregular structure. Fig. 2b shows that Amylose V is also granular and composed of larger particles (about 5 μm) than amylodextrin. Moreover, Amylose V granulates have a more regular structure than amylodextrin granulates. Metastable amylose finally consists of granulates of small platelets. The thickness of these platelets is again about 1 μm. Binding of amylodextrin, metastable amylodextrin and metastable amylose can be explained by a mechanism of fragmentation of the granules and plastic deformation of the primary particles. However, such a mechanism is not consistent with the poor binding prop-

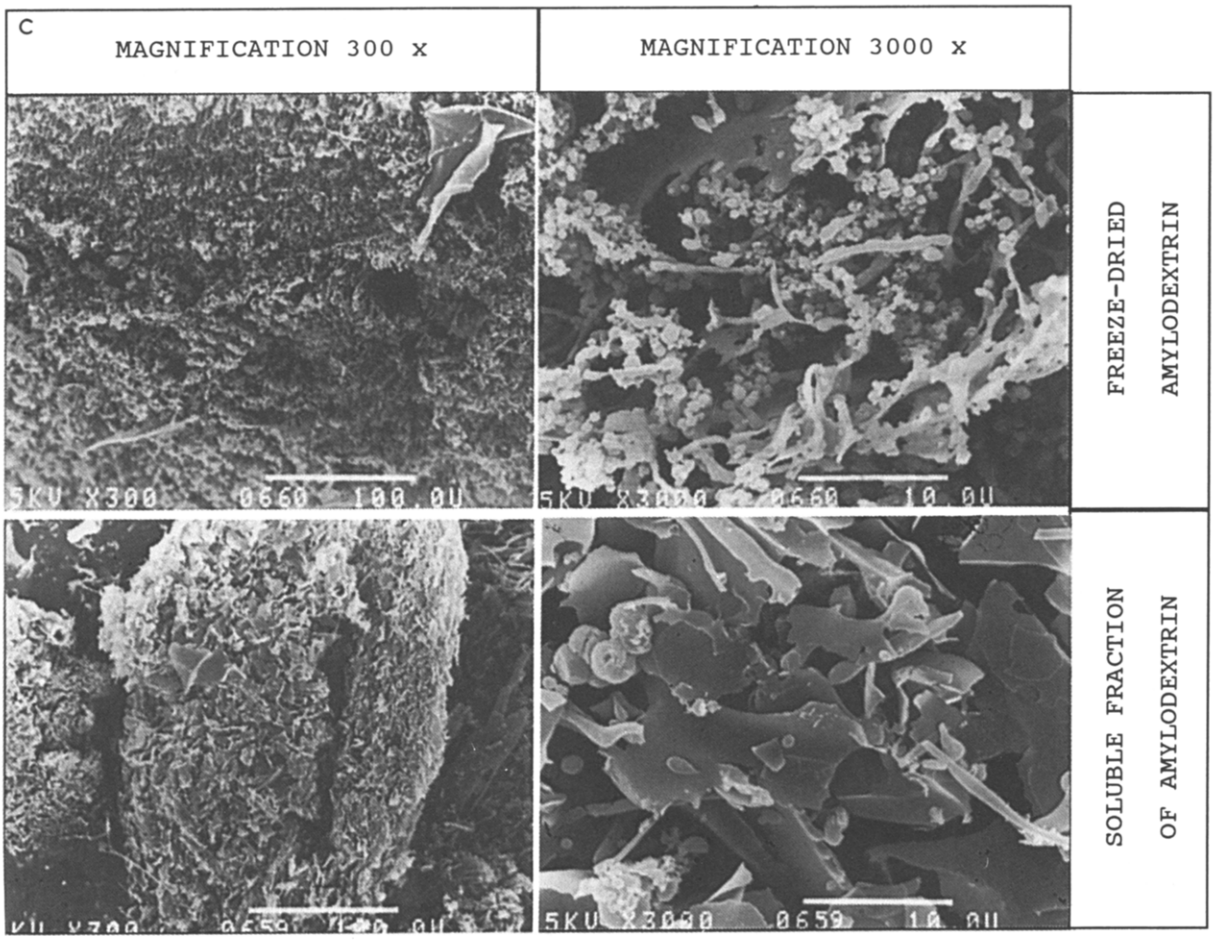

Fig. 2 (continued).

erties of Amylose V, also having a granular structure. Therefore, hydrogen bonds are assumed to play an important role in the binding of the primary particles, as has been reported for microcrystalline cellulose (Fox et al., 1963; Reier and Shangraw, 1966).

