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Research paper

Development of starch-based pellets via extrusion/spheronisation

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Abstract

A modified starch (high-amylose, crystalline and resistant starch) was evaluated as an alternative excipient to microcrystalline cellulose for pellets prepared via extrusion/spheronisation. Theophylline anhydrous (25%, w/w) was used as a model drug. A binder was necessary to obtain an acceptable yield and the addition of sorbitol improved the surface properties of the pellets. A surface response design with three formulation variables (binder, sorbitol and water level) and one process variable (spheronisation speed) was used to optimise the process and to evaluate pellet yield, sphericity (aspect ratio and two-dimensional shape factor, e_R), size (mean Feret diameter), friability and disintegration properties. Mixer torque rheometry and solid-state NMR revealed a significant influence of sorbitol on wet mass consistency and pellet properties. A high pellet yield (>90%), acceptable sphericity (AR < 1.2), low friability (<0.01%), fast disintegration (<10 min) and complete drug release in less than 20 min for all formulations, demonstrated the potential of this modified starch in formulations intended for extrusion/spheronisation.

Keywords: Extrusion/spheronisation; Pellets; Starch; Sorbitol; NMR; Experimental design

1. Introduction

The importance of microcrystalline cellulose (MCC) for the production of pellets via extrusion/spheronisation has been well documented. Most literature reports on extrusion/spheronisation use MCC as the main ingredient in the formulation as its rheological properties are ideally suited for the extrusion/spheronisation process. However, in case of low solubility drugs MCC-based pellets tend to have a prolonged drug release profile [1] due to the lack of disintegration of MCC-based pellets. Furthermore, drug decomposition in the presence of MCC [2], as well as drug adsorption onto the surface of MCC fibre has been reported [3–5].

One approach to increase drug release was to modify MCC-based pellet formulations: addition of water-soluble diluents [1,6], solubilisers [7] and disintegrants [8], increasing the pellet porosity [9], using water/ethanol mixtures [10] or 2-propanol [11] as granulation liquid, etc. Others substituted MCC by an alternative excipient that should have the advantages of MCC during extrusion/spheronisation and at the same time ensure immediate drug release. Some of these alternatives included powdered cellulose [12,13], low-substituted hydroxypropylcellulose [14], hydroxypropylmethylcellulose and hydroxyethylcellulose [15], pectinic acid [16,17], chitosan [18], κ-carragenan [19], cross-linked polyvinylpyrrolidone [20] and polyethylene oxide with methoxypolyethylene glycol [21]. The properties of those alternatives, as well as their extrusion/spheronisation behaviour compared to MCC, have recently been listed by Liew et al. [20].

Starch has also been evaluated for extrusion/spheronisation purposes. Although O'Connor et al. [22] reported the

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failure of starch as the main excipient of pellets produced via extrusion/spheronisation, Junnila et al. combined MCC with native starch and a wetting agent [23] or with waxy corn starch [24] to successfully prepare pellets. Recently Prieto et al. [25] showed that the morphology of pellets containing starch (wheat or corn) and waxy corn starch was poor, whereas spherical pellets were obtained if starch was combined with dextrin.

The aim of this study was to evaluate the potential of a specific starch grade as the main excipient for pellets prepared via extrusion/spheronisation. This modified starch was obtained by an enzymatic debranching of amylose-rich starch. After debranching, the starch was retrograded and further isolated by extrusion or drying [26] yielding a crystalline, high-amylose material consisting of D-anhydroglucose units (linked by α-1,4-D-glycosidic bonds) organised into double-helical crystalline chains. Due to its double-helical structure, the α-1,4-D-glycosidic linkages are inaccessible to α-amylase in small intestine (resistant starch).

2. Materials and methods

2.1. Materials

Anhydrous theophylline (batch no. 0406251; Roig Farma, Terrassa, Spain) was used as a model drug with medium solubility (8.3 g/L at 25 °C). A high-amylose, crystalline and resistant starch (UNI-PURE®EX starch) was used as the main excipient in the pellets and was donated by National Starch and Chemical Co. (Bridgewater, New Jersey, USA). Hydroxypropylmethylcellulose (HPMC) (Methocel® E15 LV EP Pharm, Colorcon, Dartford, UK) was used as a binder and sorbitol (Sorbidex® P 16616, Cerestar, Vilvoorde, Belgium) was added to modify the consistency of the wet mass. Demineralised water was used as granulation liquid. To compare the drug release profiles, reference pellets were prepared with microcrystalline cellulose (MCC) (Avicel® PH 101, FMC, Cork, Ireland).

The following materials were used during preliminary tests: polyvinylpyrrolidone (PVP) (Kolidon® 30, BASF, Germany), hydroxypropylcellulose (HPC) (Klucel® GF Pharm, Aqualon, USA), hydroxypropylmethylcellulose (Methocel® K4M EP Pharm, Colorcon, Darford, UK), drum dried waxy maize starch (DDWMS) (National® 5730, National Starch and Chemical Co, Bridgewater, New Jersey, USA) erythritol (Eridex® 16955, Cerestar, Vilvoorde, Belgium) and mannitol (Mannidex® 16700, Cerestar, Vilvoorde, Belgium).

