Starch Acetates—Multifunctional Direct Compression Excipients

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INTRODUCTION

Native starch grains contain polymers consisting in varying ratios of linear amylose and branched amylopectin, which are composed of glucose monomers. Glucose monomers are linked to each other mainly by α-1,4 glucosidic bonds. A glucose monomer contains three hydroxyl groups, which can be, in the present case, acetylated. Native starch grains are insoluble in water, but they are hydroscopic materials which swell in the presence of water. Starches from various natural origins and their common derivates are well-known, safe, and have been extensively investigated in tablet formulations for various purposes. Native starches are used as disintegrants, diluents, and wet binders. However, their poor flow and high lubricant sensitivity make them less favoured in direct compression. Different chemical, mechanical, and physical modifications of native starches have been used to improve both their direct compression and controlled release properties (1–5). Although, various starches and their derivatives have been studied extensively, there is still much to examine about their mechanical properties as compacts. Furthermore, starch-based formulations are usually multicomponent formulations which increase the risks of incompatibility.

In the present study, novel direct compression excipients are introduced as starch acetates (6). The preparation of these acetates was accomplished, and their chemical properties were evaluated. The effects of substitution on the starch acetates were investigated according to physical and tablet properties. The resulting starch acetates were compared to commercially available direct compression excipients.

MATERIALS

Starch acetates were prepared by partially reacting hydroxyl groups of starch polymers with acetic acid anhydride in a basic esterification reaction as previously described (VTT, Chemical Technology, Materials Technology, Rajamäki, Finland) (6). Briefly, starch acetates were synthesized by allowing native barley starch to react with varying amounts of acetic acid anhydride in the presence of a 50% sodium hydroxide solution as a catalyst. After the reaction phase, the mixture was cooled and the barley starch acetate was precipitated from water with vigorous mixing. The precipitate was filtered and washed thoroughly with water and dried by the fixed bed method. Effects of various amounts of acetic acid anhydride and catalyst, and reaction conditions on the degree of substitution (ds) were evaluated by the titration method. Prepared starch acetates were sieved and sieve fractions of 53–297 μm were used in all the performed tests.

Commercially available direct compression excipients, i.e., microcrystalline cellulose (MCC) (Avicel® PH101, FMC, Philadelphia, PA), dicalcium phosphate dihydrate (DCP) (Emcompress®, Penwest Pharmaceuticals, Patterson, NY), and modified starch (MS) (Starch 1500, Colorcon, West Point, PA), were used as supplied. Magnesium stearate (Ph. Eur.) was used as a lubricant in tableting. Lubricant was added just before experimentation and mixed in a glass vessel for 1 min with Turbula 2P mixer (W.A. Bachofen, Switzerland). Water soluble (1:20) propranolol*HCl (Ph. Eur.) was chosen as a model drug for the dissolution studies. All powders were stored at 33% relative humidity and room temperature at least seven days prior to experimentation.

METHODS

Differential scanning calorimetry (DSC) (Perkin-Elmer DSC7, Perkin-Elmer Co., USA) was used in the determination of glass transition temperatures (Tg). Samples (4–6 mg) were enclosed in perforated 50 μl aluminum pans. The following heating program was followed: 20°C to 200°C (20°C/min); cooling to 100°C (20°C/min) and a second heating to 200°C (10°C/min), where the glass transition temperature was determined and expressed as the mean of three parallel scans.

X-ray diffraction patterns of the starch acetate powders were obtained by a Philips PW1710, ADP1700 automated powder diffractometer system (Philips, The Netherlands) under the conditions reported earlier (7).

Material densities were measured as five parallel determinations by a Multi Pycnometer (Quanta Chrome, USA) using helium as a measuring gas.

The particle size and shape factor of the starch acetates were calculated from digitized images of the scanning electron micrographs (SEM) (Jeol JSM-35, Japan). The Martin's diameter was measured from at least 740 starch acetate particles and at least 400 reference material particles. The shape factor was calculated as the ratio between the equivalent diameter of a sphere having the same area, and the equivalent diameter of a sphere having the same perimeter (8).

Flowability of the three parallel samples with 0.5 % (w/w) of magnesium stearate was determined as flow rate and angle of repose values by the Ph.Eur. (2.9.16) method.

The water content of the five replicated powder samples was measured by a Karl-Fischer titrator (Mettler DL 35 Karl-Fischer titrimeter, Switzerland).

