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Research paper

Controlled release of saccharides from matrix tablets

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Abstract

The aim of this study was to design site specific, controlled release tablets of *N*-acetyl-D-glucosamine (NAG), maltose monohydrate and maltopentaose by using hydrophobic matrix formers starch acetate (SA) and ethyl cellulose (EC). The optimized matrices, which had either low porosity and high drug load or high porosity and low drug load, released the saccharides within the desired 2–4 h. In general, it was possible to control the release rate of saccharides by altering the relative amount of hydrophobic matrix former in the tablet and tablet porosity. The release type of saccharides from these formulations varied from immediate release to sustained release. In the case of sustained release formulations, it was found that the release of maltose monohydrate and maltopentaose was biphasic and slower than the release rate of NAG from similar tablets. NAG release kinetics followed square root of time kinetics, while in the case of maltose monohydrate and maltopentaose, the release kinetics were zero order in both phases. The biphasic dissolution profile was proposed to be caused by water mediated recrystallisation of the disordered material formed during the dissolution. Both SA and EC matrices were found to represent suitable controlled oral delivery vehicles for saccharides.

Keywords: Hydrophobic matrix; Tablet; Starch acetate; Controlled release; Oligosaccharides

1. Introduction

Novel drugs based on carbohydrates are predicted to be the next major breakthrough in drug discovery. In glycobiology, the role of carbohydrates (sugars) in the body is being intensely investigated. Consequently, increasing numbers of receptors are being characterized that operate through binding to specific oligosaccharide sequences on glycoproteins, glycolipids and polysaccharides. Such receptors are involved in infections (microbe–host interactions) and mechanisms of inflammation and immunity [1,2]. Most proteins contain carbohydrates, which are important for the biological function of the protein, and drugs developed using glycobiology may be used to treat cancer, infections and inflammatory diseases [3,4]. Glycobiology may also be used to develop vaccines to prevent these diseases [5,6]. Carbohydrate-based drugs, which originate from naturally occurring structures, may possess safety advantages over other types of drugs [3]. The best-known carbohydrate drug is the widely used heparin, which is isolated from the intestine of pigs and is used for the prevention and treatment of blood clotting [7]. In addition, multivalent carbohydrate based antibiotics are expected to provide a promising way to circumvent the problem of antibiotic-resistant microbes such as MRSA (methicilin-resistant *Staphylococcus aureus*) and VRE (vancomycin-resistant *enterococci*) [8]. The *Helicobacter pylori* binding oligosaccharide sequences or their chemically modified derivatives could be used as the basis for an oral drug treatment for *H. pylori* infections [9]. Thus, there is a great deal of interest to develop oral oligosaccharide formulations that provide tailor-made release precision.

Since saccharides are generally water soluble and chemically stable, direct compression matrix tablets could be potential vehicles for oral saccharide delivery. Starch acetate (SA) and ethyl cellulose (EC) are examples of interesting candidates as controlled release matrix formers. SA is a novel direct compression excipient, prepared from starch polymers by esterification. SAs having the highest degree of substitution (ds) values (2.1–3) are suitable for direct compression excipients, and can form a strong tablet matrix with sustained release properties [10]. It has been shown that the drug release

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rate from starch acetate tablets is dependent on the ds value and the starch acetate concentration in the tablet [11]. EC is an inert and hydrophobic polymer which has been widely used to prepare pharmaceutical dosage forms, i.e. matrix tablets for water soluble drugs [12,13]. In the case of water soluble drugs, release from EC matrices occurs by dissolution and diffusion of the drug through water-filled capillaries within the pore network [14]. The mechanism of drug release from SA matrices is similar, i.e. drug diffusion through the pores [11]. However, it is not known if SAs with high ds values or EC could be used for semi-sustained release of highly water-soluble saccharides.

The aim of this study was to design site-specific, controlled release tablets of different saccharides by using hydrophobic matrix formers; primarily SA and also EC. *N*-acetyl-D-glucosamine, maltose monohydrate and maltopentaose were used as models of carbohydrate-based drugs. The tablets were designed to release the saccharides within 2–4 h, starting already in the stomach but mainly in the upper part of the small intestine. Design of experiment was used to screen and optimise the SA and EC formulations. Also, the effect of physicochemical characteristics of the used saccharides on release properties was evaluated.

2. Materials and methods

2.1. Materials

The model drug compounds *N*-acetyl-D-glucosamine (NAG) (Sigma Aldrich Chemie, Germany) and maltopentaose (Seikagaku, Japan) were used as supplied. Maltose monohydrate (Seikagaku, Japan) was sieved through a 1 mm sieve. Sieve fractions of <500 μm, 500–297 μm and <149 μm for starch acetate (SA) (VTT, Rajamäki, Finland) with degree of substitution 2.8 were used. Commercially available excipients ethyl cellulose (EC) (Ethocel Standard 10 Premium) and hydroxypropyl methylcellulose (HPMC) (Methocel K15M Premium) were gift samples from DOW Europe (Germany) and Colorcon (USA), respectively, and were used as supplied.