2.2. Methods

2.2.1. Pellet preparation

Anhydrous theophylline (25%, w/w dry mass), HPMC, sorbitol and modified starch were mixed (batch size: 250 g) for 15 min in a Turbula® mixer (model T2A, W.A. Bachofen, Basel, Switzerland). The powder mixture was granulated with demineralised water for 10 min at 60 rpm by means of a planetary mixer (Kenwood Chief, Hampshire, UK) with a K-shaped mixing arm. The water level was determined based on preliminary tests and corresponded to the level resulting in the highest yield. Water was added during the first 30 s of the wet massing phase. To ensure uniform water distribution during wet massing, the material adhering to the mixing bowl was regularly removed. The wet mass was extruded at an extrusion speed of 50 rpm using a single screw extruder (Dome extruder lab model DG-L1, Fuji Paudal, Tokyo, Japan) equipped with a dome-shaped extrusion screen (thickness: 1.2 mm, perforation diameter: 1 mm). The extrudates were spheronised for 3 min in a spheroniser having a friction plate with cross-hatched geometry (Caleva Model 15, Caleva, Sturminster Newton, Dorset, UK). To evaluate the effect of densification during extrusion, the extrudates were passed through the extruder for a second time prior to spheronisation. Pellets were dried for 20 min at 60 °C in a fluid-bed drier (Uniglatt, Glatt, Binzen, Germany).

2.2.2. Rheological characterisation of the wet powder and extrudate

Consistency of wet mass, extrudates and re-extruded material (35 g) was determined by means of a mixer torque rheometer (Model MTR2, Caleva, Sturminster Newton, Dorset, UK) as described by Parker [27] and Rowe [28] at a mixer speed of 50 rpm. After premixing for 45 s, the data were acquired during 15 s. Each sample was analysed in triplicate.

2.2.3. Experimental design and data analysis

In order to evaluate non-linear responses, a Box-Behnken response surface design was used. The influence of three formulation (binder, sorbitol and water level) and one process variables (spheronisation speed) was tested at three levels. Table 1 presents the variables with their coded and actual values (water level is only presented in coded terms). The other process parameters remained constant. The total number of experiments was 29 and included 5 replicates of the central point to estimate the significance of lack-of-fit tests. Experiments were performed in randomised order.

The selection of variables and their ranges was based on the results of preliminary experiments. Water levels are displayed in coded values because the optimal water level depended on the sorbitol concentration. At different sorbitol levels (0, 7.5, 15 and 22.5% w/w, dry mass) the optimal water level was determined and plotted against the corresponding sorbitol level. Based on a quadratic function (Eq. 1) the optimal water concentration (W, % w/w, wet mass) at the sorbitol level (S, % w/w, dry mass) of interest was calculated and set as the medium water level (0). The water concentration varied by ±1.5% to obtain the low (−1) and high (+1) water levels in the experimental design.

$$W(\%) = 0.129 * S^2 - 0.7865 * S + 44.471 \qquad (R^2 = 0.9997) \tag{1}$$

Table 1
Definition of the factors used in the experimental design

Factor	Low level (−1)	Medium level (0)	High level (+1)
A: HPMC concentration (% w/w, dry mass)	3	4.5	6
B: sorbitol concentration (% w/w, dry mass)	0	11.25	22.5
C: spheronisation speed (rpm)	650	850	1050
D: water level[a]	−1	0	+1

[a] Water level is shown in coded terms as it depends on the sorbitol level.

Initially the highest sorbitol level was set at 22.5% (w/w, dry mass). However, the pellet yield of these formulations was too low (<5%) due to a large fraction of fines. Therefore, the sorbitol concentration was reduced to 20% (0.78 as coded value) in order to obtain a better prediction model for process optimisation. All experiments with the coded and actual values of the variables are listed in Table 2.

The results were analysed using Design-Expert®, v.6.0.6. (Stat-Ease, Minneapolis, USA). Pellet yield, sphericity (aspect ratio and shape factor) and size were determined for each batch of the experimental design and those values were used as responses for modelling and process optimisation. Analysis of variance (ANOVA) with $P < 0.05$ was performed for each response.

2.2.4. Pellet characterisation

2.2.4.1. Sieve analysis. Pellets (100 g) were sieved for 10 min at an amplitude of 3 mm on a shaker (Type VE 1000, Retsch, Haan, Germany) using 1400, 1000, 710, 500 and 250 μm sieves (Retsch, Haan, Germany). The pellet yield was calculated based on the pellet fraction between 710 and 1400 μm and presented as the percent of the total pellet weight. This size fraction was used for all further measurements.