The solid-liquid contact angle of the powders compressed at 255 MPa pressure was measured with the installations consisted of a video camera and digitized image equipment. A saturated aqueous solution of each compound was used as the test liquid and the volume of the drop applicated onto the tablet surface was 10 μl. The video camera took

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Table I. Powder and Tablet Properties of Starch Acetates with Different Degrees of Substitution (ds) and Some Widely Used Tableting Excipients (Mean and Standard Deviation in Parentheses)

	Particle density (g/cm^3)	Martin's diameter (μm)	Shape factor	Flowability (sec/100 g)	Angle of repose (degree)	Water content (%)	Contact angle (degree)
Starch acetate ds 0.34	1.515 (0.001)	49 (47)	0.89	4 (1)	21 (1)	7.5 (<0.1)	0
Starch acetate ds 1.19	1.461 (0.005)	32 (21)	0.88	6 (1)	22 (1)	5.1 (<0.1)	44.4 (1.0)
Starch acetate ds 2.1	1.347 (0.005)	55 (38)	0.85	5 (<1)	25 (<1)	2.3 (<0.1)	51.2 (1.6)
Starch acetate ds 2.9	1.367 (0.005)	69 (55)	0.82	8 (<1)	23 (1)	1.5 (<0.1)	53.6 (0.9)
Microcrystalline cellulose	1.656 (0.003)	30 (22)	0.78	X[a]	X[a]	5.0 (0.1)	27.9 (0.7)
Dicalcium phosphate dihydrate	2.332 (0.001)	163 (67)	0.88	3 (<1)	16 (<1)	0.7 (0.2)	0
Modified starch	1.527 (0.003)	30 (27)	0.84	3 (1)	21 (1)	8.0 (1.4)	42.5 (1.1)

[a] X = microcrystalline cellulose that did not flow through the funnel.

