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A new generation of starch products as excipient in pharmaceutical tablets. I. Preparation and binding properties of high surface area potato starch products

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Abstract

A new pharmaceutical excipient with a high binding capacity was prepared from potato starch by enzymatic degradation, followed by suitable dehydration of the precipitated and filtered retrograded starch to produce high specific surface area products. Thermal dehydration methods like drying at room or elevated temperature and spray-drying resulted in particulate solids with low specific surface area, as measured by nitrogen adsorption, and low compactibility. Both freeze-drying and chemical desiccation, like washing with ethanol or acetone, produced powders with strongly increased specific surface area and increased binding capacity. The compactibility of the final products showed a positive correlation with the specific surface area, changing at high surface areas into constant compactibility. Moreover, the binding capacity appeared to increase with the moisture content of the products.

Keywords: Compactibility; Enzymatic degradation; Dehydration; Specific surface area; Starch

1. Introduction

Most starches consist of two polymers of glucose mainly linked by α-1,4 glycosidic bonds: essentially linear amylose and branched amylopectin (Young, 1984). The glucose units with an α-1,6 glycosidic linkage are the branching points. Next to the application of starch and starch derived products in adhesives, textile, food and paper industry, native and modified starches are widely applied in pharmacy as binder (Lieberman and Lachman, 1980) or disintegrant (Lerk et al., 1982) in tablets, or as excipient in controlled release formulations (Herman and Remon, 1989).

Partial hydrolysis of starches yields dextrins which have the same chemical structure as amylose and amylopectin but a much lower degree of polymerization. A previous study (Te Wierik et al., 1993a) introduced the linear dextrin amylodextrin as a promising excipient to control drug

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release from solid pharmaceutical dosage forms (Te Wierik et al., 1993b). This feature was found to be related to the excellent dry binding properties of the products manufactured, making it also a suitable candidate for the application as filler-binder in tablets for direct compression (Te Wierik et al., 1994). Dextrins with a high degree of branching are obtained by acid or enzymatic hydrolysis of starch, containing both amylose and amylopectin. Amylodextrin can be prepared by selective enzymatic hydrolysis of the α-1,6 glycosidic bonds of amylopectin, the latter being present for almost 100% in e.g. waxy maize starch. Genetic control enabled the development of starch granules containing only amylopectin (Shannon and Garwood, 1984). However, these amylopectin starches are not yet readily available on a large scale.

The present study has been performed to explore the possibilities of using regular, amylose containing potato starch as raw material to produce linear dextrins for use as excipient in pharmaceutical dosage forms. Both debranching of the amylopectin fraction and degradation of the (20%) amylose fraction present in the raw material was performed enzymatically. The hydrolysed mass was subsequently precipitated (retrograded) and filtered. The debranched retrograded starch was finally dehydrated by thermal, chemical or physical desiccation techniques. This paper discusses the effect of the method of dehydration on the specific surface area of the final products and focuses attention on the relation between specific surface area and compactibility.

2. Materials and methods

2.1. Materials

Potato starch (food-grade) was supplied by Avebe (Foxhol, The Netherlands). Promozyme 200L® (pullulanase from *Bacillus acidopullulyticus*) and BAN 240L® (α-amylase from *Bacillus subtilis*) were from NOVO Nordisk A/S (Bagsværd, Denmark). Optimax L300® (pullulanase from *Bacillus deramificans* expressed in *Bacillus licheniformis*) was supplied by Solvay Enzymes GmbH (Hannover, Germany). Microcrystalline cellulose (Avicel PH101®) and magnesium stearate were obtained from FMC (Philadelphia, USA) and Centrachemie (Etten-Leur, The Netherlands), respectively. All other products and reagents used were of analytical grade.

2.2. Preparation of hydrated debranched retrograded starch

A suspension consisting of 1930 g potato starch (83% w/w dry substance) and 8070 g water was gelatinized in a jetcooker (Avebe Consulting and Equipment, Veendam, The Netherlands) at 155–160°C (pressure 12.5 bar, flow 10 ml/s). After cooling to 57°C debranching of the amylopectin fraction was performed at pH 4.5 by either Optimax® or Promozyme®. For both enzymes the concentration was 2% w/w, calculated on starch dry substance. After 20 h when debranching was complete the remaining amylose fraction was enzymatically degraded by 0.014% α-amylase at 75°C and pH 6.5 during 30 min. The activity of the enzymes was inhibited by decreasing the pH to 2.3. The reaction vessel was subsequently cooled down slowly to room temperature. The products precipitated within 20 h. The precipitate was separated from the mixture by filtration. The resulting product had a highly swollen, soft particulate appearance and will further be referred to as hydrated retrograded starch. The water content was about 80%.