2.2. Powder properties

The particle size distributions of starch acetate sieve fractions, HPMC, EC, NAG and maltose monohydrate were analysed by laser diffraction (Mastersizer2000, Malvern Instruments Inc., USA). Particle in air method was used for the excipients and particle in liquid (ethanol) method was used for the model saccharides. Scanning electron micrographs (SEM) of materials used were taken with a XL 30 ESEM TMP Microscope (FEI CO, Czech Republic). The samples were coated with gold (Polar Sputter Coater II-E5100, Polaron Equipment Ltd, Watford, UK) before imaging. The accelerating voltage was 20 kV. Material densities were measured in five parallel determinations with a Multi pycnometer (Quanta Chrome, USA) using helium as the measuring gas. Differential scanning calorimetry (DSC) (Perkin-Elmer DSC7, Perkin-Elmer Co., Norwalk, CT) was used in the determination of melting points of the materials. The measurements were made in duplicate using a heating rate of 10 °C/min and temperature scale of 10–250 °C. Samples of 4–6 mg in weight were crimped in 50 μl aluminium pans with holes. Similar empty pans were always used as references. All runs were performed under an atmosphere of dry nitrogen. The temperature axis was calibrated with gallium (m.p. 28.78 °C) and indium (m.p. 156.60 °C). The existence of a crystalline part of maltopentaose was qualitatively confirmed by using polarized light microscopy (Nikon Microphot-Fxa, Nikon, Tokyo, Japan).

2.3. Tablet formulations and tabletting

Tablet formulations were designed by using an experimental design program (Design-Expert 5, StatEase Corp., MN, USA). Binary powder mixtures of the excipient and saccharide for tabletting were prepared by mixing carefully by hand in a mortar. The relative amounts of the mixture components were calculated on a mass basis. The powder mixtures were compressed with a compaction simulator (PCS-1, PuuMan Ltd., Kuopio, Finland). The tablets were cylindrical, with diameters of 8, 10 or 13 mm. Tablets were compressed to the desired porosity, which was calculated using the material density of the powders and tablet dimensions and weights. The porosities of interest were chosen based on the knowledge of the relationship between SA matrix porosity and drug release obtained from previous studies on SA [10,11]. Compression profiles were sine waves for both punches or only for the upper punch, in which case the lower punch was stationary. Compression pressures varied between 42 and 345 MPa. Tablet volumetric dimensions were measured 24 h after compression with a micrometer screw (Digitrix, NSK, Japan) and weights were determined by using an analytical balance (A200S, Sartorius, Germany). Crushing strengths of tablets were measured with a universal tester (CT-5 tester, Engineering Systems, England), operated at a constant cross head speed of 1 mm/min. The tensile strength of the tablets was calculated according to Fell and Newton [15].

2.4. Dissolution tests

The dissolution behaviour of saccharides from the matrix tablets was determined in triplicate by the USP XXVIII rotating basket method, with a rotation speed of 100 rpm (Sotax AT6, Switzerland). The dissolution medium was 900 ml of pH 1.2 HCL-solution for the first 2 h, after which the tablets were transferred into 900 ml of distilled water for the next 22 h. Both media were maintained at 37 ± 0.5 °C. The amount of dissolved NAG was determined by HPLC with UV-detection at the wavelength of 210 nm [16]. The Gilson HPLC system consisted of 234 Autoinjector (Gilson, France), 321 Pump (Gilson, France), UV/Vis-151 Detector (Gilson, USA), System interface module (Gilson, USA) and Unipoint™ LC system version 3.01 software (Gilson USA). An amino column (Asahipak NH2P, 4.6×250 mm, Shodex, Japan), operating at