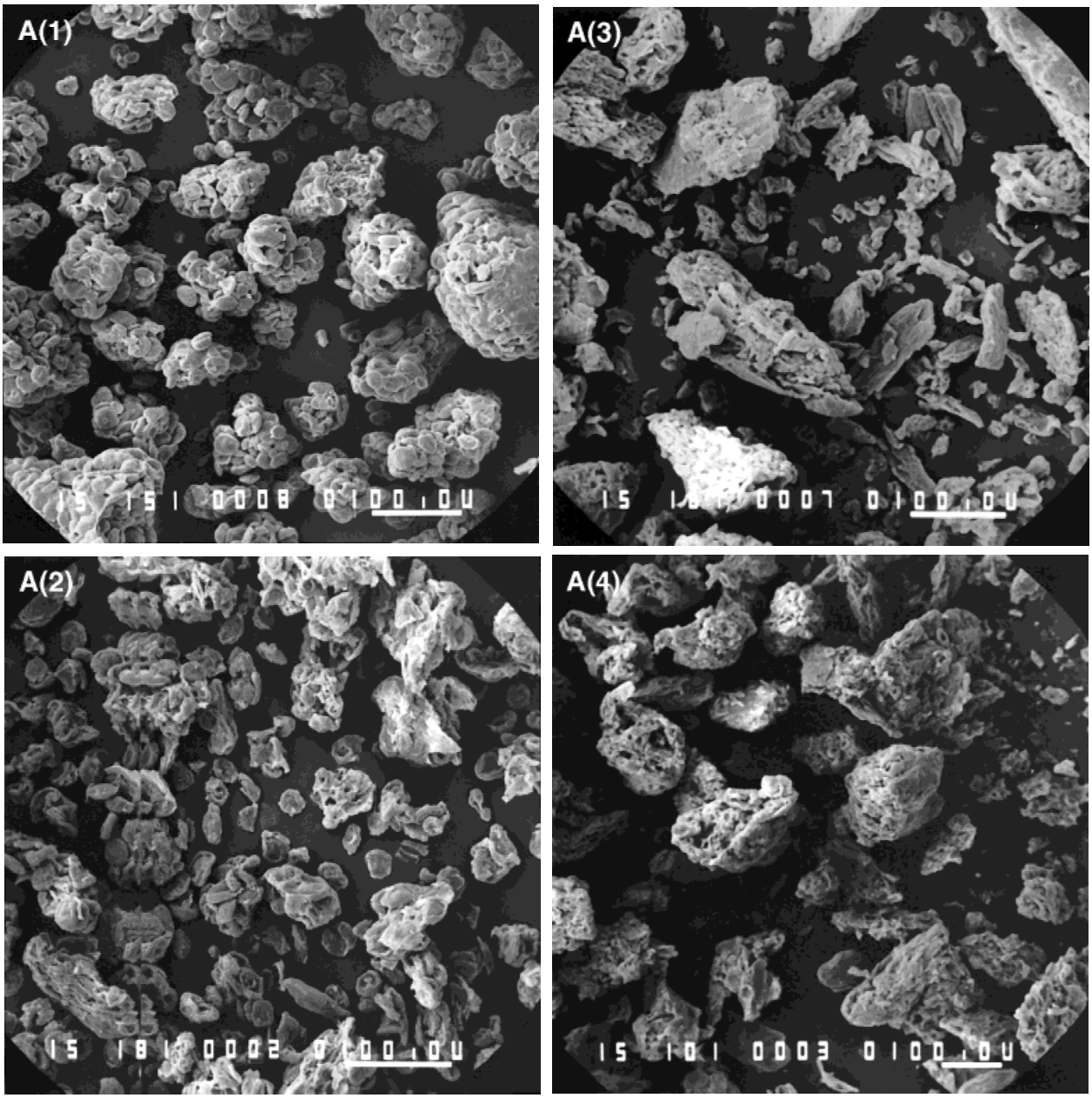

Fig. 1. SEM micrographs of starch acetate powders (A) and tablet surfaces (B) at the compression pressure of 320 MPa with 0.34 (1), 1.19 (2), 2.1 (3), and 2.9 (4) degree of substitution (ds). The bar is 100 μm.

pictures at 0.1 second intervals, where the contact angle was determined from the first four images. The test was repeated with three tablets.

Excipient tablets containing in all cases 0.5% (w/w) magnesium stearate as a lubricant and in drug release experimentation 25% (w/w) propranolol*HCl were compressed with an instrumented eccentric tablet press (Korsch EK-0, Germany), at a press speed of 30 rpm, using flat faced punches and die of 10 mm in diameter. Compression pressures of 90, 190, and 320 MPa were used. Tablet weights were adjusted to give a theoretical thickness of 1.5 mm at zero porosity, taking into account the diameter of the die and the material densities of the excipients (Table I), lubricant (1.074 g/cm^3) and drug (1.259 g/cm^3). Scanning electron micrographs were taken after compression to estimate the surface structure of the tablets.

Crushing strength, height, and diameter of the tablets were measured from six tablets after 24 hours of tableting. Crushing strengths were measured with a universal tester (CT-5 tester, Engineering Systems, England), operated at a constant cross head speed of 1 mm/min. Tensile strength of the tablets was calculated according to Fell and Newton (9).

Disintegration studies were made from three parallel tablets, according to the specifications of Ph. Eur. (2.9.1) disc method (Erweka, Germany). The disintegration medium was distilled water (800 ml) maintained at 37 ± 1.0°C.

The dissolution of propranolol*HCl from three parallel tablets was determined by the USP XXII rotating basket method, with a rotation speed of 100 rpm (Sotax AT6, Switzerland). The dissolution medium was 900 ml of 40 mmol phosphate buffer (pH 7.0) maintained at 37 ± 0.5°C. The amount of dissolved drug was analyzed by a UV spectrophotometer at a wavelength of 289 nm (Hitachi U-1100, Japan).