2.2.4.2. Pellet size and shape measurements. Pellet size and shape were determined using an image analysis system. Photomicrographs of pellets were taken with a digital camera (Camedia® C-3030 Zoom, Olympus, Tokyo, Japan), linked with a stereomicroscope system (SZX9 DF PL 1.5×, Olympus, Tokyo, Japan). A cold light source (Highlight 2100, Olympus, Germany) and a ring light guide (LG-R66, Olympus, Germany) were used to obtain top light illumination of the pellets against a dark surface. The images were analysed by image analysis software (AnalySIS®, Soft Imaging System, Münster, Germany). The magnification

Table 2
Box-Behnken design for four variables (*A*: HPMC concentration, %; *B*: sorbitol concentration, %; *C*: spheronisation speed, rpm; *D*: water concentration, %) at 3 levels and 5 replicates of the central point, presented in coded and actual terms (randomised order) and the corresponding results of pellet yield, aspect ratio (AR), two-dimensional shape factor (e_R) and Feret diameter (FD)

Run	Coded values				Actual values				Results			
	A	*B*	*C*	*D*	*A*	*B*	*C*	*D*	Yield (%)	AR	e_R	FD (μm)
1	−1	0	0	−1	3	11.25	850	35.76	83.6	1.17	0.51	1013
2	0	0	1	−1	4.5	11.25	1050	35.76	73.4	1.14	0.55	980
3	−1	0	0	1	3	11.25	850	38.76	77.2	1.15	0.54	1062
4	0	0	0	0	4.5	11.25	850	37.26	88.4	1.14	0.54	1047
5	0	0	0	0	4.5	11.25	850	37.26	87.4	1.12	0.57	1066
6	0	−1	−1	0	4.5	0	650	44.47	85.8	1.15	0.53	1140
7	−1	0	1	0	3	11.25	1050	37.26	37.4	1.13	0.55	996
8	−1	0	−1	0	3	11.25	650	37.26	90.2	1.20	0.48	1073
9	1	0	0	1	6	11.25	850	38.76	83.7	1.16	0.52	1155
10	−1	−1	0	0	3	0	850	44.47	59.2	1.13	0.56	1159
11	0	0	−1	−1	4.5	11.25	650	35.76	94.0	1.25	0.45	1095
12	−1	0.78	0	0	3	20	850	33.31	39.0	1.15	0.52	1063
13	0	0.78	−1	0	4.5	20	650	33.31	45.9	1.16	0.52	1020
14	1	0	−1	0	6	11.25	650	37.26	90.1	1.19	0.48	1168
15	0	0.78	1	0	4.5	20	1050	33.31	7.6	1.16	0.51	952
16	1	0.78	0	0	6	20	850	33.31	14.8	1.14	0.54	918
17	0	−1	0	1	4.5	0	850	45.97	71.1	1.15	0.53	1134
18	0	0	0	0	4.5	11.25	850	37.26	87.6	1.13	0.55	1071
19	0	0	0	0	4.5	11.25	850	37.26	86.6	1.11	0.58	1020
20	0	0	−1	1	4.5	11.25	650	38.76	76.3	1.15	0.52	1193
21	0	0.78	0	−1	4.5	20	850	31.81	35.5	1.19	0.48	963
22	0	−1	0	−1	4.5	0	850	42.97	75.8	1.13	0.54	1062
23	0	0	0	0	4.5	11.25	850	37.26	88.9	1.12	0.57	1054
24	1	0	0	−1	6	11.25	850	35.76	91.8	1.18	0.50	1048
25	1	−1	0	0	6	0	850	44.47	79.2	1.16	0.53	1108
26	0	0	1	1	4.5	11.25	1050	38.76	73.5	1.17	0.52	1022
27	0	−1	1	0	4.5	0	1050	44.47	42.1	1.14	0.54	1042
28	1	0	1	0	6	11.25	1050	37.26	80.9	1.14	0.54	1029
29	0	0.78	0	1	4.5	20	850	34.81	33.1	1.15	0.52	1069

was set in a way that one pixel corresponded to 5.7 μm and around 300 pellets were analysed for every batch. Each individual pellet was characterised by mean Feret diameter (FD) (average of 180 calliper measurements with an angle of rotation of 1°), aspect ratio (AR) (ratio of longest Feret diameter and its longest perpendicular diameter) and two-dimensional shape factor (e_R) (as described by Podczeck and Newton [29]) (Eq. 2):

$$e_r = \frac{2\pi r}{P_m} - \sqrt{1 - \left(\frac{b}{l}\right)^2} \quad (2)$$

where r is pellet radius, P_m is perimeter, l is the length of pellet (longest Feret diameter) and b is a pellet breadth (longest diameter perpendicular to the longest Feret diameter).

2.2.4.3. Friability. A sample of pellets (F_s, 10 g) was placed in an abrasion wheel together with 200 glass beads (diameter: 4 mm) and fitted to a friabilator (Type PTF, Pharma Test, Hainburg, Germany). The sample was subjected to falling shocks for 10 min at a rotational speed of 25 rpm. Afterwards the fines were removed by sieving through a 250 μm mesh for 5 min (2 mm amplitude). The fraction above 250 μm (F_a) was used to calculate the friability of pellets according to equation:

$$\text{Friability}(\%) = [(F_s - F_a)/F_s] * 100 \quad (3)$$

2.2.4.4. Scanning electron microscopy. Scanning electron microscopy (SEM) was used to visualise the surface morphology. Pellets were coated with platinum by means of a sputter coater (Auto Fine Coater, JFC-1300, Jeol, Tokyo, Japan) to assure conductivity. Photomicrographs were taken with a scanning electron microscope (Jeol JSM 5600 LV, Jeol, Tokyo, Japan).