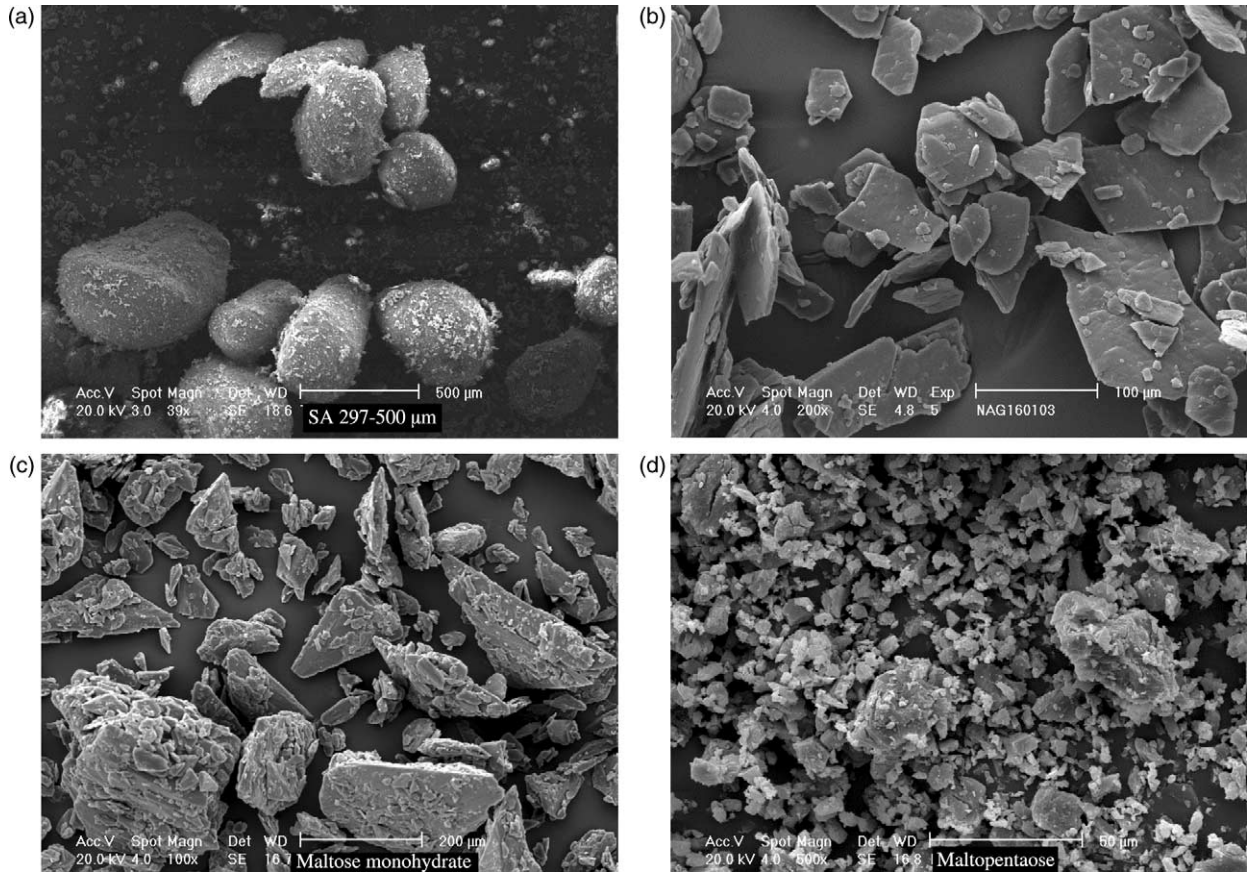

Fig. 1. Scanning electron micrographs of; (a) starch acetate 297–500 μm sieve fraction; (b) *N*-acetyl-D-glucosamine; (c) maltose monohydrate; (d) maltopentaose. Bar lengths as indicated in the figure.

40 °C, was used. The sample injection volume was 20 μl, the mobile phase was acetonitrile–water (70:30) and its flow rate was 1 ml/min. The retention time of NAG was 5 min. The amount of dissolved maltose and maltopentaose was determined by HPLC with evaporative light scattering (ELS) detection. The Merck LaChrom HPLC system consisted of D-7000 Interface, L-7250 Autosampler and injector, L-7100 Pump, D-7000 HPLC system manager software (all from Hitachi, Tokyo, Japan) and Sedex 55 ELS detector (Sedere, Vitry-Sur-Seine, France). An Asahipak NH2P -column was used, the sample injection volume was 10 μl, the mobile phase was acetonitrile–water (48:52) and its flow rate was 1 ml/min [17]. The detector temperature was 42 °C and the pressure of the nebulizing gas (dry and filtered air) was 2.2 bar. The retention times of maltose and maltopentaose were 3.55 and 4 min, respectively.

3. Results and discussion

3.1. Powder characterisation

The starch acetate particle size fractions consisted of particles having fairly round shapes and smooth surfaces (e.g. 297–500 μm fraction, Fig. 1a.). Instead, NAG and maltose monohydrate were found to be flaky shaped, crystalline materials (Fig. 1b. and c, respectively). Maltopentaose particles were small and irregular (Fig. 1d.). The powder characteristics of the starch acetate particle size fractions, EC, HPMC and model saccharides, are given in Table 1.

Table 1
Physical properties of starch acetate (SA), ethyl cellulose (EC), hydroxypropyl methylcellulose (HPMC), *N*-acetyl-D-glucosamine (NAG), maltose monohydrate and maltopentaose

Material	Particle density (g/cm^3)	Volume mean particle size (μm)	Melting point (°C)[a]
SA < 500 μm	1.326 ± 0.004	131[b]	nd
SA 297-500 μm	1.358 ± 0.005	372[b]	nd
SA < 149 μm	1.310 ± 0.011	23[b]	nd
EC	1.192 ± 0.005	227[b]	nd
HPMC	1.311 ± 0.007	79[b]	nd
NAG	1.483 ± 0.008	141[c]	213.7 ± 0.7
Maltose monohydrate	1.525 ± 0.004	138[c]	125.5 ± 0.6
Maltopentaose	1.481 ± 0.008	nd	116[d]

nd, not determined.
[a] Onset-value.
[b] Particle in air method.
[c] Particle in ethanol method.
[d] Partially amorphous (confirmed by polarized light microscopy), melting point of the crystalline part.

Table 2
Tablet formulations designed by Plackett-Burman design of experiment for evaluation of the effect of six process and formulation variables on the release rate and mechanism of *N*-acetyl-D-glucosamine (NAG) from the starch acetate (SA) tablets

Formulation code (NAG%/SA%)	Amount of NAG (mg)	Tablet mass (mg)	Duration of compression (ms)	Type of compression[a]	Tablet porosity (%)	SA particle size fraction (μm)
A1 (25/75)	150	600	500	−1	7.5	297–500
A8 (25/75)	150	600	1500	1	15	297–500
B2 (50/50)	150	300	500	1	7.5	<149
B7 (50/50)	150	300	1500	−1	15	<149
C3 (17/83)	50	300	500	−1	15	297–500
C6 (17/83)	50	300	1500	1	7.5	297–500
D4 (8/92)	50	600	500	1	15	<149
D5 (8/92)	50	600	1500	−1	7.5	<149

[a] Type of compression: 1, double sided, −1, single sided.