2.3. Dehydration of the retrograded starch

The bulk water of the retrograded starch products was removed by different dehydration techniques. The thermal methods used were drying at room or elevated temperatures and spray-drying. The latter was carried out in a Büchi 190 (flow 400 normliter/h, T_{in} 170 or 100°C, T_{out} 60°C). As non-thermal methods, washing with ethanol or acetone and freeze-drying in a Lyolab A (Marius Instrumenten, Nieuwegein, The Netherlands) at -55°C and 0.04 mbar were experienced. The amount of ethanol or acetone used was two

times the weight amount of hydrated retrograded starch whereas the number of washing steps was varied. Powders were obtained after evaporation of the liquid. Sieve fractions < 180 μm were used for all final products and were stored at a temperature of 20°C and a relative humidity of 45%.

2.4. Scanning electron microscopy and particle size analysis

Electron micrographs were made 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 particle size distribution of dry powders, aqueous and ethanolic suspensions was measured by laser diffractometry (Sympatec Compact, Goslar, Germany).

2.5. Determination of moisture content and specific surface area

The moisture content of the materials was determined by drying at 120°C until constant weight. The specific surface area of the powders was measured by nitrogen adsorption in a Quantasorp gas adsorption apparatus (Quantachrome Corp., Syosset, USA).

2.6. Compactibility

Tablets with a weight of 300 mg and a diameter of 13 mm were compacted from the final products on an instrumented hydraulic press (ESH Testing, Brierley Hill, UK) using flat-faced punches. The compaction load was 3 kN which was built up in 10 s and applied during 0.1 s. The compactibility studies were performed on both unlubricated and lubricated powders. The latter were prepared by mixing with 1% magnesium stearate during 2 min. 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.

3. Results and discussion

3.1. Dehydration methods

Table 1 shows the specific surface area and compactibility of final products obtained from retrograded starch after dehydration by different methods. Hydrated retrograded starch was produced by debranching of the amylopectin fraction of potato starch by Promozyme® followed by hydrolysis of the amylose fraction with α-amylase, added after completed debranching (Arends-Scholte et al., 1994). The data show both a relatively low specific surface area and a low binding capacity for all products obtained by thermal dehydration, either by drying at normal or elevated temperature or by spray-drying. Drying at 120°C even resulted in a decreased specific surface area and a strongly decreased binding capacity, as compared to drying at room temperature. The spray-dried products exhibited, independent on the inlet temperature, an increased specific surface area, as compared to normal drying, but no increased compactibility. The products obtained after chemical desiccation of the retrograded starch with either ethanol or acetone and the products obtained by freeze-drying, all demonstrated both a strikingly increased specific surface area and a strongly increased compactibility. It is noted that the crushing strength of these tablets was found to be twice the strength of corresponding tablets compressed from the generally applied filler-binder microcrystalline cellulose; 160 kN for the ethanol dried starch product as compared to 83 N for Avicel PH101. Moreover, these high surface area starch products proved to be insensitive to the addition of magnesium stearate, whereas both the thermally dehydrated starch products (Table 1) and Avicel PH101 strongly lose binding capacity on lubrication. For tablets compressed from the latter a crushing strength of 60 N was found upon lubrication.

The surface texture of all products was characterized by scanning electron microscopy. Fig. 1a–c illustrates the surface texture of final products obtained from the retrograded starch by either ethanol washing or freeze-drying. Both products are shown to consist of porous granules composed

Table 1
Specific surface area of products prepared by dehydration of debranched retrograded potato starch and crushing strength of tablets (300 mg, ϕ 13 mm) compressed from these products, with and without magnesium stearate, at 3 kN

