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Modified starches as hydrophilic matrices for controlled oral delivery.
I. Production and characterisation of thermally modified starches

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Summary

Thermal modified starches are introduced as hydrophilic matrices for controlled oral delivery systems. Three native starches, varying in their amylose/amylopectin content were pregelatinized by extrusion, drum-drying and a controlled pregelatinization–spray-drying technique in order to produce cold water-swellable starches. Partial pregelatinized starch could only be produced by the controlled pregelatinization–spray-drying technique. The influence of the amylose/amylopectin content and of the technique and degree of pregelatinization on the properties of the final products was evaluated. As regards the application as hydrogel matrices in controlled release tablets, promising results were seen for the extruded and drum-dried starches containing a medium to a high amount of amylopectin.

Introduction

Several hydrophilic polymers have been investigated for their use in the formulation of prolonged release tablets. Mechanisms of drug release from hydrophilic matrices are complex and were characterised by Bamba et al. (1979). The successful use of hydroxypropylmethylcellulose in the production of prolonged release tablets is well documented (Buri and Doelker, 1980). Modified starches have never been investigated thoroughly as possible matrix-forming excipients. Only few investigators mention the possible use of some modified starches in the formulation of sustained release preparations (Körössyovà et al., 1979; Vitkovà et al., 1981, 1982; Rak et al., 1983; Van Aerde and Remon, 1988).

This paper reports the production and characterization of thermally modified starches which may be used as hydrophilic matrices for oral drug delivery. The type of starch, the degree of pregelatinization and the pregelatinization technique may have an influence on the drug release from hydrophilic starch matrices. Therefore, the sources of all starches under investigation are native starches of corn and hybrids of corn containing different amounts of amylose and amylopectin. Because native starches do not swell extensively in cold water, pregelatinization is used in order to

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produce cold water-swellable starches. Different processes are proposed for pregelatinization: drum-drying, extrusion and a controlled pregelatinization–spray-drying technique. Drum-drying and extrusion are common techniques for pregelatinization in the food industry. Pregelatinized spray-dried starches are not commercially available and were consequently produced in our laboratory.

Materials and Methods

Materials

The 3 native starches used for spray-drying were characterized by a different amylose–amylopectin ratio: waxy maize (±100% amylopectin) (Meriwax, Amylum, Aalst, Belgium), corn starch (±70% amylopectin) (Meritena, Amylum, Aalst, Belgium), high-amylose starch (±75% amylose) (Hylon VII, National Starch, Bridgewater, NJ). Spray-dried products were produced in our laboratory. The extruded and drum-dried starches were obtained from Cerestar (Vilvoorde, Belgium). An overview of all products used is given in Table 1.

TABLE 1

Native and modified starches under investigation

	Waxy maize	Corn starch	High amylose
Native starch	NSWM	NSCS	NSHA
Spray-dried, not pregelat.	SDWMO	SDCSO	SDHAO
Spray-dried, partially pregelat.	SDWMP	SDCSP	SDHAP
Spray-dried, totally pregelat.	SDWMT	SDCST	SDHAT
Drum-dried	DDWM	DDCS	–
Extruded	EWM	ECS	EHA

– = high amylose cannot be drum-dried at atmospheric pressure because of the gelatinization temperature being higher than 100 °C.

System design for the production of spray dried starches.

Fig. 1 shows the design of a controlled continuous preheating system, connected to a pilot spray-drier (Anhydro, type A1, Copenhagen, Denmark) in order to produce spray-dried starches of a varying degree of pregelatinization. The preheating system consists of a 50 litre tank equipped with a stirrer and is directly connected to a pump (Seepex type 012-12NK/110-4440-4.0.4-26.8, Verhoeven, Schoten, Belgium). The pump, driven by a stepless adjustable engine (Bockwordt, type CBO-71N/4D, Verhoeven, Schoten, Belgium) provides a pressure-independent flow below 1.2×10^6 Pa from 0 to 20 $l \cdot h^{-1}$. The preheating body consists of several disconnectable tubes enclosed

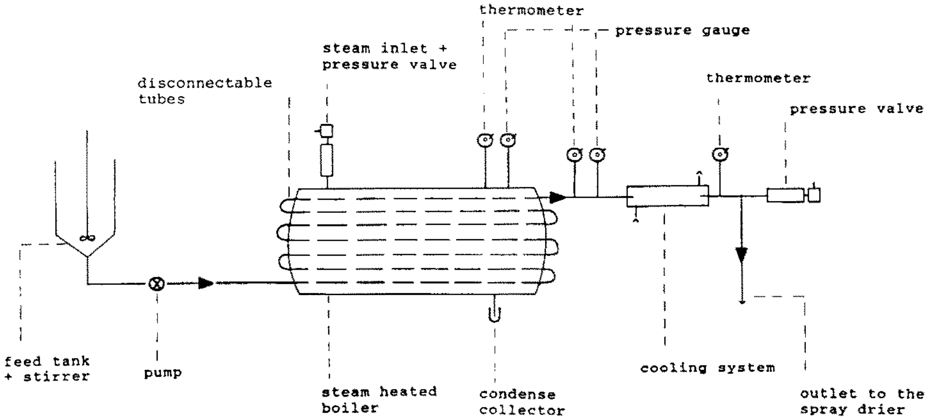

Fig. 1. Design of a controlled preheating system for the pregelatinization of starches prior to spray-drying.