3.2. Dissolution characteristics of N-acetyl-D-glucosamine

In order to evaluate the effects of six process and formulation variables on the release rate and mechanism of NAG from SA tablets, formulations were designed by a Plackett–Burman 2-level factorial design of experiment (Table 2). The in vitro release profiles of these formulations are shown in Fig. 2. Three formulations studied (A8, B2 and B7) released NAG within the intended time, i.e. within 2–4 h. In the case of formulation A8, the porosity of the tablet was 15% and a larger SA particle size fraction was used. The tablets contained 25% of NAG. Instead, in the formulations B2 and B7 the porosities were 7.5 and 15%, respectively, and a smaller SA particle size fraction was used. The amount of NAG in these tablets was 50% of the tablet mass. In general, the NAG release rate could be modeled ($R^2=0.999$) and predicted ($Q^2=0.998$) well. It was found that the most significant factors affecting the release rate were the amount of NAG in the tablet ($P<0.0001$), the porosity of the tablet ($P<0.001$), the duration of compression ($P<0.001$) and the tablet mass ($P<0.01$). Faster release corresponded to higher amount of NAG in the tablet, a higher porosity of the tablet, shorter duration of compression and lower tablet weight. The particle size of SA had no significant effect on the release rate. This is in accordance with previous studies [18] and the experimental dissolution results, which show that the fastest releasing formulations have either a high amount of NAG in the tablet or have high porosity. Also the tensile strengths of the tablets (Table 3) correlated well with the porosity and dissolution rate, i.e. the higher the porosity and dissolution rate, the smaller the tensile strength.

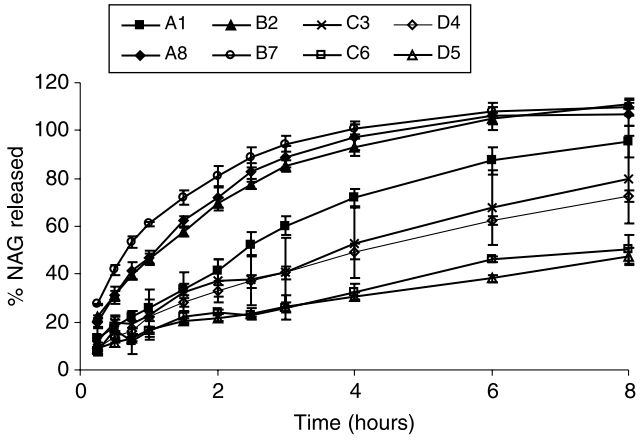

Fig. 2. Percentage of *N*-acetyl-D-glucosamine released from formulations designed by Plackett–Burman design of experiment. The explanations of the formulation codes are given in Table 2. Standard deviations are given as y-error bars ($n=3$).

The release kinetics of NAG from the SA matrices were evaluated by using Korsmeyer-Peppas model [19] Eq. (1)

$$f_t = at^n \quad (1)$$

where f_t is the cumulative amount of released drug at the time t, a is a constant incorporating structural and geometric characteristics of the dosage form and n is the release exponent, which indicates the drug release mechanism [19]. In the case of a cylinder, the n value of 0.45 indicates Fickian diffusion, i.e. square root of time kinetics, and n values between 0.45 and 0.89 or $n=0.89$ indicate that mass transfer is following non-Fickian model. In the evaluation of the release kinetics of the formulations, the first six timepoints were used for the n value calculation. The resulted n values are shown in Table 3. It was found that according to Eq. (1), the release of NAG from two formulations (B2 and D5) followed square root of time kinetics, while with the other formulations, NAG release kinetics was anomalous transport. In the B2 and D5 formulations, the smaller SA particle size fraction was used and the tablet porosity was 7.5%. Although it was possible to model and predict the NAG release rate, it was not possible to construct a reliable model for predicting NAG release kinetics from the studied matrix tablets.

Following the screening of the most significant factors affecting NAG release, the release from SA tablets was

Table 3
Tensile strength of the tablets ($n=5$) and n values from the Korsmeyer–Peppas equation of the tablet formulations according to Table 2

Formulation	Tensile strength (MPa)	n
A1	4.15±0.11	0.55
A8	2.87±0.20	0.63
B2	4.60±0.31	0.49
B7	1.86±0.12	0.40
C3	2.73±0.60	0.53
C6	5.97±0.51	0.56
D4	4.17±0.24	0.63
D5	5.04±0.09	0.46

Table 4
Tablet formulations designed by a 2-level factorial design for optimizing the *N*-acetyl-D-glucosamine (NAG) release rate from the starch acetate tablets

Formulation	Tablet porosity (%)	Amount of saccharide (%)[a]
1	20	50
2	25	75
3	15	25
4	25	25
5	15	75

Tablet porosity and the amount of saccharide in the tablet were chosen as variables according to the results from the Plackett-Burman experimental design. The same design was used when the release of NAG was studied from ethyl cellulose and hydroxypropyl methylcellulose matrices and also in the case of maltose monohydrate formulations.