2.2.4.5. Disintegration. The pellet disintegration time was measured in a disintegrator (Type PTZ, Pharma Test, Hainburg, Germany) using a method modified from the Eur. Ph. 4th ed. monograph for tablet disintegration: a 500 μm mesh cloth was placed at the bottom of the tubes. Discs were used to increase the mechanical stress on the pellets. Water was used as the disintegration medium and the sample amount was 100 mg. Results are presented as the average of six determinations.

2.2.4.6. Dissolution tests. The dissolution tests were performed according to the USP basket apparatus (VK 8000, VanKel, New Jersey, USA) at a rotational speed of 50 rpm and at a temperature of 37 °C. Demineralised water (900 mL) was used as the dissolution medium and the sample amount used for analysis (300 mg) was adjusted to obtain sink conditions. The samples of 5 mL were withdrawn from the dissolution vessel at 5, 10, 15, 20, 30, 45 and 60 min. The samples were spectrophotometrically analysed at 272 nm by means of a double-beam spectrophotometer (Perkin-Elmer UV/VIS λ12, Norwalk, CT, USA). Each batch was analysed in triplicate.

2.2.5. Solid-state NMR

The solid-state ^{13}C CP/MAS NMR spectra of pellets containing anhydrous theophylline (25% w/w, dry mass), HPMC (4.5% w/w, dry mass), sorbitol (0, 7.5, 11.25 and 20% w/w, dry mass) and UNI-PURE®EX starch were recorded at room temperature on an Inova 200 Varian spectrometer operating at a static magnetic field of 4.7 T. Magic angle spinning was performed at 5 kHz using ceramic Si_3N_4 rotors. The proton spin-lattice relaxation time (T_{1H}) was measured via the chemical shift selective carbon nuclei by means of the inversion-recovery method. Because of the long T_{1H} and T_{CH} (time needed to build up the cross-polarisation) of anhydrous theophylline, two independent experiments were performed. A fast experiment was performed in order to determine the short T_{1H}'s of UNI-PURE®EX starch and sorbitol by means of a fixed contact time CT of 1 ms and a variable evolution time between 0.05 and 8 s. A longer experiment was set up to determine the extremely long T_{1H} of anhydrous theophylline by means of a fixed contact time CT of 7.5 ms (a sufficient build up of theophylline magnetisation) and a variable evolution time between 0.05 and 240 s. The recycle time was always set to 5 times T_{1H} and a spin-lock field of 50 kHz was used for cross-polarisation. The following equation (Eq. 4) was used for the T_{1H} analysis of the integrated signals:

$$M(t) = M_o(1 - 2\exp(-t/T_{1H})) \quad (4)$$

where t is the variable evolution time and M_o is the intensity of the resonance at equilibrium. The proton spin-lattice relaxation time in the rotating frame $T_{1\rho H}$ was measured by means of the variable contact time method, in which the proton magnetisation is kept in spin lock before it is cross-polarised to the carbon nuclei: CT was varied between 0.5 and 12.5 ms and a short recycle time of 4 s was used to suppress the theophylline contribution. The integrated signals were analysed according to the equation:

$$M(\text{CT}) = M_o \exp(-\text{CT}/T_{1\rho H}) \quad (5)$$

2.2.6. X- ray diffraction

X-ray diffraction patterns of pure UNI-PURE®EX starch, anhydrous theophylline, sorbitol, HPMC, as well as of pellets containing anhydrous theophylline (25% w/w, dry mass), HPMC (4.5% w/w, dry mass) combined with sorbitol (0, 11.25 and 20% w/w, dry mass) were determined using an X-ray diffractometer (D-500, Siemens, Germany) with CuK_λ radiation (0.154 nm). The angular range (2θ) varied from 10 to 60° with steps of 0.02° and the measuring time was 1 s/step.

3. Results and discussion

UNI-PURE®EX starch had a favourable extrusion/spheronisation behaviour: it could be extruded with minimal

resistance (generating limited friction and heat), the extrudate fragmented evenly during spheronisation and the fragments could easily be spheronised. Preliminary tests revealed that the addition of a binder was required to obtain pellets with an acceptable size distribution as without binder a large fraction of fines was obtained. Using PVP and HPC as less adhesive binders was not beneficial, since the strength of the extruded material was reduced and the end product still contained too many fines. In contrast, HPMC and DDWMS improved the binding efficiency of the extrudates, yielding sufficiently large pellets after spheronisation. HPMC has already been used as a binder in pellet formulations containing chitosan as the main excipient [18]. Chatlapalli et al. [15] even investigated the extrusion/spheronisation behaviour of formulations using HMPC as the main ingredient. In our study, a low viscosity HPMC-grade (Methocel® E15 LV Pharm, 15 mPac for a 2% w/w solution at 20 °C) was selected for further experiments, because it provided the best binding properties combined with minimal sticking of the extrudates during spheronisation. Preliminary work also showed that polyols increased the mechanical strength of the extruded material. Evaluation of erythritol, sorbitol and mannitol as additives revealed that sorbitol had the best effect on the consistency of the wet mass, improving its strength without reducing the pellet sphericity. This beneficial effect of sorbitol was concentration dependent.