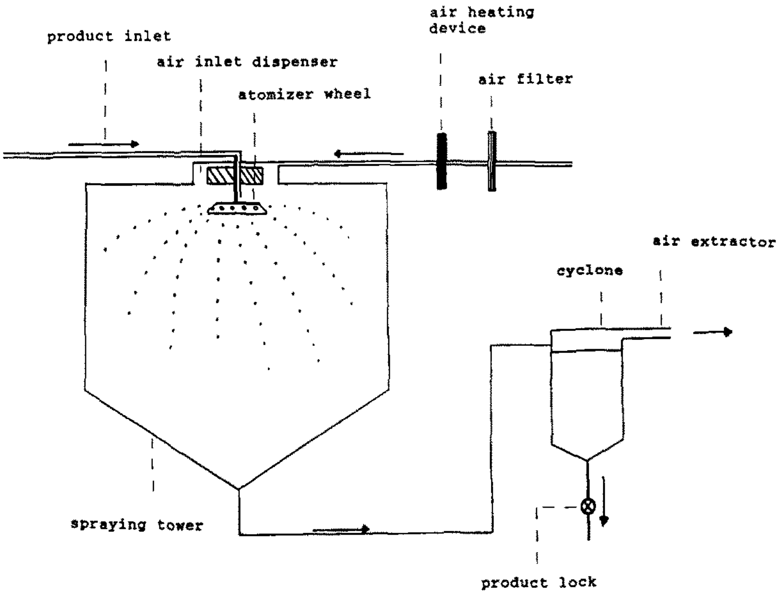

Fig. 2. Spray-drying system for non-, partially and fully pregelatinized starches.

in a steam-heated boiler. The total length of the tubes is variable from 1 to 30 m, corresponding to a volume varying from 0.2 to 6 litres. The steam inlet, to maintain the boiler's temperature, is controlled by a pressure-driven valve. The boiler is fitted with a thermometer, a pressure gauge and a condense collector. All materials in contact with the starch slurry are made of teflon or stainless steel.

TABLE 2

Operating conditions for the pretreatment of different starch dispersions prior to spray-drying

Product	Starch concentration (%; w/v)	Heating temperature (° C)	Time of residence in the preheating system (min)
SDWMO	10	25	1
SDWMP	6	61	3
SDWMT	6	70	3
SDCSO	10	25	1
SDCSP	6	62	3
SDCST	6	65	9
SDHAO	10	25	1
SDHAP	8	77	9
SDHAT	8	107	20

The outlet of the last tube is connected to a cooling unit avoiding an abrupt expansion of the boiling slurry when released into the spray-drier. The outlet of the cooling unit is connected to a counter-pressure valve, controlling the temperature of the slurry. The starch slurry is then atomized in the spray-drier (Fig. 2) equipped with an atomizer wheel (Anhydro atomizer, Denmark) rotating at ±25,000 rpm resulting in a peripheral velocity of 120 $m \cdot s^{-1}$. The drying air is filtered over an Ashrea 85 filter and is preheated by an electrical heating device. The ceiling air inlet blades of the spray-drier are shaped to force a circulating co-current flow.

During all productions, the feeding rate was 20 $l \cdot h^{-1}$ and additional cooling before entering the atomizer was only necessary in the case of SDHAT. The air inlet temperature in the spray-drier was 170 °C and the outlet air temperature was 95 °C. The specific operating conditions are given in Table 2.

Molecular weight distribution and dextrose equivalents of native and modified starches

In comparison to the native starches, the modified starches were analysed for their molecular weight distribution by high-pressure gel permeation chromatography. Samples were injected via a WISP 710A injector (Millipore, Brussels, Belgium) and eluted with demineralized water over two columns (Ionpack S 805 + Ionpack S 804, 50 cm length each, Shodex, Eupen, Belgium) at 70 °C and a total pressure of 1100 psi. An Erma refractive index detector (type ERC-7510, Brussels, Belgium) was used at 35 °C. The determination of the polymer length was calculated with regard to two standard solutions containing equal parts of Pullulan standards (Shodex, P-82), with a M_w ranging from 850,000 to 12,200 and 380,000 to 5800, respectively.

Dextrose equivalents were determined using the method described by The Commission of he European Communities (Method 8, No. L 239 47).

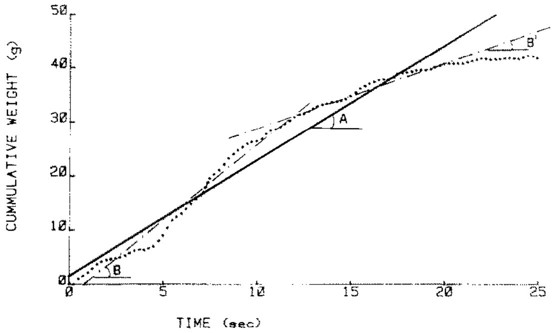

Fig. 3. Representative hypothetical powder flow plot. A indicates the slope of the best fitting line between all individual points of the up-going part of the plot. Slope B and B′ represent the slope of the first and the last medium part of the plot respectively.

Particle size and shape analysis

Prior to analysis, the starches were dispersed in isopropylmyristate, in which the particles do not swell, at a concentration of 1% (w/w). The particle size analysis was performed using a light microscope (Carl Zeiss Photomicroscope, Carl Zeiss, F.R.G.). The mean size of 50 individual particles was measured using a calibrated ocular lens. The particle shape was investigated by scanning electron microscopy (JEOL, SXA-50, A-electron probe, Japan).