[a] The amount of saccharide in the tablet was always 50 mg.

optimized by using a full 2-level factorial design, where the two factors studied were the amount of drug in the tablet and tablet porosity (Table 4). Since SA particle size had no effect on the NAG release, the SA fraction $<500\,\mu m$ was subsequently used. The SA–NAG formulations were compared to similar formulations in which hydrophobic EC or hydrophilic HPMC were used as matrix formers. The in vitro release profiles of these formulations are shown in Fig. 3a–c and the tensile strength values of the tablets are reported in Table 5. The SA formulations 2 and 5 disintegrated in the dissolution bath and released NAG immediately. However, three optimal SA formulations, which released NAG within 2–4 h, were found (formulations 1, 3 and 4). The best two formulations, 3 and 4, contained 25% of NAG and the porosities of the tablets were 15 and 25%, respectively. In the formulations A8, B2 and B7 (Table 2, Fig. 2) the porosities of the tablets were generally lower (15, 7.5 and 15%, respectively) and drug load higher (25, 50 and 50%, respectively) than in the formulations 1, 3 and 4 (porosities 20, 15 and 25%, drug load 50, 25 and 25%, respectively). Thus, for optimal NAG release in 2–4 h, either lower porosity and a higher amount of NAG in the tablet or higher porosity and a lower amount of NAG in the tablet was required. It was also observed that the release characteristics of NAG from EC tablets were almost similar to SA tablets (Fig. 3a, b). The NAG-EC formulations 3 and 4 possessed the desired NAG release profile. In the case of water-soluble drugs, release from hydrophobic EC matrices occurs by dissolution and diffusion of the drug through water-filled capillaries of the pore network [14]. The mechanism of drug release from SA matrices is identical [11]. Thus, in the case of similar SA and EC formulations the NAG release rate depends on the properties of the molecule and similar dissolution profiles for these formulations was to be expected. However, when hydrophilic HPMC was used as a matrix former, the release of NAG was delayed considerably (Fig. 3c) and formulations 2 and 5 showed almost the desired 2–4 h NAG release. The NAG release mechanism from HPMC formulations was found to be diffusion. HPMC is a swelling and erodible polymer. The release of water soluble compounds, such as saccharides, from the HPMC matrix involves the successive processes of penetration of medium into the matrix,

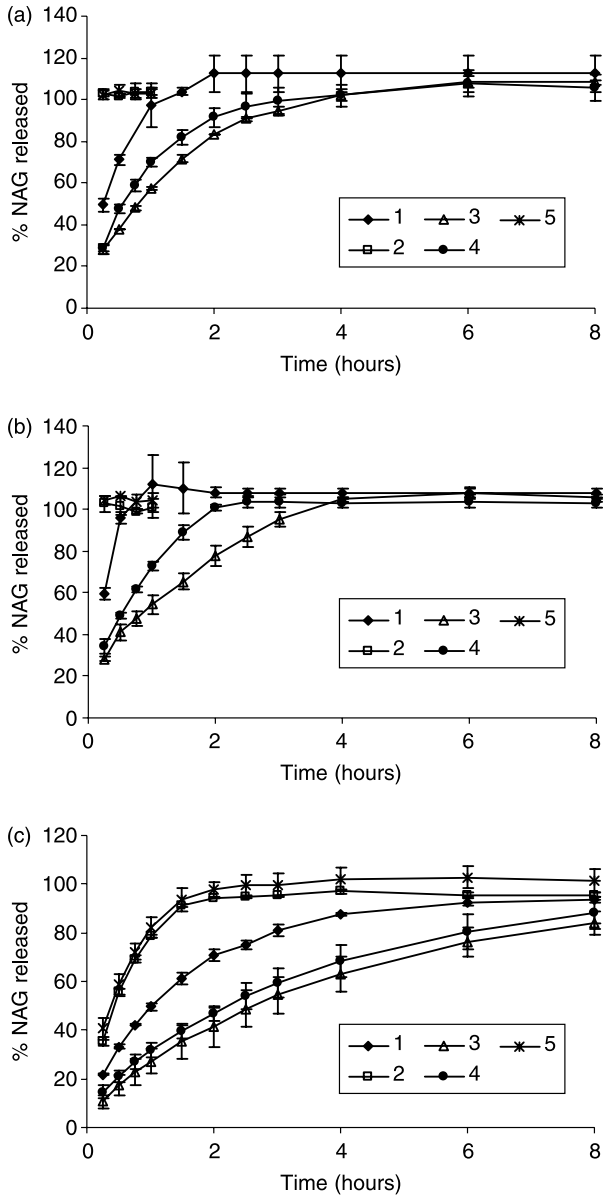

Fig. 3. Percentage of *N*-acetyl-D-glucosamine (NAG) released from; (a) starch acetate; (b) ethyl cellulose; (c) hyrdoxypropyl methylcellulose formulations designed by 2-level factorial design. From the formulations which released NAG immediately (formulations 2 and 5 from Table 4) only the first four data points are shown.

hydration and swelling of the matrix, dissolution of the drug in the matrix and then diffusion of the dissolved drug through the channels [20].

3.3. Dissolution characteristics of maltose monohydrate

The release characteristics of maltose monohydrate from SA tablets were studied by using a similar full 2-level factorial design as with NAG. Also these formulations were compared to similar formulations of EC. The in vitro release profiles of these formulations are shown in Fig. 4 and the tensile strengths of the tablets are reported in Table 5. Again, the release characteristics of EC were found to be similar to SA. It was

Table 5
Tensile strength of starch acetate (SA), ethyl cellulose (EC) and hydoxypropyl methylcellulose (HPMC) tablets ($n=5$) of *N*-acetyl-D-glucosamine (NAG) and maltose monohydrate (formulation codes from Table 4)

Formulation	Tensile strength (MPa)				
	NAG			Maltose	
	SA	EC	HPMC	SA	EC
1	1.16±0.08	0.50±0.02	1.09±0.29	2.16±0.20	1.05±0.07
2	0.17±0.06	nd	nd	0.37±0.04	0.22±0.03
3	3.46±0.29	1.59±0.06	3.09±0.14	4.68±0.31	2.71±0.06
4	1.57±0.06	0.49±0.02	1.18±0.04	1.91±0.10	0.89±0.03
5	0.18±0.06	0.70±0.35	nd	1.86±0.06	1.51±0.16

nd, not determined.