Dehydration method	Spec. surface area (m^2/g)	Crushing strength unlubricated (N)	Crushing strength lubricated (N)
Drying at 20°C	0.15	41 ± 5	25 ± 3
Drying at 40°C	0.16	23 ± 2	15 ± 3
Drying at 120°C	<0.1	2 ± 1	<1
Spray-drying (T_{in} 170°C)	1.7	40 ± 6	30 ± 2
Spray-drying (T_{in} 100°C)	1.7	39 ± 1	31 ± 3
Washing with ethanol	16.8	160 ± 4	177 ± 3
Washing with acetone	24.6	160 ± 5	165 ± 5
Freeze-drying	22.5	169 ± 5	168 ± 3

of small primary particles. The granular texture agrees with the results as reported previously for amylodextrin (Te Wierik et al., 1994). In contrast, the product dried at 20°C is shown to consist of large non-porous particles with smooth surfaces (Fig. 1d,e). The retrograded starch containing 80% water, as obtained after enzymatic hydrolysis, is assumed to be a flocculated dispersion. Thermal dehydration is supposed to cause coagulation, resulting in non-porous coarse particles, as illustrated by Fig. 1d–f. Coagulation may not occur on chemical desiccation or on sublimation of water by freeze-drying of the flocculated dispersion. These non-thermal dehydration processes result in porous granules, characterized by a high specific surface area. In contrast, the coarse particles with smooth surfaces of the thermally dehydrated products evidently exhibit a low specific surface area.

The dehydration procedure with ethanol was further explored on its effect on specific surface area and compactibility of the final products (Table 2). All ethanol washing steps were performed with two times the amount of ethanol on weight amount of retrograded starch to be dehydrated. One time washing with either ethanol 96% or absolute ethanol resulted in a product with a specific surface area of about 1.3 m^2/g and a crushing strength of the tablets compacted of about 80 N. Both the specific surface area and compactibility were strongly increased by a second washing step. A third ethanol washing showed only a small increase in specific surface area and no increase in compactibility. Highest increase in both specific surface area and compactibility was obtained by using absolute ethanol as final washing step. It is noted that a crushing strength of 125 N, as shown by the tablets compressed from the product prepared after two washing steps with ethanol 96%, is about 1.5 times better than that of corresponding tablets compressed from the most commonly used filler-binder microcrystalline cellulose.

Similar results were obtained on applying Optimax® as debranching enzyme instead of Promozyme®. Dehydration of retrograded starch, prepared by debranching of the amylopectin fraction of potato starch with Optimax® followed by enzymatic hydrolysis of the amylose fraction, again resulted in low specific area products with low binding capacity on thermal dehydration at room or elevated temperature. High specific surface area products with excellent dry binding properties were obtained on chemical desiccation, like washing with ethanol or acetone, and on freeze-drying.

Both the intermediate hydrous retrograded starch and the final dehydrated products were analyzed on particle size distribution by laser diffractometry. Dispersion of the hydrated retrograded starch in either water or ethanol 96% resulted in a bimodal frequency distribution, showing primary particles with a peak diameter of 4–6 μm and agglomerated particles with a peak diameter of 36 μm (Table 3). Dispersion of the final products in air showed no change in particle