Powder flow determination

The flowability of the starches was determined using a computerized strain-gauge balance as described by De Greve et al. (1986). During the test with a 50 g powder sample, the cumulative weight value on the balance was registered at regular time intervals. The flow speed was deduced from the slope (slope A) of the powder flow plot as shown in Fig. 3 and expressed as $ml \cdot s^{-1}$ as the slope value ($g \cdot s^{-1}$) was multiplied by the bulk volume ($ml \cdot g^{-1}$) of the powder. The flow uniformity is derived from the correlation between the individual points of the curve. The correlation is calculated by the least-squares method. The influence of powder densification on the powder flow is calculated from the difference in slope between the first (slope B) and last half part (slope B′) of the powder flow plot. The flow uniformity and the influence of powder densification were expressed as dimensionless numbers and are assumed to be acceptable between 0% to 100%, and −100% to +100%, respectively. These arbitrary limits are set up by comparison with a lot of products as Emcompress (c.n. Schmidt, Adam, The Netherlands), Tablettose (DMV, Veghel, The Netherlands) and Avicel pH 102 (Pharmachemic, Antwerpen, Belgium) which flow characteristics are believed to be acceptable.

The Hausner ratio was determined as the ratio of the bulk volume to the tap volume of the powder. Therefore the volume of a 50 g sample, which was poured into a graduated cylinder, was read before and after 100 taps (J. Engelsman, Ludwigshafen, F.R.G.).

Determination of the degree of pregelatinization

Quantitative characterization of the degree of pregelatinization was performed by determination of the pregelatinization enthalpy using a differential scanning calorimeter (DSC 2, Perkin-Elmer, Norwalk, U.K.). The sample cups were filled with an accurately weighed amount of a homogeneous starch dispersion in deionized water (1/3; w/w). The cups are hermetically sealed to prevent water evaporation. The temperature of analysis ranges from 25 °C up to 150 °C at a heating rate of $10\,°C \cdot min^{-1}$. The pregelatinization energy and peak temperature were deduced from the DSCplots as described by Lund (1983) and the degree of pregelatinization was calculated referring to a calibration ($-\Delta H = 28.45$ J · g^{-1}, m.p. = 156.4 ° C) with indium.

Moisture content

The water content of 0.1 g samples, stored at ambient conditions, was determined using the Karl Fischer method. Equilibrated samples were predried at 60 ° C and 26.7 kPa for one week. The loss of weight of a 2 g sample was determined by weighing, and expressed as a percent. In comparison to that result, the moisture content was determined by a Karl Fischer titration on a 0.1 g sample of the same product. The loss of weight was also determined for starch samples predried at 120 ° C and 26.7 kPa for 72 h. All determinations were performed in 3-fold.

Determination of moisture uptake and sorption hysteresis

Nine samples of each starch, weighing about 2 g, were put into Petri dishes and were vacuum-dried at 26.7 kPa and 60 ° C until constant weight.

Three samples of each starch were dried at 26.7 kPa and 120 ° C for 72 h and weighed again. This value reveals the dry weight base.

Three other samples were kept successively in relative humidity conditions of 30%, 40%, 65%, 85% and 96% at 20 ° C during one week each. The increase of weight was calculated on dry weight basis.

Desorption curves were determined by storing the remaining 3 samples of each starch in a relative humidity of 96% at 20 ° C until constant weight. Next, the humid samples were kept successively at 85%, 65%, 40%, 30% and 10% R.H. at 20 ° C during one week each. The loss of weight was calculated on dry weight basis and expressed as percentage.

Determination of gel strength

The hardness and cohesiveness were determined using the Instron Universal testing machine (Instron, U.K.). The determination was done on a starch/saccharose/water mixture (150 : 350 : 900 w/w/w). Sample preparation was as follows: all powders were sieved through a 500 μm sieve and mixed in a Hobart planetary mixer (Hobart type K45SS, Troy, OH, U.S.A.) at 70 rpm for 5 min using a "K"-shaped mixer blade. The water was added all at once and the paste was mixed for 1 min at 210 rpm using a "whisk" mixing arm; 250 ml paste was filled in 300 ml hermetically closed beakers and allowed to stand for 4 h at 20 ° C prior to determination. Due to a rapid water absorption of the cold swellable starches, the water uptake could be obstructed after the initial absorption phase. Therefore saccharose was added to the dry mixture prior to wetting to prevent lump formation. The plunger penetrated a depth of 10 mm into the gel. The hardness of this gel was derived from the height of the force peak on the first compression cycle (Fig. 4) and is expressed as Newtons. The cohesiveness is dimensionless as it is defined as the ratio of the positive force area under the first and second compression cycle.

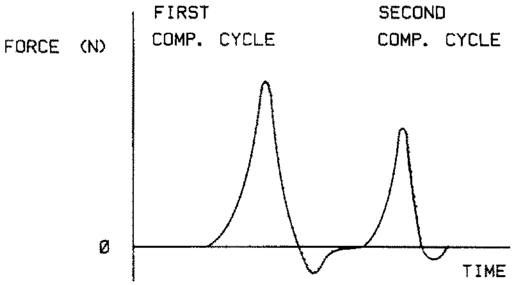

Fig. 4. Plot of a replicated compression cycle of a starch paste using an Instron Universal testing machine.