Dry binding of microcrystalline cellulose is dominated by intermolecular hydrogen bonds between O_1 and O_6 (Hüttenrauch, 1971). These bonds cannot be formed between Amylose V molecules because the positions mentioned are occupied by intramolecular hydrogen bonds, resulting in a folded conformation (Te Wierik et al., 1993a). This might explain the relatively poor binding properties of Amylose V (Fig. 1). In contrast, intramolecular hydrogen bonds are absent in the amylodextrin, metastable amylodextrin and metastable amylose molecules. Consequently, O_1 and O_6 are available in these molecules for the formation of intermolecular hydrogen bonds, resulting in excellent binding properties.

The better dry binding properties of metastable amylose, as compared to amylodextrin and the metastable amylodextrins, are assumed to be caused by the difference in DP. Longer chain molecules might be able to form a more stable system of hydrogen bonds. This assumption was subsequently tested by comparing the compactibility of freeze-dried amylodextrin (mean DP = 35) with that of the freeze-dried soluble fraction of amylodextrin (mean DP = 24). Table 1 presents the crushing strength of tablets compressed from these compounds at 3 kN. For reasons of comparison, Table 1 also includes the values as found for amylodextrin, metastable amylodextrin, Amylose V and metastable amylose. Tablets compressed from freeze-dried amylodextrin indeed showed a higher crushing strength than shown by the soluble fraction of amylodextrin. Surprisingly, binding is almost as high as that found for metastable amylose. However, since freeze-dried amylodextrin exhibits a low bulk density this product is less suitable for direct compression into tablets. The differences in crushing strength of the tablets compacted from amylodextrin and freeze-dried amylodextrin, respectively, both containing 35 glucose units per molecule, consequently cannot be explained by the DP but by differences in texture. Fig. 2a and c demonstrates a great difference in texture between amylodextrin and freeze-dried amylodextrin. Instead of granulates, as shown by amylodextrin, freeze-dried amylodextrin has a very fine structure of small particles. Compounds with this structure are generally obtained on freeze-drying solutions and show good binding properties. The freeze-dried product obtained from the soluble fraction of amylodextrin showed a comparable texture.

TABLE 1

Crushing strength of tablets compressed from various compounds at 3 kN

Compound	Crushing strength (N) tablet (300 mg, ∅ 13 mm, compr. force 3 kN)
Amylodextrin (AD) (DP = 35)	57.9 ± 7.7
Metastable AD (DP = 35)	59.5 ± 8.1
Freeze-dried AD (DP = 35)	201.0 ± 6.0
Soluble fraction of AD (DP = 24)	87.0 ± 6.5
Amylose V (DP ≈ 1000)	5.8 ± 1.2
Metastable amylose (DP ≈ 1000)	217.8 ± 14.5

Fig. 3 depicts the crushing strength of amylodextrin tablets vs the specific surface area of the uncompressed powder. The tablets were compressed at 3 kN from six batches containing about 10% w/w water. Fig. 3 shows that there seems to

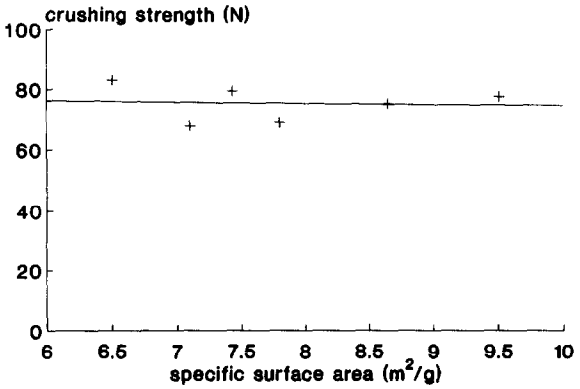

Fig. 3. Relationship between the crushing strength of amylodextrin tablets compressed at 3 kN and the specific surface area of the starting materials all containing 10% w/w moisture.