Table 3
ANOVA results for yield, aspect ratio and Feret diameter

Source	*P* value	Source	*P* value
Yield			
Model	< 0.0001	Lack-of-fit	0.0724
A: HPMC	0.0010	R^2	0.9977
B: sorbitol	<0.0001	Adjusted R^2	0.9951
C: spheronisation speed	<0.0001		
D: water	<0.0001		
A^2	<0.0001		
B^2	<0.0001		
C^2	<0.0001		
AB	<0.0001		
AC	<0.0001		
BC	0.0296		
CD	0.0002		
A^2C	<0.0001		
AB^2	0.0003		
AC^2	<0.0001		
B^2C	<0.0001		
Aspect ratio			
Model	<0.0001	Lack-of-fit	0.1817
C: spheronisation speed	0.0011	R^2	0.7149
D: water	0.0249	Adjusted R^2	0.6529
C^2	0.0017		
D^2	0.0009		
CD	0.0010		
Feret diameter			
Model	<0.0001	Lack-of-fit	0.1008
B: sorbitol	<0.0001	R^2	0.7314
C: spheronisation speed	<0.0001	Adjusted R^2	0.6991
D: water	0.0010		

To elucidate the influence of HPMC and sorbitol on the quality of starch-based pellets, an experimental design was set up which included binder and sorbitol concentration in combination with spheronisation speed and water as variables.

The ANOVA analysis of pellet yield (Table 3) suggested that a reduced cubic model can be used for data fitting ($P < 0.05$) and process optimisation. The lack-of-fit was not significant ($P > 0.05$) and the predicted R^2 value was in reasonable agreement with the R^2 value adjusted for the degrees of freedom. All linear and quadratic factors of the model (except the quadratic term of water) were significant ($P < 0.05$) as well as some interaction terms. Therefore, when evaluating the influence of a specific factor (variable) on process yield, significant interactions between spheronisation speed and the other variables and between sorbitol and binder level should be considered. The regression equation in terms of the coded values is the following:

$$\begin{aligned}\text{Yield}(\%) = {} & 88.11 + 3.67 * A - 32.83 * B - 5.85 * C \\ & - 3.27 * D - 4.82 * A^2 - 47.61 * B^2 \\ & - 8.55 * C^2 - 14.18 * A * B + 10.91 * A * C \\ & - 2.62 * B * C + 4.43 * C * D \\ & - 9.62 * A^2 * C - 7.83 * A * B^2 + 7.18 * A * C^2 \\ & - 18.62 * B^2 * C \end{aligned} \quad (6)$$

Fig. 1 presents 3D-surface response diagrams of pellet yield as a function of sorbitol and binder level for a fixed (medium) water level at different spheronisation speeds. The

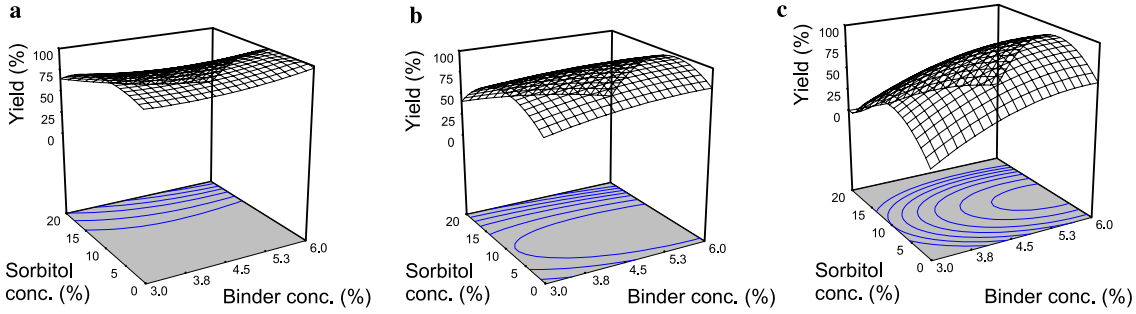

Fig. 1. 3D surface response diagrams of pellet yield as a function of sorbitol and binder level for fixed amount of water (medium level) and fixed spheronisation speed: (a) 650 rpm (low), (b) 850 rpm (medium), and (c) 1050 rpm (high).

graphs show that a high yield was obtained (>90%). Pellet yield was the highest at medium or low spheronisation speed (Fig. 1a and b). At the highest spheronisation speed, yield increased with increasing binder concentration (Fig. 1c). A higher binder level promoted binding of the wet mass and additionally made the extrudate more resistant to friction forces at higher spheronisation speed. However, at each spheronisation speed, the lowest yield was obtained for the highest sorbitol level. When reducing the sorbitol amount to the medium value, the influence of spheronisation speed on pellet yield was less pronounced, being lower only for a lower binder concentration combined with the highest spheronisation speed. A formulation without sorbitol resulted in a lower yield at a higher spheronisation speed and lower binder concentration.