Swelling characteristics

Swelling capacity. The method described by Bowen and Vadino (1984) was used. 5 g of starch were poured into a 100 ml volumetric cylinder and the bulk volume was measured (V_1). Next 90 ml of deionized water (20 ° C) were added and the dispersion was well shaken for 5 min. Water was added up to 100 ml. The dispersion was allowed to stand for 24 h before the sedimentation volume was read (V_2). The swelling volume is calculated as V_2/V_1.

Water retention capacity. A dispersion was prepared as indicated for the determination of the swelling volume. 15 ml of the freshly prepared dispersion were transferred to a polypropylene tube and centrifuged for 30 min at 4500 rpm. The supernatant was discarded and the residue weighed (W_1). Next the residue was dried at 60 °C until constant weight (W_2). The water retaining capacity is calculated as W_1/W_2 (Ring, 1985; Kimihiko et al., 1981).

Amount of solubles. 10 ml of the discarded supernatant of the previous test were dried at 110 °C until constant weight. The dry weight is defined as the amount of solubles and is expressed as the percentage of the initial weight of the starch samples (Kimihiko et al., 1981).

Viscosity determination of starch in function of pH and ionic strength. The viscosity of starch dispersions was determined at 20 °C (± 0.5 °C) with a rotary viscosimeter (Haake V12, Karlsruhe, F.R.G.) using an MVI body. Above 40,000 mPa · s, the viscosity was determined with a Brookfield viscosimeter (Model C, Stoughton, MA, U.S.A.) using a spindle (type 7). All values were read after 10 minutes. The influence of ionic strength was determined at neutral pH in deionized water, 0.9% NaCl solution (= 0.154 M) and 3.0% NaCl solution (= 0.505 M). The influence of pH was evaluated using a hydrochloric acid buffer (pH 1.2) solution, an acid phthalate buffer (pH 3), phosphate buffers (pH 7 and 8) and an alkaline borate buffer (pH 9), according to the U.S.P. XXI. The ionic strength of all these buffers was equalized at $\mu = 0.136$ M by the addition of NaCl.

Results and Discussion

Native starches have to be heated in water to make them cold water-swellable. Fully pregelatinized starches can be produced by heating the starch slurry above the gelatinization temperature (Goering et al., 1974) using drum-drying or extrusion. The energy required for the pregelatinization is proportional to the amylose content of the native starches (Wootton and Bamanuarachchi, 1979). Starches containing a high amount of amylose (70%) cannot be fully pregelatinized by drum-drying because of the gelatinization temperature being higher than the operating temperature. A controlled pregelatinizing–spray-drying technique enabled us to produce non-, partial-, and fully pregelatinized starches of all sources.

Spray-drying of a starch slurry is characterized by the very short contact time of the dispersed starch particles with the hot drying air. This method does not enable the starch particles to swell extensively (Wurzburg, 1968). In order to prepare pregelatinized–spray-dried products, a production design was set up for preheating the starch slurry at a fixed temperature during a certain time, just before entering the spray-drier. The process consists of the following steps: non-, spatial or full pregelatinization, atomization, drying, air extraction and collection of the dry residue. Individual operating conditions, indicated in Table 2, were applied for the production of starches of a particular degree of pregelatinization. Starches with a high degree of amylose need a pregelatinization temperature above 100 °C. This can only be achieved using a pressure above 1 atm., creating an additional problem of slurry expansion before entering the atomizer. Therefore an additional cooler was placed before the spray-drier.

Table 3 indicates the molecular weight distribution for all starches under investigation. As one would expect, the polymer weight is related to the amylopectin–amylose ratio. The extrusion procedure in all cases and drum-drying procedure for corn starch only, cause a reduction in polymer length. A low M_w/M_v value, especially for the extruded starches, indicates a small polymer length distribution. All dextrose equivalent values, representing the amount of reducible end groups, are low (< 1.0) indicating a low degree of depolymerisation during the thermal treatment.

The mean particle size of the different starches is given in Table 4. Independent of the amylose–amylopectin ratio, the particle size ranges between 8 and 15 μm for non- and partially pregelatinized starches. The fully pregelatinized starches have a higher average particle size characterized by a broader distribution. Fig. 5 shows SEM pictures of the different starches in comparison to the native ones. The pregelatinized starches have lost their original starch grain shape. The reason for the increase of particle size particularly for drum-dried and extruded starches, can be explained by the mechanical grinding after pregelatinization re-

TABLE 3

The molecular weight distribution of all starches under investigation expressed as percent

	$> 5 \times 10^6$	$10^6 < 5 \times 10^6$	$2 \times 10^5 < 10^6$	$25 \times 10^3 < 2 \times 10^5$	$< 25 \times 10^3$	M_w/M_n
NSWM	74.3	14.5	4.4	3.7	3.1	73.0
SDWMO	74.5	13.9	4.4	4.0	3.2	75.6
SDWMP	73.7	16.1	4.2	3.0	3.0	65.2
SDWMT	75.4	15.8	4.0	3.3	1.5	25.3
DDWM	75.5	18.9	3.4	1.6	0.6	11.8
EWM	0.1	64.8	27.3	6.1	1.7	6.1
NSCS	52.1	16.1	11.9	11.9	8.0	120.0
SDCSO	46.9	16.7	13.3	13.7	9.4	129.6
SDCSP	52.9	16.2	11.9	11.5	7.5	100.0
SDCST	52.1	17.1	11.9	11.0	7.9	106.5
DDCS	3.5	47.4	28.2	16.3	4.6	60.1
ECS	0.3	54.0	28.9	13.7	3.1	10.5
NSHA	24.1	14.0	17.3	27.1	17.5	119.8
SDHAO	21.7	13.8	17.6	27.9	19.0	123.8
SDHAP	24.6	14.3	17.2	26.7	17.2	121.5
SDHAT	24.2	15.0	16.7	32.2	11.9	109.9
EHA	0.4	36.7	29.1	25.4	8.4	16.0

sulting in flaky shaped products. The fully pregelatinized–spray-dried starches retain their shell but lost their content as can be seen in Fig. 5.