found that formulations 2 and 5 (Table 4) released maltose monohydrate immediately but release from formulation 1 occurred in the desired 2 h, as in the case of NAG. However, the release of maltose monohydrate from formulations 3 and 4 was considerably slower than NAG release from similar formulations. Thus it seems that physicochemical properties of the saccharides also affect the release rate from hydrophobic SA and EC tablets. Moreover, the release profiles of maltose monohydrate SA/EC -formulations 3 and 4 were found to consist of two linear phases with different release rates. The release rate slowed at the time point of 2 h. However, a similar phenomenon was observed when the whole dissolution study was performed only in pH 1.2 HCl-solution or in water, thus this biphasic dissolution behaviour was not caused by the change of the dissolution medium.

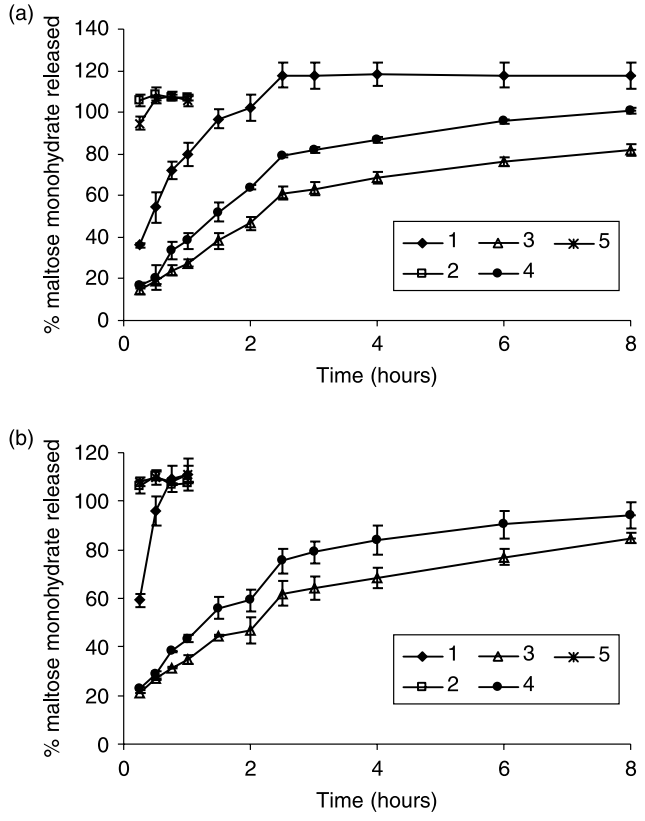

Fig. 4. Percentage of maltose monohydrate released from; (a) starch acetate formulations; (b) corresponding ethyl cellulose formulations. From the formulations which released maltose immediately (formulations 2 and 5 from Table 4, and also formulation 1 in the case of ethyl cellulose) only the first four data points are shown.

The slowing of release rate could be caused by activation of maltose monohydrate during tabletting. It is well known that polymorphic transition or formation of amorphous regions on particles can be induced by application of mechanochemical stress, such as occurs during tabletting [21,22], and that this can have an effect on the dissolution rate of the drug [23]. During the tabletting process, maltose monohydrate could be converted to a metastable (more soluble) form and during the dissolution test it could revert back to monohydrate (less soluble) after a certain lag time, which could explain the initial faster dissolution and consequent slowing of release rate at the point of 2 h. A biphasic dissolution caused by this phenomenon has been previously reported for calcium carbonate [24].

The possibility of formation of disordered areas of maltose monohydrate was studied by taking starch acetate tablets of maltose monohydrate out of dissolution medium at 0.5, 1, 2, 2.5 and 4 h timepoints and by analyzing the tablets by DSC. Also, the physical mixture of maltose monohydrate and starch acetate and the tablet before dissolution were analyzed. A statistically significant difference ($P<0.01$ in a *t*-test) was found between the melting points of maltose monohydrate determined from dispersed tablets prior to dissolution test and after keeping the tablet 2 h in the dissolution bath (average 130.2 °C) and those determined from the physical mixture and from tablets taken out of the dissolution bath after 2.5 h or later (average 131.3 °C) (Table 6). This indicates that maltose

Table 6
Melting point ranges ($n=2$) of physical mixture of maltose monohydrate and starch acetate, tablets before dissolution and tablets removed from the dissolution bath at various timepoints

Sample	Time in the dissolution bath (h)	Melting point (°C)[a]
Physical mixture	–	131.4–132.2
Tablet	–	130.2–130.2
Tablet	0.5	129.2–130.3
Tablet	1	129.7–131.7
Tablet	2	129.8–130.2
Tablet	2.5	130.7–131.5
Tablet	4	130.0–132.0

Physical mixture and tablets are based on formulation 3 (Table 4).
[a] Peak-values were used due to the large water dehydration peak, which interfered with onset-value determination.