Mixer torque rheometry (MTR) has been widely used to determine the optimal water level in formulations intended for extrusion and spheronisation. Since the preliminary experiments revealed that sorbitol affected the wet mass consistency, MTR was used to characterise the rheological properties of formulations containing varying amounts of sorbitol (Fig. 2). All formulations contained 4.5% (w/w, dry mass) HPMC, 25% (w/w, dry mass) theophylline and an optimal water level. Rheological properties revealed that the main densification of the wet mass occurred during extrusion. The mean torque values of wet granules containing UNIPURE®EX starch as the main excipient were lower (<0.1 Nm) compared to MCC-based wet granules (0.27–0.33 Nm, [27]). Furthermore, it was observed that sorbitol concentration significantly influenced the consistency of the extruded material: the mean torque value was higher when increasing the sorbitol concentration. However, at the highest concentration (22.5% w/w, dry mass) the mean torque dropped dramatically. This wet mass behaviour correlated well with the low pellet yield observed in the experimental design for formulations containing the highest sorbitol level. Extrudates from those formulations could not resist the friction forces during spheronisation and a high amount of fines was formed. Furthermore, additional densification of the wet mass via re-extrusion affected the wet mass rheology as the mean torque of re-extruded material was higher compared to product extruded only once. Re-extrusion probably assured a better distribution of water through the wet mass and a smoother extrudate surface was obtained (Fig. 3). Consequently, the fragmentation of the extrudates at the beginning of the spheronisation was uniform and resulted in a reduction of fines and a higher yield.

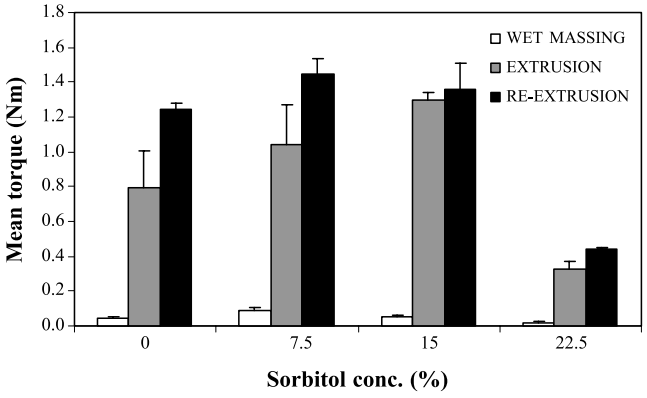

Fig. 2. Mean torque values ($n = 3$) of wet mass after granulation, extrusion and re-extrusion as a function of sorbitol concentration. All formulations contained 4.5% (w/w, dry mass) HPMC, 25% (w/w, dry mass) anhydrous theophylline and an optimal water level.

Since MTR measurements revealed the importance of sorbitol to obtain the optimal wet mass consistency for successful extrusion/spheronisation, solid-state NMR spectroscopy and relaxometry were used to study the molecular miscibility at nano-scale and the intermolecular interactions in UNI-PURE®EX starch-based formulations. Information about the level of mixture heterogeneity can be obtained from the proton relaxation decay times T_{1H} and $T_{1\rho H}$. Indeed the intrinsic relaxation decay times of the pure components will be averaged out towards a single decay time if homogeneous mixing is achieved or if the dimensions of existing molecular domains are smaller than the maximum path length over which proton–proton spin diffusion can occur. Table 4 presents the T_{1H} values of pure components and blends with variable sorbitol content. Note that for the mixtures the decay times of the resonances 2, 3 and 4 were determined by using a relative short cross-polarisation contact time (1 ms) and recycling delay (5 s). In this way, the contribution of theophylline to resonance 2 was completely suppressed. In all blends, regardless of the sorbitol content, sorbitol and UNI-PURE®EX starch were mixed homogeneously on the T_{1H} scale, since a single decay time is observed for the corresponding resonances 2, 3 and 4. Both components clearly relaxed very efficiently via the short T_{1H} of UNI-PURE®EX starch. It was remarkable that this T_{1H} value goes through a maximum for a blend containing 11.25% sorbitol. In contrast,

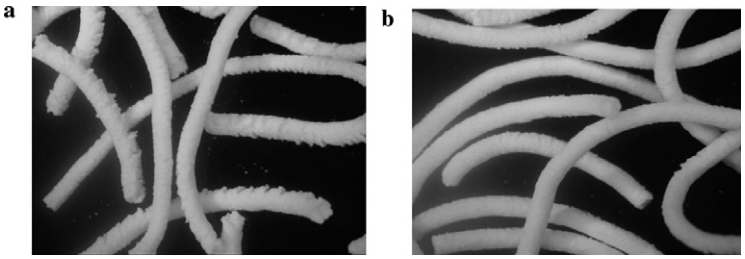

Fig. 3. Photomicrographs of extrudates (without sorbitol): (a) after extrusion, and (b) after re-extrusion.