TABLE 4

The mean particle size (mean value ± S.D., n = 50) of the starches under investigation, determined by light microscopy

	Mean particle size (μm)
NSWM	13.0 (±2.8)
SDWMO	11.1 (±2.8)
SDWMP	12.4 (±3.7)
SDWMT	25.2 (±13.2)
DDWM	24.7 (±14.1)
EWM	24.2 (±17.8)
NSCS	13.8 (±4.0)
SDCSO	12.9 (±4.7)
SDCSP	13.7 (±4.4)
SDCST	24.7 (±8.9)
DDCS	25.4 (±10.5)
ECS	28.0 (±9.0)
NSHA	8.7 (±2.6)
SDHAO	8.3 (±2.7)
SDHAP	15.4 (±6.8)
SDHAT	18.9 (±8.1)
EHA	35.0 (±45.7)

The powder flow characteristics of the starches indicated in Table 5 are compared to some widely used excipients such as Tablettose, Emcompress and Avicel pH 102. The flow speed is expressed as $\mathrm{ml \cdot s^{-1}}$ as this value takes density differences of the excipients into account. This value does not describe how the powder behaves during the flow. Therefore, two new values, flow uniformity and the influence of powder densification, are introduced. The flow uniformity gives an idea about the instantaneous changes in flow speed. The influence of powder densification on the powder flow gives an idea about the change of the flow speed all over the curve. This can be important because the flow characteristics of powders can be altered by densification which is induced by vibration of the feeding hopper. All extruded starches show excellent powder flow characteristics (Table 5) which is very important to achieve a constant die filling during tablet production. Apart from the relatively low flow speed, the flow uniformity and influence of densification of the drum-dried products is acceptable. All the other starches show a poor flowability. Extremely poor flow characteristics are seen for the fully pregelatinized spray-dried starches. For these starches, a low flow

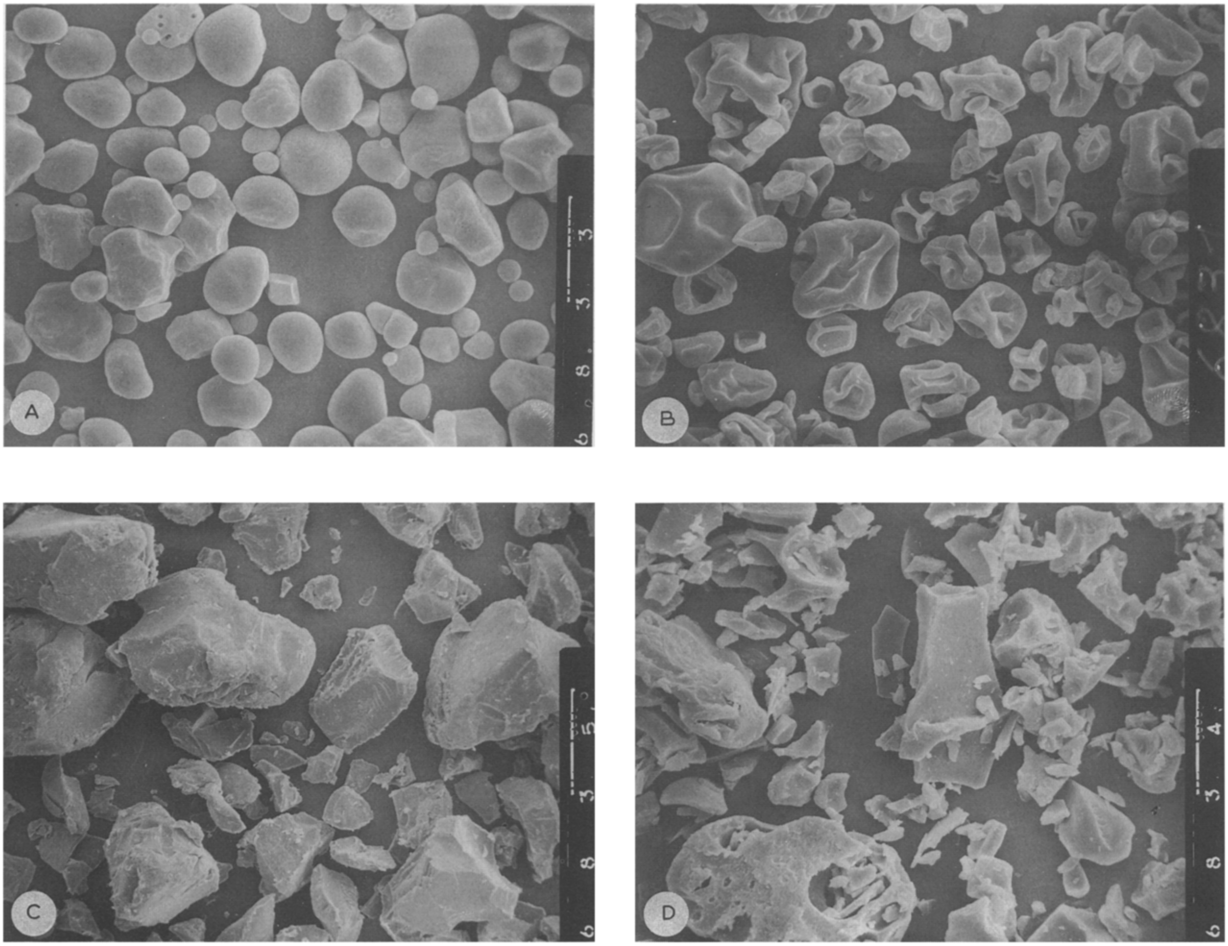

Fig. 5. SEM pictures of native corn starch (A, ×1000), fully pregelatinized spray-dried corn starch (B, ×500), extruded corn starch (C, ×100) and drum-dried corn starch (D, ×500).