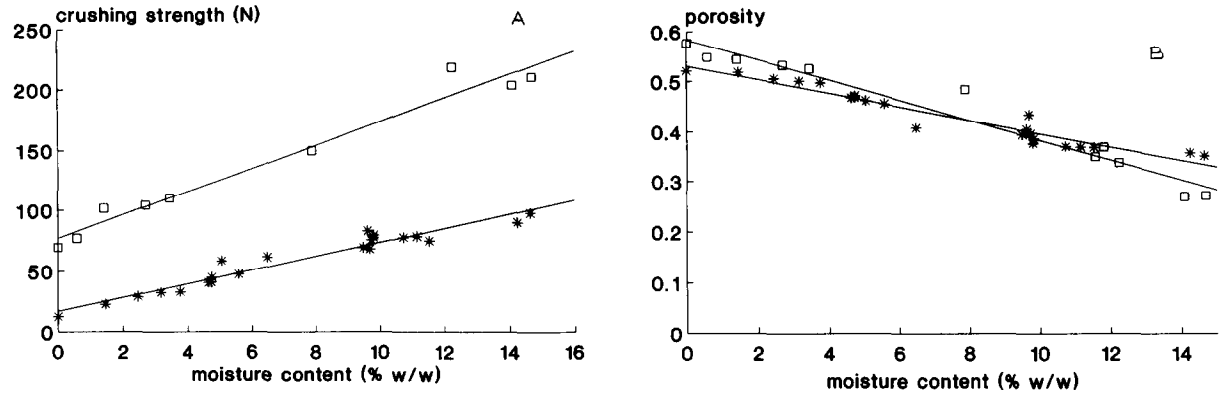

Fig. 4. (a) Relationship between the crushing strength of tablets containing amylodextrin (*) or metastable amylose (□) and the moisture content of the starting materials. The tablets were compressed at 3 kN. (b) Relationship between the porosity of tablets containing amylodextrin (*) or metastable amylose (□) and the moisture content of the starting materials. The tablets were compressed at 3 kN.

be no correlation between crushing strength of the tablets and specific surface area of the corresponding powders. For metastable amylose a comparable result was obtained, which is not included in Fig. 3.

Fig. 4a depicts the crushing strength of tablets compressed at 3 kN from amylodextrin and metastable amylose, respectively, vs the moisture content. As demonstrated in Fig. 4a a positive correlation is shown for both compounds between compactibility and moisture content. In contrast to native starches (Bos et al., 1987), no optimum at 10% w/w H_2O is observed. The positive correlation between compactibility and moisture content endorses the assumption that the formation of hydrogen bonds is one of the factors determining the binding of amylodextrin and metastable amylose.

The influence of moisture content on compactibility was further analyzed by plotting tablet porosity vs moisture content. Fig. 4b shows for both amylodextrin and metastable amylose a negative correlation between porosity and moisture content. This observation may be explained by two phenomena. Firstly, a higher water content may result in a greater gliding effect, resulting in a lower tablet porosity. In this case, water acts as an internal lubricant. Indeed, amylodextrin and metastable amylose both showed good self-lubrication. Secondly, moisture improves plastic deformation, resulting in smaller pores in the tablet.

Fig. 5 shows the force-displacement curves of compressions of amylodextrin at different compaction loads varying from 3 to 22 kN. Fig. 5 demonstrates at all forces predominantly plastic deformation and almost no elasticity. Similar curves were recorded for metastable amylose.

The non-occurrence of fragmentation of primary particles during compression was demonstrated by measuring the specific surface area of tablets compressed at increasing compaction loads from amylodextrin and metastable amylose, respectively. Fragmentation of excipient particles

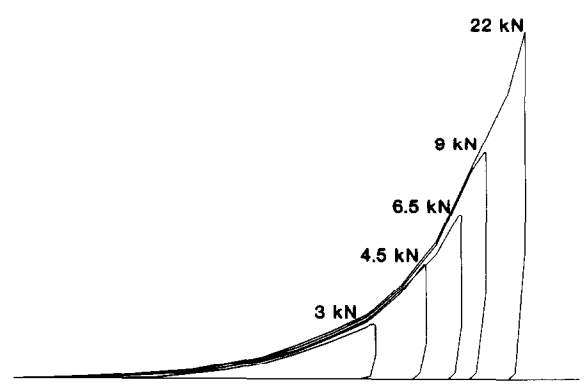

Fig. 5. Force displacement curves of compressions of amylodextrin at different compaction loads.