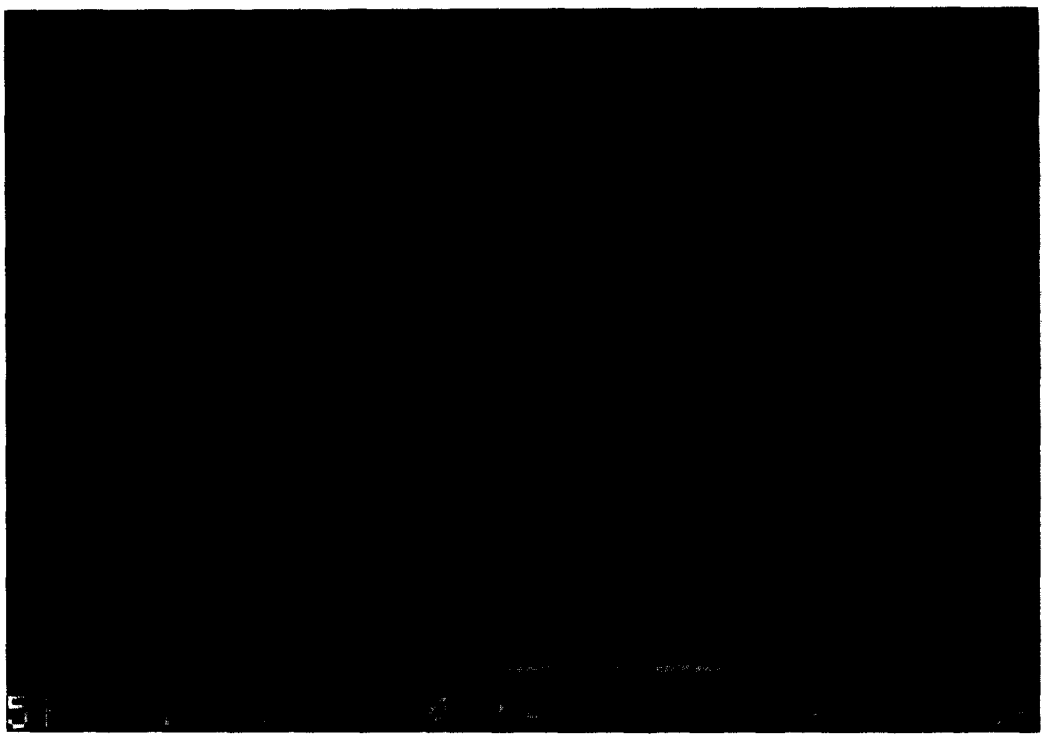

Fig. 1A

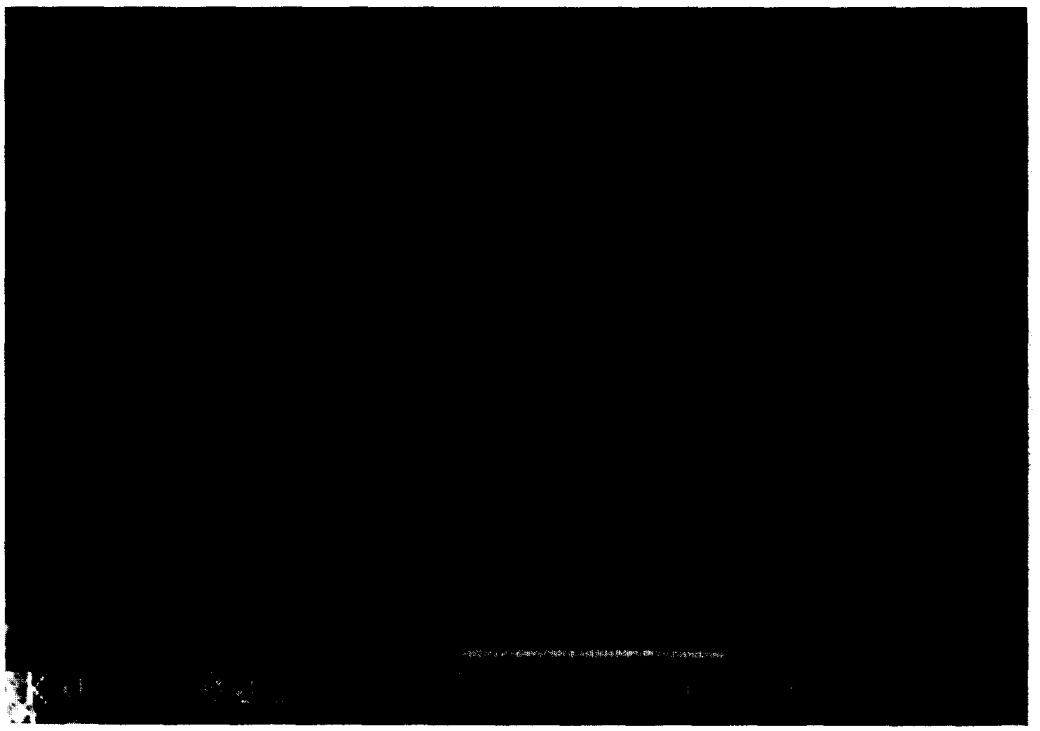

Fig. 1B

Fig. 1. Scanning electron micrographs of products prepared by enzymatic degradation of potato starch followed by washing with ethanol (a,b), freeze-drying (c), drying at 20°C (d,e) and spray-drying (f), respectively. Magnifications: × 30 (d) × 30, × 300 (a,c). × 3000 (b,e,f).