speed and flow uniformity as well as a high influence of densification are observed. Even when the flow characteristics are not influenced by the densification of the powder due to vibrations, the densification of the powder may cause a raise of the tablet weight during tabletting. This can be predicted by a high Hausner ratio (Table 5) as in the case of the fully pregelatinized–spray-dried starches.

The degree of gelatinization is determined as the change of enthalpy during heating of the sample using differential scanning calorimetry (DSC). The gelatinization point (onset temperature of the endothermal peak) as well as the thermal energy required for pregelatinization of the different native starches were reported previously by Wootton and Bamanuarachchi (1979). In general, the thermal energy reported here is lower compared to the values reported by the previously mentioned authors (Table 6), but they mention that differences in thermal energy may be due to variations in the origin of the starch and a different scanning rate ($10\,^\circ\mathrm{C} \cdot \mathrm{min}^{-1}$ in this work in comparison to $16\,^\circ\mathrm{C} \cdot \mathrm{min}^{-1}$ used by Wootton and Bamanuarachchi (1979)). Table 6 makes clear that a higher gelatinization temperature is observed

TABLE 5

Powder flow characteristics of the starches under investigation, compared to other tabletting excipients. Data are indicated as mean values (± S.D.), n = 3

Product	Hausner ratio	Flow speed ($ml \cdot s^{-1}$)	Flow uniformity (accept. > 0)	Densificat. infl. (−100 < accept. < 100)
NSWM	1.39 (0.02)	1.2 (0.1)	56.7 (8.2)	6.7 (0.3)
SDWMO	1.26 (0.01)	1.9 (0.6)	83.9 (2.4)	−10.6 (2.1)
SDWMP	1.35 (0.04)	1.2 (0.1)	60.0 (3.3)	−2.7 (2.1)
SDWMT *	1.46 (0.03)	0.3 (0.2)	−173.8 (24.0)	55.5 (8.4)
DDWM	1.35 (0.02)	3.6 (0.3)	78.2 (4.9)	0.0 (1.7)
EWM	1.21 (0.06)	19.0 (0.9)	86.0 (2.1)	11.4 (1.7)
NSCS	1.26 (0.04)	1.0 (0.3)	14.8 (28.1)	−40.7 (9.2)
SDCSO	1.20 (0.05)	0.6 (0.1)	1.4 (19.0)	−36.8 (12.3)
SDCSP	1.28 (0.02)	1.5 (0.2)	59.3 (6.3)	−4.4 (3.3)
SDCST *	1.48 (0.04)	0.1 (0.1)	−1427.9 (123.3)	−353.7 (36.7)
DDCS	1.42 (0.03)	2.0 (0.1)	37.3 (12.4)	6.7 (2.9)
ECS	1.19 (0.03)	17.0 (0.2)	86.2 (2.0)	−6.5 (4.5)
NSHA *	1.24 (0.04)	0.4 (0.1)	−121.5 (118.4)	6.1 (2.8)
SDHAO	1.19 (0.05)	0.6 (0.2)	24.7 (12.3)	9.9 (6.7)
SDHAP *	1.40 (0.01)	0.4 (0.2)	−256.7 (96.7)	2.0 (0.9)
SDHAT *	1.55 (0.10)	0.2 (0.2)	−342.6 (143.7)	35.9 (1.9)
EHA	1.20 (0.02)	15.2 (0.4)	73.2 (4.1)	−14.3 (5.0)
Avicel pH 102	1.28 (0.01)	11.1 (0.8)	10.2 (0.8)	−10.2 (1.8)
Emcompr.	1.16 (0.01)	16.6 (0.4)	46.9 (9.3)	−6.6 (7.9)
Tablet.	1.23 (0.01)	14.1 (0.5)	60.0 (9.1)	2.4 (1.1)

* These products have a non-acceptable flowability.

and simultaneously more energy is required for the pregelatinization of native starches with increasing amylose/amylopectin ratio.

Several methods have been described to determine the moisture content of solids (Roth, 1966). While for most starch grains the results of the oven-drying and the Karl Fisher procedure are in close agreement, differences have been mentioned for corn starch (Hart and Neustadt, 1957; Sair and Fetzer, 1942). The differences between oven-drying and Karl Fisher determination are even more pronounced in this study considering the predried starches (Table 7). The starches do contain a considerably large amount of moisture at ambient conditions. As free water may interfere with drug stability in solid dosage forms (Delonca et al., 1969), it is important to know whether this relatively large amount of water is available or not. The loss of weight after a mild drying technique (60 °C, 26.7 kPa, one week) indicates that only for the native and extruded starches most of the water content is easily removed by this technique. For the other starches even a drastic oven-drying method (120 °C, 26.7 kPa, 72 h) was not sufficient to remove a large amount of water. So, in particular, extruded starches and to a lesser extent native starches release most of their water content during a mild drying technique, which implies that, in contrast to the other starches, this water is also easily available to interfere in the drug stability. On the other hand, the water absorbed or adsorbed due to the hygroscopic character of the starches could also alter the stability of drugs in the solid dosage form. The more disrupted the granular structure is (extruded and drum-dried starches) the more easily the water can be absorbed, especially in high humidity conditions (Fig. 6). The moisture hysteresis curves show that above 70% relative humidity, the starches contain a high amount of water which