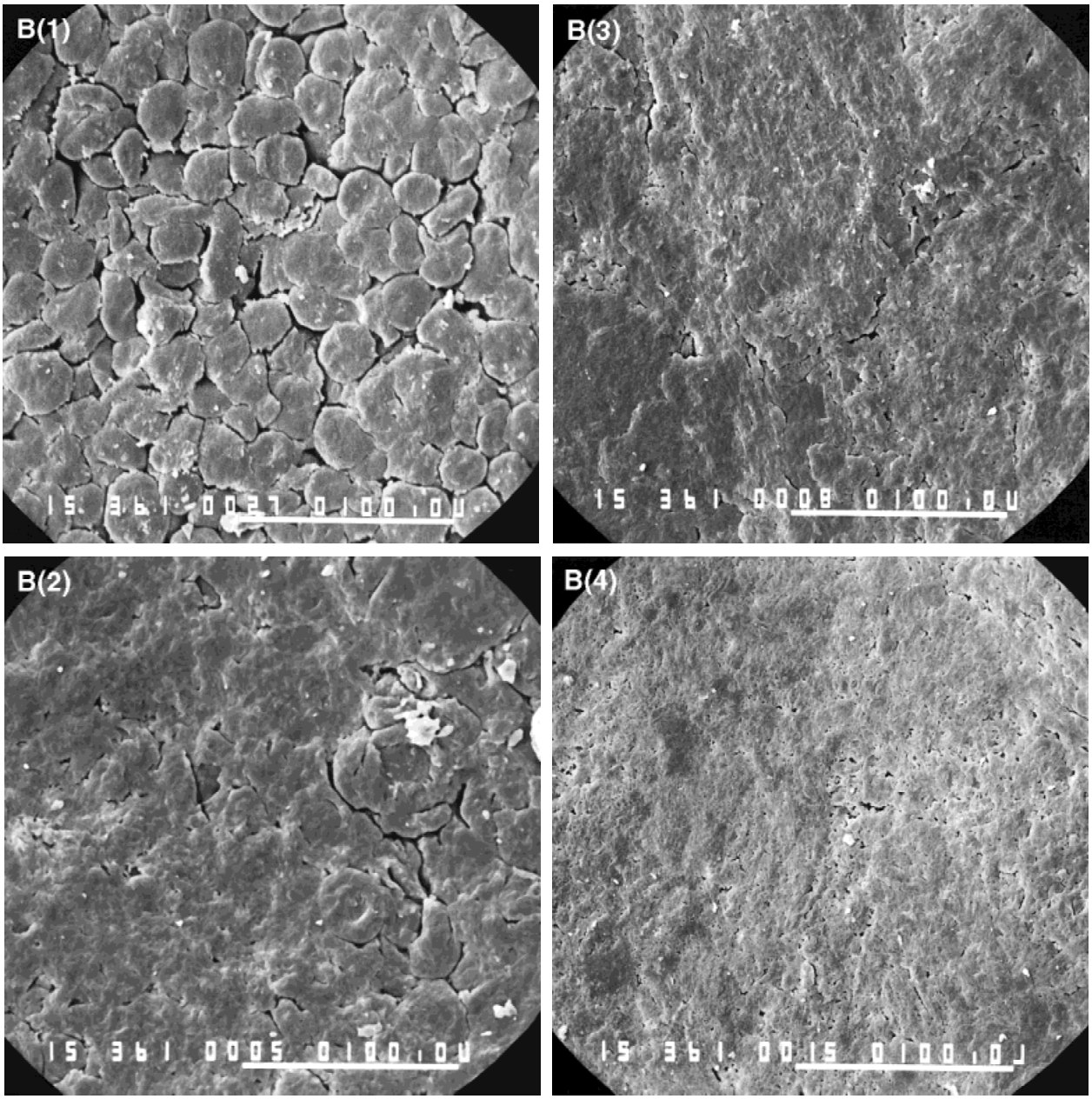

Fig. 1. *Continued.*

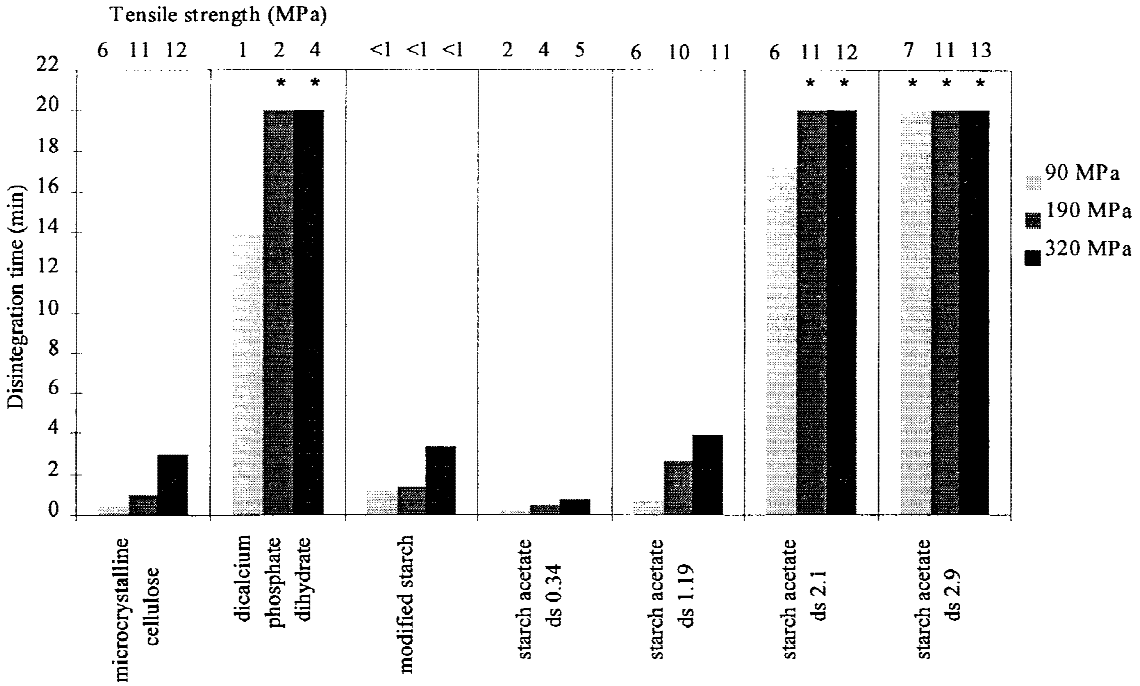

Fig. 2. Tensile strengths and disintegration times of tablets made of starch acetates with different degrees of substitution (ds) or commercial excipients compressed at different pressures. * = Tablets did not disintegrate during the measurement time of two hours.

RESULTS AND DISCUSSION

The controlled reaction conditions employed produced ds values of 0.34, 1.19, 2.1, and 2.9 from barley starch acetates. The Tg of these starch acetates were obtained from the second DSC heating cycle with values of 159 ± 1.1, 159 ± 0.3, 166 ± 0.9, and 156 ± 0.6°C, respectively. These results show that the glass transition point of barley starch does not change according to acetylation, as observed by the Tg values.

Powder X-ray diffraction patterns revealed that the starch acetates having ds values of 1.19, 2.1, and 2.9 exist in a totally amorphous state. For the starch acetate having the lowest ds value some small reflections were apparent, which indicates that the molecular structure included some highly ordered crystalline regions, although it was mostly amorphous. Thus, increased acetylation of the molecular structure results in starch acetates of a more amorphous form.

In general, the material density of the starch acetates decreased as the ds increased (Table I). Particle diameters of the starch acetates were quite small (Fig. 1) (Table I). Particles with ds of 0.34 are actually clusters which are primarily composed of spherical particles. According to shape factor, the starch acetate particle shape became slightly more irregular as ds increased (Table I) (Fig. 1). Decreased particle size usually increases cohesion and hinders flowability (10). Although the starch acetates exhibited relatively small particle diameters, they also demonstrated fairly good flowing properties (Table I). Comparison to the values of the