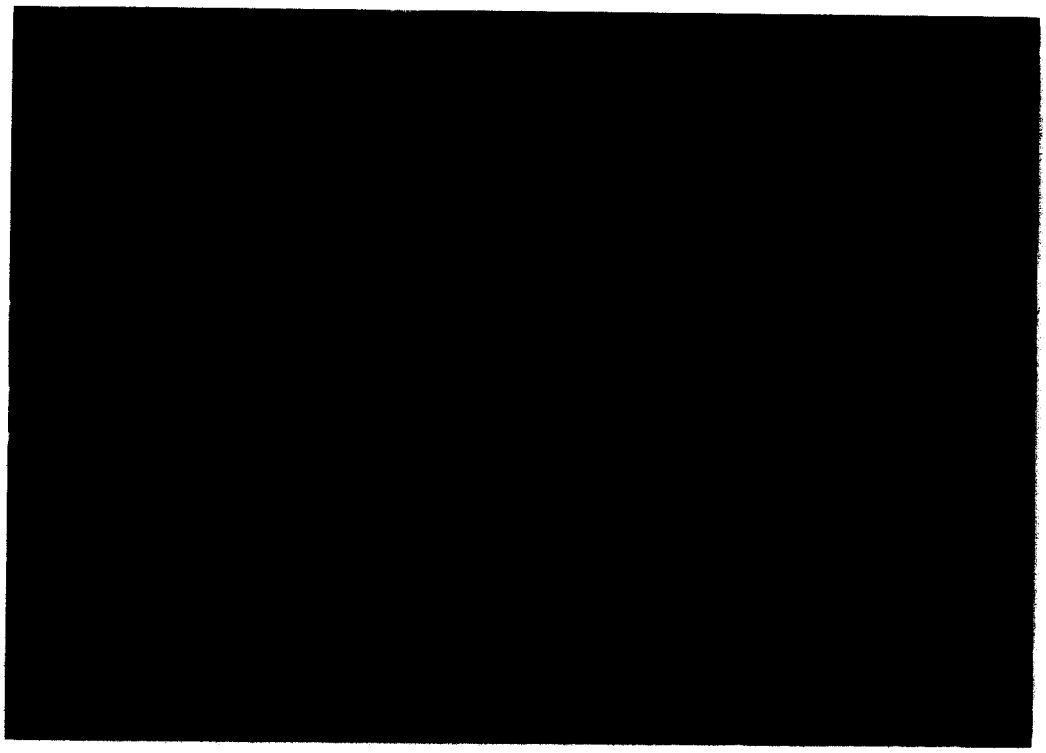

Fig. 1C.

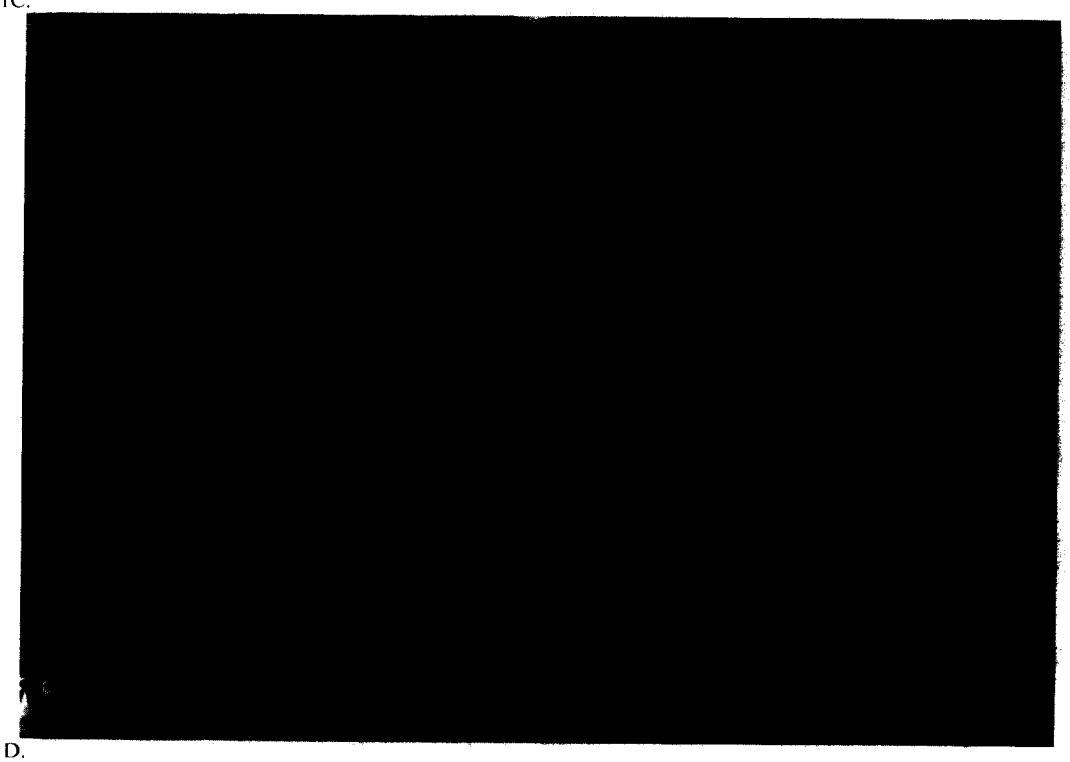

Fig. 1D.