TABLE 6

Gelatinization characteristics of starch dispersions in water determined by differential scanning calorimetry (n = 1)

Product	Peak temperature of gelatinization (°C)	Gelatin. energy $-\Delta H$ (J·g^{-1})	Degree of gelatinization (%)
NSWM	69.0	15.9	0.0
SDWMO	70.8	15.5	2.6
SDWMP	71.7	8.4	47.7
SDWMT	–	0.0	100.0
DDWM	–	0.0	100.0
EWM	–	0.0	100.0
NSCS	69.0	18.4	0.0
SDCSO	73.0	17.6	4.5
SDCSP	74.0	10.9	40.9
SDCST	–	0.0	100.0
DDCS	–	0.0	100.0
ECS	–	0.0	100.0
NSHA	72.5 (H_1)	29.7 *	0.0
SDHAO	70.0 (H_1) 97.0 (H_2)	29.3 *	1.4
SDHAP	* (H_1) 95.5 (H_2)	6.3 *	78.9
SDHAT	–	0.0	100.0
EHA	–	0.0	100.0

* Due to a wide and obtuse endothermal peak, the gelatinization enthalpy as well as the gelatinization point are not accurately measurable.

H_1 = first endotherm; H_2 = second endotherm due to other crystalline regions.

TABLE 7

Water content of the starches stored at room conditions and stored at 60 °C for one week and 72 h, respectively, at 26.7 kPa. All values are compared to the original weight of the starches at room conditions

Product	Storage cond.			
	Room condition	60 °C, 26.7 kPa for one week		120 °C, 26.7 kPa during 72 h
	Water cont. K.F. (%)	Weight ↓ oven (%)	Water cont. K.F. (%)	Weight ↓ oven (%)
NSWM	8.5	5.8	3.1	4.2
SDWMO	6.1	5.7	0.4	1.3
SDWMP	3.8	3.0	0.8	1.6
SDWMT	4.8	3.7	0.2	0.9
DDWM	3.0	3.0	0.0	0.7
EWM	6.5	1.5	5.0	5.8
NSCS	8.5	6.0	2.5	3.9
SDCSO	6.1	5.5	0.6	1.7
SDCSP	7.2	5.4	1.9	3.0
SDCST	4.8	4.7	0.1	1.0
DDCS	3.3	3.3	0.0	1.2
ECS	6.9	2.0	4.6	5.5
NSHA	8.9	7.1	1.9	2.9
SDHAO	7.1	7.1	0.0	1.0
SDHAP	6.3	6.2	0.1	0.8
SDHAT	5.8	5.8	0.0	1.1
EHA	5.8	1.7	4.1	4.8

The maximum standard deviation is 0.1% for the oven method and 0.4% for the Karl Fisher method ($n = 3$).

may be important for drug stability and tablet formulation stability. Although, according to the classification of Callahan et al. (1982), all starches under investigation are said to be only slightly hygroscopic.

The release rate of a drug from a hydrogel matrix is a complex mechanism. One of the major influencing factor is the rate of erosion of the gel layer of the wetted matrix tablet. Two properties dominate the erosion of the gel layer; the gel strength of the swollen gel and the cohesiveness. As can be seen from Table 8, a minimal amount of amylose seems to be an essential component to achieve a high hardness while the amylopectin seems to be responsible for the cohesive character of the gel. Amylose has an apparent negative effect on the cohesiveness of the swollen tablet.

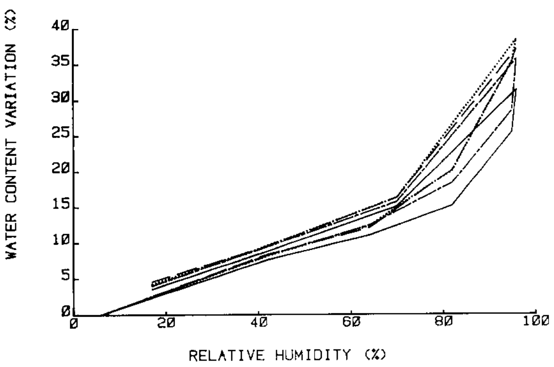

Fig. 6. Moisture hysteresis curve of native waxy maize (———), fully pregelatinized spray-dried waxy maize (- — — - -), extruded waxy maize (— — —) and drum-dried waxy maize (······).

TABLE 8

Gel strength characteristics of starch pastes (15% w/v in water) measured using the Instron Universal testing machine. Data are indicated as mean values ± S.D. (n = 3)

Product	Hardness (N) (±S.D.)	Cohesiveness (dimensionless) (±S.D.)
SDWMT	0.116 (0.003)	0.790 (0.069)
DDWM	0.115 (0.003)	0.833 (0.049)
EWM	0.104 (0.004)	0.833 (0.019)
SDCST	1.450 (0.061)	0.671 (0.024)
DDCS	3.810 (0.042)	0.694 (0.091)
ECS	0.558 (0.035)	0.676 (0.052)
SDHAT	1.481 (0.077)	0.539 (0.017)
EHA	0.606 (0.037)	0.496 (0.009)

For starches containing at least 25% amylose, the production process has an important influence on the hardness of the gel (Table 8). Starches not mentioned in this table yield a gel strength too low to provide a reasonable resistance against erosion.