reference excipients (Table I) indicates that the flowing properties of the starch acetates are suitable for direct compression. However, particle size, shape, as well as powder flowing properties of starch acetates can be affected and adjusted by optimizing the precipitation and drying conditions of the manufacturing process.

Both water content and contact angle results show that the hydrophilicity of starch acetates is directly proportional to their hydroxyl content and inversely proportional to the hydrophobic acetyl content (Table I). Contact angle characterizes the chemical nature of a material surface, and is used as a measure of wettability, which is a critical stage in the disintegration of tablets and dissolution of drug (11). The surfaces of lower ds tablets were more hydrophilic and wetted more easily than surfaces of higher ds tablets. The contact angle of MCC and MS tablets were lower than those of the starch acetate tablets. The contact angle of DCP was practically zero as the tablets wetted completely almost immediately, a result of the hydrophilic nature of DCP (11).

When the ds value was increased above 0.34, i.e., to 1.19 or more, the tensile strength of the starch acetate tablets proved to be overwhelming compared with other tested excipients, excluding MCC, which is known to have excellent binding properties (12) (Fig. 2). In the surfaces of the low ds value (0.34 and 1.19) starch acetate tablets, interparticulate borderlines were still visible after compression (Fig. 1). In the higher ds value starch acetate tablets, the interparticulate borderlines, or separated deformed particles, can hardly be seen. A possible explanation for this is that the starch acetates of high ds values undergo an interparticular plastification phenomenon under compression. Tablets formed of the starch acetate ds 2.9 were monolithic, homogeneous, and formed a very firm polymeric matrix, having a smooth surface (Fig. 1).