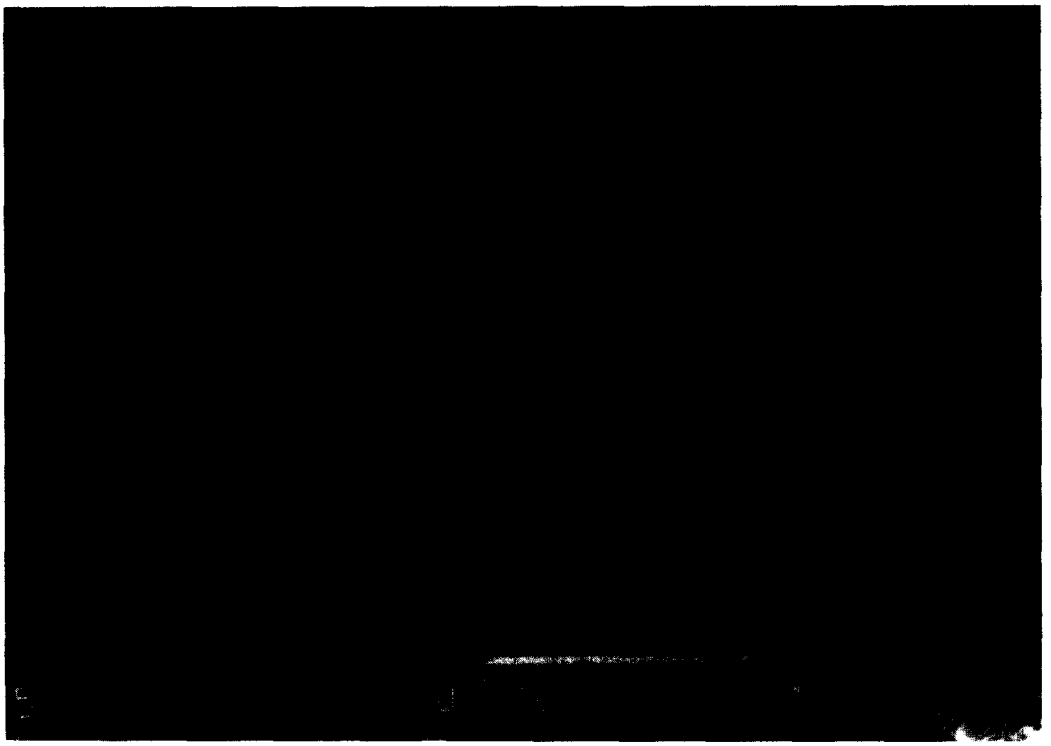

Fig. 1E.

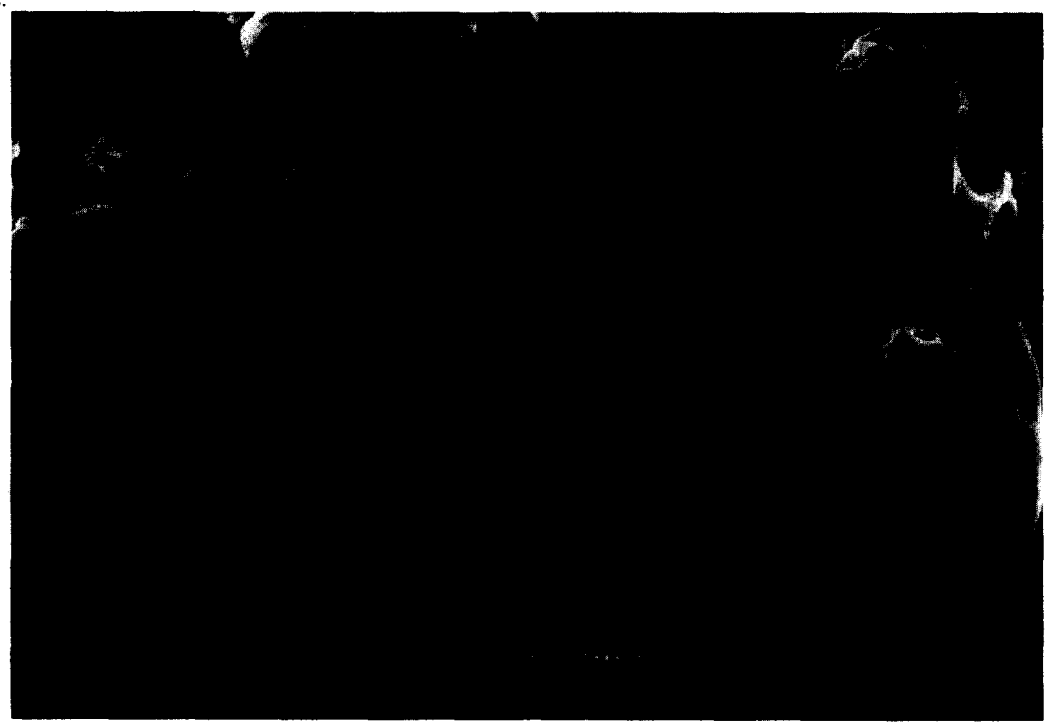

Fig. 1F.