The swelling characteristics of the different starches are described in Table 9. For pregelatinized starches, the swelling capacity, water retention capacity and amount of solubles are all related to the amylopectin content. A low swelling capacity is seen for pregelatinized starches containing a high amount of amylose because amylose tends to precipitate in water in contradiction to amylopectin which is said to be partially water-soluble (Young, 1984) resulting in a high amount of water solubles for amylose-free starches. Pregelatinized high amylose starches do not present a high water-retaining capacity because amylose tends to degrade. Still, a difference is seen between fully pregelatinized spray-dried starches on the one hand and extruded and drum-dried starches on the other hand. This may be due to the larger degree of disruption of the latter ones which is seen on the scanning electron micrographs (Fig. 5). Non-regelatinized starches show low values for all tests carried out because the amylopectin enclosed in the undisrupted starch grains is not able to come into action.

Ion strength and pH are two important parameters that may influence the viscosity of hydrogels. The viscosity of the starch dispersion is not influenced by a variation of the ionic strength and pH between 3 and 7 (Table 10). At pH 1.2, equal to the pH of the gastric fluid, the viscosity is very

TABLE 9

Swelling characteristics for all starches under investigation. Data are indicated as mean values ± S.D. (n = 3)

Product	Swelling volume (±S.D.)	Water retaining capacity (±S.D.)	Solubles (%) (±S.D.)
NSCS	0.92 (0.12)	2.3 (0.0)	0.04 (0.01)
SDCS O	0.79 (0.04)	2.3 (0.3)	0.05 (0.00)
SDCS P	0.68 (0.17)	3.6 (0.2)	0.06 (0.04)
SDCS T	≫ –	8.2 (0.8)	2.59 (0.12)
DDCS	≫ –	19.5 (1.9)	4.54 (0.08
ECS	≫ –	13.4 (2.1)	4.37 (0.02)
NSWM	0.80 (0.01)	2.0 (0.0)	0.03 (0.00)
SDWM	0.78 (0.33)	2.9 (0.3)	0.05 (0.00)
SDWM P	1.77 (0.33)	2.9 (0.1)	0.08 (0.00)
SDWM T	4.47 (0.19)	7.4 (1.0)	0.18 (0.03)
DDWM	6.88 (0.48)	12.4 (0.9)	2.41 (0.09)
EWM	6.54 (0.29)	11.9 (1.2)	2.68 (0.08)
NSHA	1.08 (0.21)	2.4 (0.2)	0.02 (0.00)
SDHA O	0.89 (0.13)	2.5 (0.0)	0.01 (0.00)
SDHA P	2.33 (0.03)	3.7 (0.7)	0.19 (0.03)
SDHA T	3.47 (0.38)	6.1 (0.7)	0.30 (0.02)
EHA	3.60 (0.17)	4.5 (0.9)	0.48 (0.07)

TABLE 10

Influence of the pH and ionic strength on the viscosity (mPa · s) of starch dispersions at 25 °C

Starch type	Starch conc. (%)	Solution conditions							
		Water	NaCl 0.9%	NaCl 3.0%	pH 1.2	pH 3.0	pH 7.0	pH 8.0	pH 9.0
NSWM	45	70	61	138	22	73	62	62	51
SDWMO	40	57	62	55	22	67	63	62	68
SDWMP	25	117	114	174	12	154	145	332	66 533
SDWMT	14	287	253	263	16	243	257	422 400	934 400
DDWM	14	280	273	292	21	233	248	763 733	3285 333
EWM	14	101	115	111	12	115	116	2 181	4 425
NSCS	50	53	54	48	18	56	54	59	43
SDCSO	45	47	51	37	13	48	59	53	51
SDCSP	30	17	10	21	12	10	15	16	22
SDCST	10	226	238	273	21	202	217	293	345
DDCS	8	151	164	199	12	121	144	989	28 907
ECS	10	84	118	103	1	106	121	1 766	2 671
NSHA	40	34	34	57	8	33	32	33	34
SDHAO	40	85	88	77	12	102	94	105	81
SDHAP	20	125	140	147	13	134	141	143	147
SDHAT	15	229	199	203	20	236	207	265	334
EHA	15	12	28	31	7	36	24	24	29

low, due to the hydrolysis of the starch polymers (Whistler and Daniel, 1984). For pregelatinized starches, above pH 7, a sharp increase in viscosity is observed which is related to the amount of amylopectin that the starches contain. This increase in viscosity was higher for the drum-dried starches than for the extruded and spray-dried starches which can be explained by the eclipsing of the glycopyranoside units in aqueous alkaline solutions, resulting in a reorientation of the hydrogen groups from the axial to the equatorial position (Reeves and Blouin, 1957). This optical rotation tends to expand the random coil (Colson et al., 1974). These phenomena result finally in an increase in the viscosity of the starch dispersion. The eclipsing occurs easier for glucopyranoside units of amylopectin rather than for amylose because of the branching preventing a high degree of hydrogen bonding which hinders the eclipsing. Generally speaking, above pH 7 the influence of the pH on the viscosity of starch gels is increased by pregelatinization and a high amount of amylopectin.

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