during compression would imply increasing tablet specific surface areas with increasing compaction loads. However, the results as presented in Table 2 show decreasing tablet specific surface areas with increasing compaction loads for both amylodextrin and metastable amylose. Hence, fragmentation of primary particles of amylodextrin or metastable amylose does not occur during compression. The decreasing tablet surface areas are explained by increasing inaccessibility for nitrogen, due to the formation of bonds between the primary particles. Because metastable amylose forms stronger bonds than amylodextrin, the metastable amylose tablets are assumed to be less accessible for nitrogen than the corresponding amylodextrin tablets and indeed show a steeper decrease in specific surface area (Table 2).

In conclusion, binding of amylodextrin and of metastable amylose under compression is suggested to occur by disaggregation of the granules and plastic deformation of the very small primary particles, followed by the formation of hydrogen bonds resulting in strong binding. This mechanism is consistent with the binding mechanism of the chemically familiar microcrystalline cellulose (Stamm and Mathis, 1976) and with the compaction of very small ceramic particles, as reported recently by Kumar et al. (1992). They demonstrated that nanostructured titania, which is composed of ultrafine particles with an average grain size of less than 100 nm, showed an enormous plastic deformation without fragmentation during compaction. The resulting compact showed a high crushing strength. This observation is consistent with the properties of amylodextrin and metastable amylose, both composed of primary particles of 1–2 μm and both showing plastic deformation during compaction resulting in compacts with high crushing strength.

TABLE 2

Specific surface area of amylodextrin and metastable amylose powder and of tablets compressed from these excipients at different compaction loads

Compaction load (kN)	Specific surface area (m^2/g)	
	Amylodextrin	Metastable amylose
0 (powder)	7.5	7.8
1	6.7	5.6
3	5.7	3.9
5	5.0	3.0
10	4.4	1.4

Both amylodextrin and metastable amylose showed good self-lubrication. However, since self-lubrication may be lost on blending of amylodextrin or metastable amylose with an active ingredient and other excipients, incorporation of a lubricant in tablets compressed from these mixtures is mostly desired. Magnesium stearate, which is added to tablet formulations in a concentration of 0.2–1% w/w, is the most widely used pharmaceutical lubricant (Strickland et al., 1956). However, it can have a strong negative effect on the crushing strength of the tablet. When the lubricant is mixed with a directly compressible excipient, it is distributed either as a free fraction or as a surface film on the base material (Bolhuis et al., 1975; Johansson and Nicklasson, 1986). The surface film is responsible for the strong negative effect on the binding properties. The formation of this film depends upon the texture, specific surface area and the flowing properties of the directly compressible filler-binder.

Around smooth particles (Riepma et al., 1993) generally a coherent matrix of magnesium stearate is formed, whereas a discontinuous layer of lubricant is formed around irregularly shaped granule particles (Lerk and Sucker, 1988). Moreover, in the latter case, part of the magnesium stearate will be trapped into the asperities and cavities of the granules and is therefore not available for the formation of a lubricant film. For amylodextrin and metastable amylose both having a granular structure (Fig. 2a and b) the formation of a discontinuous lubricant layer around the granulates seems most probable.

The relation between the concentration of lubricant (W_{mm}) needed to obtain a monomolecular film of lubricant and the specific surface area of the filler-binder (S_{N2}) was reported by Müller (1976):

$$W_{mm}\,(\%) = \frac{S_{N2}}{200} \times 100 = \frac{S_{N2}}{2}$$

For amylodextrin (specific surface area = 7.5 m^2/g) theoretically a lubrication concentration of 3.75% would be needed to obtain a monomolecular layer of magnesium stearate around the primary particles. For metastable amylose (specific surface area = 7.8 m^2/g) this concentration is 3.9%. For both excipients complete formation of a surface film around the particles seems improbable on mixing with magnesium stearate in the generally applied concentration of 0.5%. In contrast, for Amylose V (specific surface area = 0.16 m^2/g) a lubricant concentration of 0.08% is sufficient to achieve the covering of all particles with a lubricant film.