All tablets of the starch acetate ds 0.34 were completely disintegrated within a few minutes, while tablets of the starch acetates ds 2.1 and 2.9 did not disintegrate at all during the measurement time of two hours (Fig. 2). Tablets of reference excipients also disintegrated within a few minutes, excluding DCP, which as a water insoluble and unswellable material (13) did not disintegrate at all over a period of two hours. As

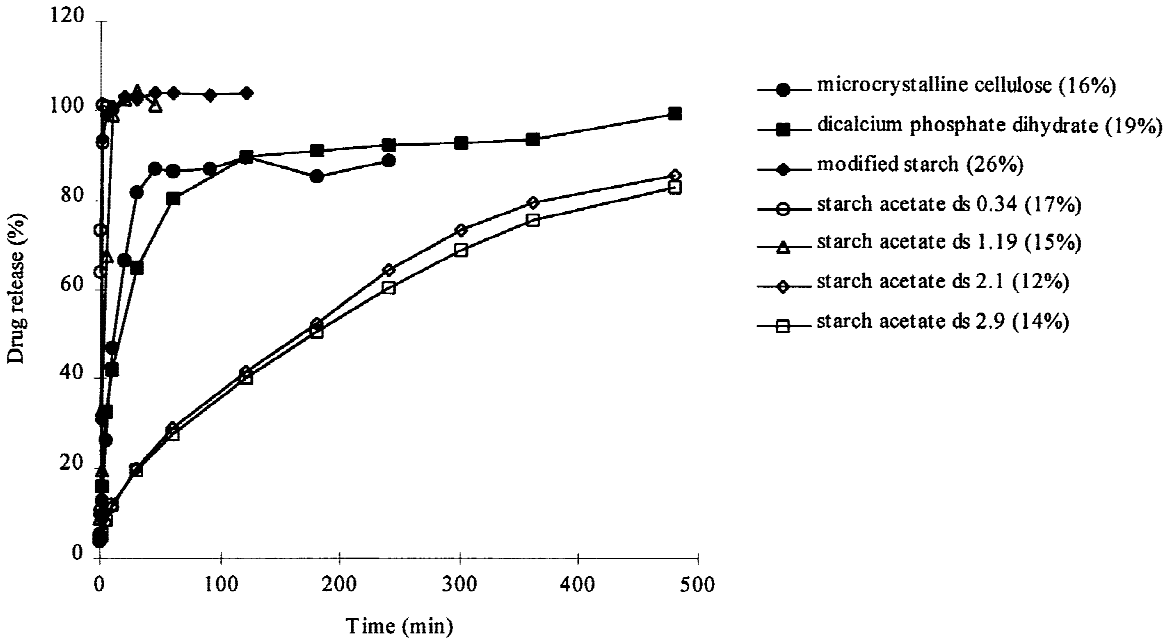

Fig. 3. Dissolution of propranolol*HCl from different excipient tablets at a compression pressure of 190 MPa. Tablet porosity in parenthesis.

the compression pressure increased, the disintegration time increased.

Disintegration behaviours of the tablets are in agreement with the contact angle results (Table I). The surface areas of the starch acetate ds 0.34 tablets were more porous, which enhanced water penetration into the tablets, compared to the smooth surface of starch acetate ds 2.9 tablets (Fig. 1). In addition, hydrophilicity and possibly swelling properties of low ds starch acetate might also accelerate disintegration of tablets.

Propranolol*HCl was released from the starch acetate tablets having ds values of 0.34 and 1.19 within a few minutes (Fig. 3). The rapid drug release rates can be attributed to short disintegration times of the tablets and, thus, immediate dissolution of propranolol*HCl. The starch acetate tablets with ds 2.1 and 2.9 demonstrated sustained-release profiles with a small surface initiated burst effect. The tested reference direct compression excipients had neither sustained nor controlled release properties. Dissolution results showed that the starch acetates having the highest ds values could act as matrix-forming agents in tablets, where the release of a drug can be significantly sustained.

The drug-release mechanism from ds 2.1 and 2.9 intact and monolithic matrix tablets is diffusion, where water penetrates at a slow rate into the tablet pores, causing Fickian diffusion of propranolol*HCl through the formed water channels. This conclusion was confirmed by fitting the release data representing from 10 to 80 % of maximum propranolol*HCl release to the Korsmeyer-Peppas equation (14). The exponent n got the value 0.5 with $r^2 \pm$ SD being 0.995 ± 0.001 and 0.997 ± 0.002 for ds 2.1 and 2.9 starch acetate tablets, respectively.

As a conclusion, starch acetates are potentially useful as multifunctional direct compression excipients, and may be promising tools for novel formulation design. They could be used as filler-binders as well as controlled released substances in direct compression formulations. This creates several possibilities to obtain a desired, versatile, and modifiable rate of release of a drug by using a starch acetate formulation of a particular degree of substitution. Furthermore, by using similar excipients, possible incompatibility and stability risks can be minimized.

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