Table 4
T_{1H} and $T_{1\rho H}$ decay times of the pure components and of blends with variable sorbitol concentration as measured by ^{13}C solid-state NMR

	Resonance					Resonance				
	1	2	3	4	5	1	2	3	4	5
	T_{1H} (s)					$T_{1\rho H}$ (ms)				
UNI-PURE®EX starch		0.76	0.75	0.70			4.6	3.9	4.2	
Sorbitol			10.5	10.5				11.0(21%)	11.0(21%)	
								172(79%)	172(79%)	
Theophylline	51.2	45.2			54.0	ND	ND			ND
0% sorbitol	50.0	0.61	0.61	0.62	51.0	ND	4.5	4.6	5.0	ND
7.5% sorbitol	48.4	0.68	0.67	0.65	49.6	ND	2.6	2.4	2.5	ND
11.25% sorbitol	52.2	0.76	0.74	0.72	46.3	ND	2.8	2.4	2.3	ND
20% sorbitol	48.3	0.67	0.66	0.65	50.7	ND	1.9	1.8	2.1	ND

Resonances 1 and 5 originate from theophylline, 2 from theophylline and UNI-PURE®EX starch, 3 and 4 from UNI-PURE®EX starch and sorbitol. The extremely long $T_{1\rho H}$ of theophylline cannot be determined experimentally (ND: not determined).

theophylline remained phase separated and the extremely long T_{1H} relaxation time of about 50 s indicated the preservation of the crystalline state in the blends.

Table 4 also presents the $T_{1\rho H}$ decay times of pure components and of mixtures with variable sorbitol content. The $T_{1\rho H}$ relaxation of pure sorbitol behaved biexponentially with both a short and very long decay time. This pointed to a (semi) crystalline state which could also explain the rather long T_{1H} decay time. In the processed blends sorbitol became amorphous with only a short $T_{1\rho H}$ decay time. Additionally, sorbitol in the mixtures also relaxed via the efficient pathway of UNI-PURE®EX starch, which indicated that they are homogeneously mixed on the nm-level. Furthermore, the relaxation occurred more efficiently at higher sorbitol concentration. The $T_{1\rho H}$ decay time of theophylline is so extremely long that it could not be determined experimentally, confirming the crystalline state of theophylline in the blends. As a conclusion, it was demonstrated that the T_{1H} relaxation time increased with the amount of sorbitol, reaching a maximum for a blend containing 11.25 % sorbitol. The relaxation is completely determined by UNI-PURE®EX starch. Adding sorbitol to the formulation reduced the molecular mobility of starch with an increase of T_{1H}. However, in blends with higher sorbitol concentration (20%), sorbitol acted as a plasticiser, providing increased starch mobility and reducing the T_{1H} value. These observations are in good agreement with MTR measurements: at lower sorbitol levels the mean torque increased due to strong starch-sorbitol interactions and a lower molecular mobility, whereas at the highest sorbitol level (20%, w/w) the mean torque decreased due to the plasticising effect of the higher molecular mobility. Gaudin et al. [30] already described the plasticising and anti-plasticising effect of sorbitol on starch as a function of sorbitol concentration: at low sorbitol levels brittle starch–sorbitol films were formed, whereas the mechanical strength of these films increased at sorbitol concentrations above 21%. These interactions between starch and sorbitol were also confirmed by NMR, showing that at low sorbitol levels the molecular mobility was lower due to strong hydrogen bonding between sorbitol and starch molecules. When exceeding a critical sorbitol concentration, other interactions were identified, namely starch–sorbitol–sorbitol interactions. This clustering of sorbitol molecules was associated with a higher system mobility and therefore sorbitol exhibited a plasticising effect.

X-ray diffractograms of raw materials and pellets (Fig. 4) support the solid-state NMR findings that theophylline preserved its crystallinity, while sorbitol became amorphous during processing. Furthermore, no differences between diffraction patterns of formulations with different sorbitol content were observed (data not shown).

The amount of water is a critical parameter for the extrusion/spheronisation process. The optimal water level depended on the sorbitol concentration, being lower if a higher sorbitol level was used. Sorbitol as a water-soluble component dissolved in water during wet massing, reducing the solids amount and inducing pellet agglomeration during spheronisation. Similar relationships between the solubility of drug and filler and the optimal water concentration were reported by Baert et al. [31], Hileman et al. [32] and Lustig-Gustafsson et al. [33].

The response surface graphs (Fig. 5) showed that at medium sorbitol level, a high binder level did not increase pellet yield. This is probably due to the low molecular weight of sorbitol, which interacts with the starch molecules and additionally accumulates in the cavities between HPMC molecules and thereby reduces the adhesion of HPMC polymer chains. This effect of low molecular weight materials on self-adhesion of polymers has been described by Millili et al. [34].