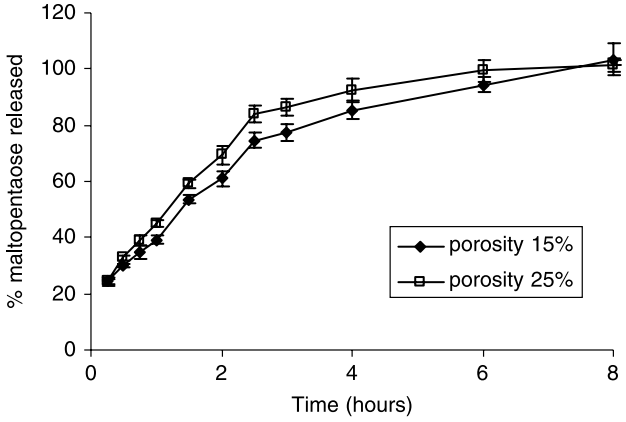

Fig. 5. Percentage of maltopentaose released from starch acetate formulations similar to maltose monohydrate-starch acetate formulations 3 and 4 from Table 4.

monohydrate had been activated during tablet compression and this change in solid-state structure reverted or started to revert back to the original condition when the tablets had been in the dissolution bath for more than 2 h. However, it is not possible to quantitatively evaluate the amount of activated maltose monohydrate in the tablets by DSC [22].

3.4. Dissolution characteristics of maltopentaose

An oligomer of maltose monohydrate, maltopentaose, was used to evaluate the effect of saccharides molecular size on the release from SA formulations. SA formulations 3 and 4 were prepared by using maltopentaose instead of maltose monohydrate (Table 4). The in vitro release profiles of these formulations are shown in Fig. 5. The release of maltopentaose from SA-tablets was found to be almost similar to maltose monohydrate from the corresponding formulations. Maltopentaose dissolved slightly faster than maltose monohydrate presumably due to its mainly amorphous nature, this being observed (Fig. 6) by using polarized light microscopy [25], but the small particle size (Fig. 1) could also mask the effect of molecular size on the release rate. We also observed slowing of its release rate in a fashion similar to that seen with maltose monohydrate formulations. This could be due to the existence of a small crystalline fraction in the maltopentaose particles (Fig. 6, Table 1). The amorphous part of the material dissolved faster than the crystalline part, which might explain the change in the dissolution profile. In addition, the slowing of the release rate of maltopentaose formulations could also be due to recrystallisation of the amorphous maltopentaose in the dissolution medium during the dissolution test [24].

4. Conclusions

The study showed that it is possible to control the release rate of saccharides over a wide time scale by altering tablet porosity and the relative amount of hydrophobic matrix former in the tablet. In general, depending on the drug load and tablet porosity, the saccharide release type could be designed to be in range of intermediate to prolonged (in 24 h) release. The desired 2–4 h saccharide release profiles were obtained with SA and EC matrices that had either relatively low porosity and a high amount of saccharide in the tablet or high porosity and a low amount of saccharide in the tablet. The release of maltose monohydrate and maltopentaose was biphasic and slower than the release rate of NAG from similar tablets. This biphasic dissolution profile was proposed to be attributable to water mediated recrystallisation of the disordered phases present in the maltose monohydrate and maltopentaose. Thus, the physicochemical properties of saccharides also affect their release properties. The hydrophobic SA and EC tablet matrices showed similar saccharide release properties.

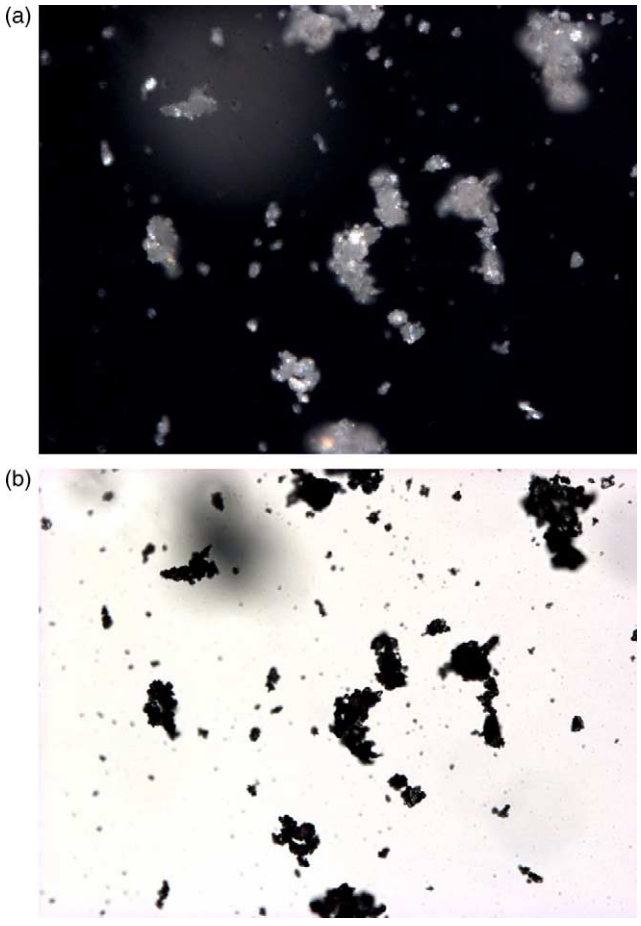

Fig. 6. Photographs of maltopentaose particles in polarized light microscope; (a) showing the crystalline fractions as bright areas; (b) no bright areas can be seen when polarization is turned off.

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References

[1] T. Feizi, F. Fazio, W. Chai, C. Wong, Carbohydrate microarrays—a new set of technologies at the frontier of glycomics, Curr. Opin. Struct. Biol. 13 (2003) 637–645.

[2] S. Toppila, R. Renkonen, L. Penttilä, J. Natunen, H. Salminen, J. Helin, H. Maaheimo, O. Renkonen, Enzymatic synthesis of α3′sialylated and multiply α3fucosylated biantennary polylactosamines, Eur. J. Biochem. 261 (1999) 208–215.