Table 2
Specific surface area of products prepared by washing with ethanol of debranched retrograded potato starch, and crushing strength of tablets (300 mg, ϕ 13 mm) compressed from these products at 3 kN

Number of washing steps with ethanol	Specific surface area (m^2/g)	Crushing strength (N) tablet (300 mg, 13 mm)
1 × ethanol 96%	1.3	78 ± 4
1 × absolute ethanol	1.3	84 ± 2
2 × ethanol 96%	7.8	125 ± 3
3 × ethanol 96%	8.8	122 ± 3
1 × ethanol 96% followed by 1 × absolute ethanol	10.5	146 ± 5
2 × ethanol 96% followed by 1 × absolute ethanol	17.5	158 ± 3

size distribution when obtained by chemical desiccation or freeze-drying. In contrast, drying of the retrograded starch at room temperature resulted in the detection of particles with diameters over 100 μm, whereas the primary particles even disappeared. This endorses the complete coagulation of primary particles into large aggregates upon a thermal dehydration method resulting in a low specific surface area. The coagulation may be ascribed to an interaction between water and carbohydrate particles.

In conclusion, starch products with high specific surface area and excellent dry binding properties can be obtained by enzymatic degradation of potato starch followed by dehydration of the aqueous retrograded starch by non-thermal methods like washing with ethanol or acetone or by freeze-drying. These products are suitable candidates for application both as filler-binder in tablet formulations for direct compression and as excipient in controlled release systems.

Table 3
Peak diameters (modes) derived from size frequency curves of hydrated retrograded potato starch after dispersion in water or ethanol, and of final products, obtained from the intermediate retrograded starch by dehydration, after dispersion in air

Product	Peak diameter (μm)	
Retrograded starch, dispersion:		
in water	3.7	36
in ethanol 96%	6.0	36
Final products, dehydrated by:		
drying at 20°C		123
washing 2 × with ethanol 96% or acetone	7.5	36
freeze-drying	7.5	36

3.2. Compactibility and specific surface area

The observation of increased compactibility was analyzed by plotting the crushing strength of compacted tablets versus the specific surface area of the products to be compressed (Fig. 2). The products, prepared by debranching with Optimax® and hydrolysis with α-amylase and subsequently dehydrated by different methods, showed up to a specific surface area of about 15 m^2/g, a positive correlation between crushing strength and surface area. This is explained by increasing numbers of binding points with an increasing surface area of the particulate solid. A further increase in surface area, measured by nitrogen adsorption and created by (micro)porous structures of aggregated particles, evidently does not contribute to an increased number of contact points. This is indeed shown by the products demonstrating a maximum binding capacity at higher specific surface area values, being about 120 N.

Next, the effect of moisture content on the compactibility of the final products was studied. Retrograded starch, again produced by debranching with Optimax® and α-amylolysis, was dehydrated by washing twice with 96% ethanol. The final product was equilibrated to moisture contents varying from 0% up to about 16% and

Table 4
Specific surface area of final products prepared by dehydration of potato starch recrystallized with magnesium sulphate, and crushing strength of the tablets compressed from these products at 3 kN

Dehydration	Specific surface area (m^2/g)	Crushing strength (N) tablet (300 mg, 13 mm)
Drying at 20°C	<0.1	4 ± 1
Washed twice with ethanol 96%	17.9	80 ± 3