The formation of a lubricant film during the mixing process may be delayed or even prevented for filler-binders with poor flowing properties, as was demonstrated for different types of lactose (Vromans et al., 1988) and for starch and cellulose (Bos et al., 1991). Since Amylose V has better flowing properties than amylodextrin and metastable amylose, the formation of a lubricant film seems more probable for Amylose V. Thus, regarding specific surface area and flowing properties it is expected that a coherent lubricant film is formed around Amylose V particles but not around amylodextrin and metastable amylose particles.

The consolidation characteristics of the filler-binder are known to have considerable influence on its susceptibility to lubrication. Fragmenting materials were generally assumed to be less sensitive to magnesium stearate lubrication because of the formation of lubricant-free surfaces during compaction (Duberg and Nyström, 1982). The originally present lubricant-coated particle surfaces were suggested to be distributed at random within the compact. However, recent research reported fragmenting materials to be more sensitive to magnesium stearate lubrication than expected from the increase in surface area during compression (Riepma et al., 1993). A coherent matrix of lubricant is shown to be highly sustained during compaction. Highest sensitivity to magnesium stearate lubrication is shown by plastically deforming materials (De Boer et al., 1978).

Table 3a–c presents the crushing strength of tablets without and with magnesium stearate compressed from Amylose V, amylodextrin and metastable amylose, respectively, at three compaction loads. Amylose V showed decreased binding on mixing with magnesium stearate (Table 3a). This result is consistent with the literature (Bolhuis et al., 1975; De Boer et al., 1978) and is explained by the formation of the coherent lubricant film around the primary particles undergoing plastic deformation. In contrast, the surfaces of amylodextrin and metastable amylose primary particles are mainly lubricant-free and were hence expected to show no lubricant susceptibility. Indeed, Table 3b and c shows for lubricated tablets compressed from amylodextrin and metastable amylose, respectively, no decrease in crushing strengths, as compared to the unlubricated tablets.

TABLE 3

Influence of the incorporation of magnesium stearate on the crushing strength of (a) Amylose V tablets, (b) amylodextrin tablets and (c) metastable amylose tablets

Compaction load (kN)	Crushing strength of tablets (N)	
	Unlubricated	With 0.5% Mg stearate
(a) Amylose V		
10	31.4 ± 2.1	4.8 ± 0.4
15	45.4 ± 1.5	12.8 ± 3.0
20	57.8 ± 2.3	15.2 ± 0.4
(b) Amylodextrin		
3	93.4 ± 9.6	99.0 ± 7.3
6	190.8 ± 14.6	215.0 ± 19.8
9	296.2 ± 7.5	296.4 ± 7.8
(c) Metastable amylose		
1	89.4 ± 5.0	90.3 ± 6.0
2	148.7 ± 10.2	150.1 ± 12.5
3	217.8 ± 14.5	222.0 ± 12.2

In conclusion, both amylodextrin and metastable amylose show excellent binding properties, which are not decreased on lubrication with magnesium stearate. They have unique possibilities for application in tablets as dry binder or as excipient for programmed drug release.

Acknowledgements

The authors wish to acknowledge the cooperation with TNO Nutrition and Food research and

discussions with Dr A.C. Besemer. They are very grateful to Mr A.H. De Boer for performing the scanning electron microscopy and to Mrs J. Beekhuis for critically reading the manuscript.

References

Bolhuis, G.K. and Lerk, C.F., Comparative evaluation of excipients for direct compression. I. *Pharm. Weekbl.*, 108 (1973) 469–481.

Bolhuis, G.K., Lerk, C.F., Zijlstra, H.T. and De Boer, A.H., Film formation by magnesium stearate during mixing and its effects on tableting. *Pharm. Weekbl.*, 110 (1975) 317–325.

Bos, C.E., Bolhuis, G.K., Van Doorne, H. and Lerk, C.F., Native starch in tablet formulations: properties on compaction. *Pharm. Weekbl. Sci. Ed.*, 9 (1987) 274–282.