[3] S. Park, Y. Lai, C. Kim, Immunopotentiating and antitumor activities of the purified polysaccharides from *Phellodendron Chinese* SCNEID, Life Sci. 75 (2004) 2621–2632.

[4] J.M. De la Fuente, A.G. Barrientos, T. Rojas, J. Rojo, J. Cañada, A. Fernández, S. Penadés, Gold glyconanoparticles as water-soluble polyvalent models to study carbohydrate interactions, Angew. Chem. Int. Ed. Engl. 40 (2001) 2258–2261.

[5] M.M. Levine, F. Noriega, A review of the current status of enteric vaccines, P. N. G. Med. J. 38 (1995) 325–331.

[6] C. Lee, Quality control of polyvalent pneumococcal polysaccharide-protein conjugate vaccine by nephelometry, Biologicals 30 (2002) 97–103.

[7] R.E. Scutgens, E.U. Esseboom, R.J. Snijder, F. Verzijlbergen, H.K. Nieuwenhuis, T. Lisman, D.H. Biesma, Low molecular weight heparin (dalteparin) is equally effective as unfractionated heparin in reducing coagulation activity and perfusion abnormalities during the early treatment of pulmonary embolism, J. Lab. Clin. Med. 144 (2004) 100–107.

[8] H. Tanaka, Y. Nishida, Y. Furuta, K. Kobayashi, A convenient synthetic pathway for multivalent assembly of aminoglycoside antibiotics starting from amikacin, Bioorg. Med. Chem. Lett. 12 (2002) 1723–1726.

[9] H. Miller-Podraza, S. Teneberg, J. Ångström, K.A. Karlsson, J. Natunen, J. Helin, Novel binding epitopes for helicobacter pylori and use thereof, World Patent Information, 2,004,065,400, 2004.

[10] O. Korhonen, P. Raatikainen, P. Harjunen, J. Nakari, E. Suihko, S. Peltonen, M. Vidgren, P. Paronen, Starch acetates—multifunctional direct compression excipients, Pharm. Res. 17 (2000) 1138–1143.

[11] S. Pohja, E. Suihko, M. Vidgren, P. Paronen, J. Ketolainen, Starch acetate as a tablet matrix for sustained drug release, J. Control. Release 94 (2004) 293–302.

[12] N.A. Shaikh, S.E. Abidi, L.H. Block, Evaluation of ethylcellulose as a matrix for prolonged release formulations, Part 1. Water soluble drugs—acetaminophen and theophylline, Drug Dev. Ind. Pharm. 13 (1987) 1345–1369.

[13] G.S. Rekhi, S.S. Jambhekar, Ethylcellulose—a polymer review, Drug Dev. Ind. Pharm. 21 (1995) 61–77.

[14] M.M. Crowley, B. Schroeder, A. Fredersdorf, S. Obara, M. Talarico, S. Kucera, J.W. McKinity, Physicochemical properties and mechanism of drug release from ethyl cellulose matrix tablets prepared by direct compression and hot-melt extrusion, Int. J. Pharm. 269 (2004) 509–522.

[15] J.T. Fell, J.M. Newton, Determination of tablet strength by the diametrical-compression test, J. Pharm. Sci. 59 (1970) 688–691.

[16] H. Sashiwa, S. Fujishima, N. Yamano, N. Kawasaki, A. Nakayama, E. Muraki, K. Hiraga, K. Oda, S. Aiba, Production of *N*-acetyl-D-glucosamine from α-chitin by crude enzymes from *Aeromonas hydrophila* H-2330, Carbohydr. Res. 337 (2002) 761–763.

[17] http://www.shodex.com/english/dc030314.htmI

[18] B. van Veen, J. Pajander, K. Zuurman, R. Lappalainen, A. Poso, H.W. Frijlink, J. Ketolainen, The effect of powder blend and tablet structure on drug release mechanisms of hydrophobic starch acetate matrix tablets, Eur. J. Pharm. Biopharm. 61 (2005) 149–157.

[19] P. Costa, J.M. Sousa Lobo, Modeling and comparison of dissolution profiles, Eur. J. Pharm. Sci. 13 (2001) 123–133.

[20] K. Tahara, K. Yamamoto, T. Nishihata, Overall mechanism behind matrix sustained release (SR) tablets prepared with hydroxypropyl methylcellulose 2910, J. Control. Release 35 (1995) 59–66.

[21] H.K. Chan, E. Doelker, Polymorphic transformation of some drugs under compression, Drug Dev. Ind. Pharm. 11 (1985) 315–332.

[22] A. Saleki-Gerhardt, C. Ahlneck, G. Zografi, Assessment of disorder in crystalline solids, Int. J. Pharm. 101 (1994) 237–247.

[23] N.V. Phadnis, R. Suryanarayanan, Polymorphism in anhydrous theophylline—implications on the dissolution rate of theophylline tablets, J. Pharm. Sci. 86 (1997) 1256–1263.

[24] M. Mosharraf, T. Sedhatu, C. Nyström, The effects of disordered structure on the solubility and dissolution rates of some hydrophilic, sparingly soluble drugs, Int. J. Pharm. 177 (1999) 29–51.

[25] S.R. Byrn, R.R. Pfeiffer, J.G. Stowell, Solid-State Chemistry of Drugs, SSCI, Inc, West Lafayette, 1999, p. 71.