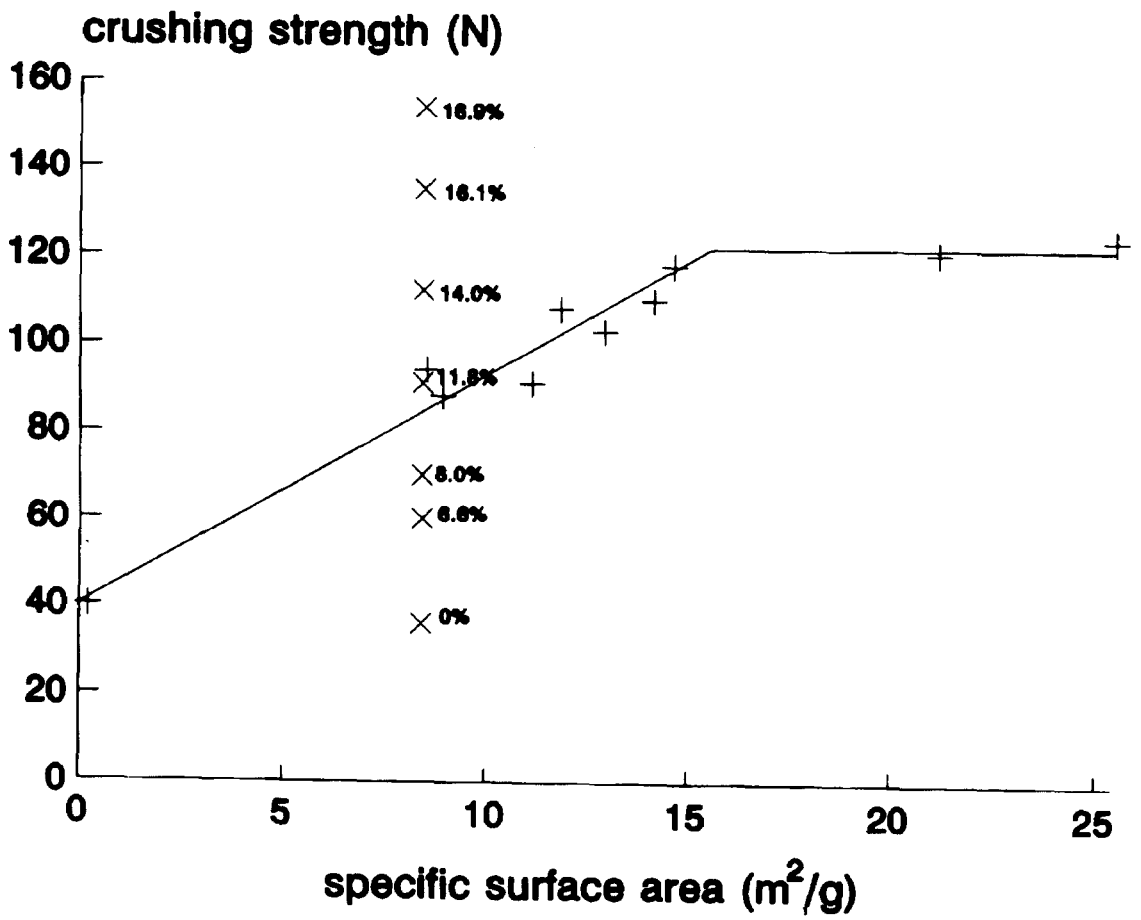

Fig. 2. Crushing strength of tablets (300 mg, ϕ 13 mm) compressed at 3 kN from differently dehydrated starch products prepared by debranching and α-amylolysis of potato starch versus specific surface area of the products with a moisture content of 12% (+); different moisture contents are indicated in the figure.

subsequently tested on compactibility. The differently equilibrated products, all having the same specific surface area, demonstrated a strongly increasing compactibility with increasing moisture content, explained by increasing plastic deformation and improved gliding of the particles on compaction (Fig. 2). This phenomenon emphasizes the importance of storage of the product at a constant temperature and relative humidity.

In order to verify whether products with a high specific surface area can only be obtained from enzymatically debranched retrograded starch, or

that this principle holds for strongly hydrated, insoluble starches in general, some experiments were performed on the basis of soluble potato starch, recrystallized in the presence of magnesium sulphate. The product, which contained both amylose and amylopectin, was dried at room temperature and washed twice with ethanol, respectively. As observed for the other materials studied, the product dehydrated by washing with ethanol indeed showed both an increased specific surface area and a high binding capacity, as compared to the product dried at room temperature (Table 4). However, the compactibility appeared to be lower as compared to similar products prepared by enzymatic degradation of potato starch.

In conclusion, starch exhibiting poor dry binding can be modified into products with excellent compactibility by debranching the amylopectin fraction by pullulanase and degradation of the amylose fraction by α-amylolysis, followed by suitable dehydration of the precipitated and filtered retrograded starch to produce high specific surface area products. Chemical desiccation and freeze-drying proved to result in high specific surface area products, related with high binding capacities. The latter is strongly affected by the moisture content of the final product.

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