Bos, C.E., Vromans, H. and Lerk, C.F., Lubricant sensitivity in relation to bulk density for granulations based on starch or cellulose. *Int. J. Pharm.*, 67 (1991) 39–49.

De Boer, A.H., Bolhuis, G.K. and Lerk, C.F., Bonding characteristics by Scanning Electron Microscopy of powders mixed with magnesium stearate. *Powder Technol.*, 20 (1978) 75–82.

Duberg, M. and Nyström, C., Studies on direct compression of tablets: VI. Evaluation of methods for the estimation of particle fragmentation during compaction. *Acta Pharm. Suec.*, 19 (1982) 421–436.

Fox, C.D., Richman, M.D., Reier, G.E. and Shangraw, R.F., Microcrystalline cellulose in tableting. *Drug Cosm. Ind.*, 92 (1963) 161–164.

Hüttenrauch, R., Nachweis der Bindungskräfte in Cellulose-Komprimaten. *Pharmazie*, 26 (1971) 645–646.

Hüttenrauch, R., Modification of starting materials to improve tableting properties. *Pharm. Ind.*, 45 (1983) 435–440.

Johansson, M.E. and Nicklasson, M., Influence of mixing time, particle size, and colloidal silica on the surface coverage and lubrication of magnesium stearate. *Proc. 5th Pharm. Techn. Conf., Harrogate, U.K.*, Solid Dosage Research Unit, Liverpool, U.K., 1986, pp. 217–225.

Kumar, K.-N.P., Keizer, K., Burggraaf, A.J., Okubo, T., Nagamoto, H. and Morooka, S., Densification of nanostructured titania assisted by a phase transformation. *Nature*, 358 (1992) 48–51.

Lerk, P.C. and Sucker, H., Interaction of magnesium stearate and talc upon tabletting mixtures: II. Effect on wettability of powder blends. *Acta Pharm. Technol.*, 34 (1988) 72–76.

Müller, B.W., Tribologische Gesetzmäßigkeiten und Erkenntnisse in der Tablettentechnologie: 2. Mitt.: Untersuchungen über den Aufbau von Schmierstoffschichten. *Pharm. Ind.*, 38 (1976) 394–398.

Reier, G.E. and Shangraw, R.F., Microcrystalline cellulose in tableting. *J. Pharm. Sci.*, 55 (1966) 510–514.

Riepma, K.A., Vromans, H. and Lerk, C.F., A coherent matrix model for the consolidation and compaction of an excipient with magnesium stearate. *Int. J. Pharm.*, 97 (1993) 195–203.

Stamm, A. and Mathis, C., Etude de la comprimabilité de differents excipients pour compression directe. *Sci. Techn. Pharm.*, 5 (1976) 245–253.

Strickland, W.A., Nelson, E., Busse, L.W. and Higuchi, T., The physics of tablet compression: 9. Fundamental aspects of tablet lubrication. *J. Am. Pharm. Assoc. Sci. Ed.*, 45 (1956) 51–55.

Te Wierik, G.H.P., Eissens, A.C., Besemer, A.C. and Lerk, C.F., Preparation, characterization and pharmaceutical application of linear dextrins: I. Preparation and characterization of amylodextrin, metastable amylodextrins and metastable amylose. *Pharm. Res.*, 10 (1993a) 1274–1279.

Te Wierik, G.H.P., Eissens, A.C. and Lerk, C.F., Preparation, characterization and pharmaceutical application of linear dextrins. Part IV. Drug release from capsules and tablets containing amylodextrin. *Int. J. Pharm.*, 98 (1993b) 219–224.

Vromans, H., Bolhuis, G.K., Lerk, C.F. and Kussendrager, K.D., Studies on tableting properties of lactose: VII. The effect of variations in primary particle size, percentage of amorphous lactose on the tableting properties of spray-dried lactose products. *Int. J. Pharm.*, 35 (1987) 29–37.

Vromans, H., Bolhuis, G.K. and Lerk, C.F., Magnesium stearate susceptibility of directly compressible materials as an indication of fragmentation properties. *Powder Technol.*, 54 (1988) 39–44.