Table 3 lists the results of the ANOVA of the aspect ratio as the response value. The quadratic model was significant ($P < 0.05$) and the statistics (insignificant lack-of-fit and agreement of predicted and adjusted R^2 values) indicated that the model can be used to describe the data and optimise the process. Spheronisation speed, water level (linear and quadratic functions) as well as their interactions were significant factors ($P < 0.05$), while the binder and sorbitol level did not have a significant influence on pellet sphericity. The regression equation in terms of the coded factor values can be presented by the following equation:

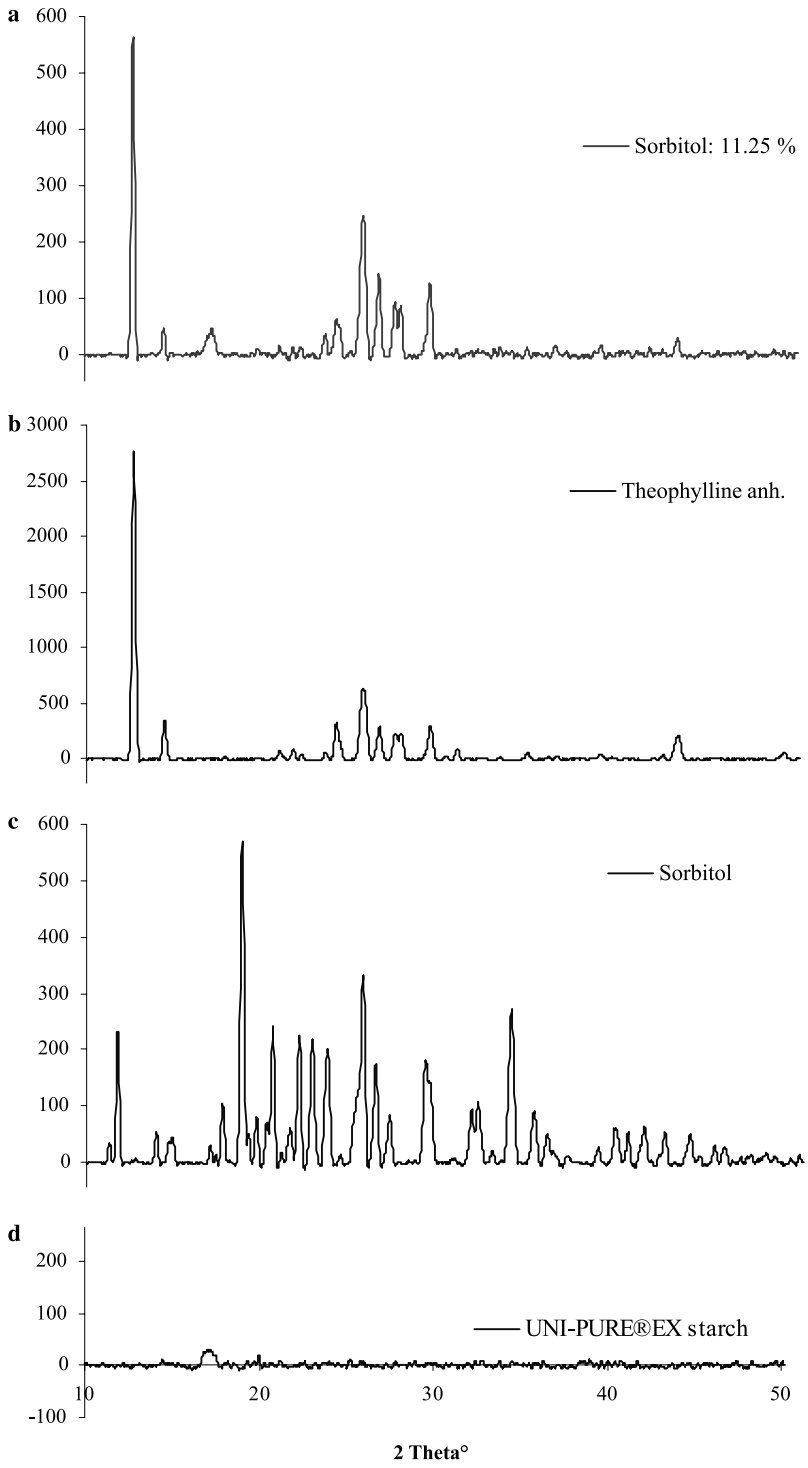

Fig. 4. X-ray powder diffraction patterns of (a) pellets containing 11.25%, w/w sorbitol, (b) anhydrous theophylline, (c) sorbitol, and (d) UNI-PURE® EX starch.

$$\text{Aspect ratio} = 1.135 - 0.018 * C - 0.012 * D + 0.023 * C^2 + 0.024 * D^2 + 0.032 * C * D \quad (7)$$

An increase of spheronisation speed has been already reported as beneficial for pellet sphericity [35–37]. For this pellet formulation, we confirmed that increasing spheronisation speed lowered the aspect ratio. Using a suboptimal amount of water resulted in dumbbells, whereas at higher water concentrations agglomeration occurred. Results (Fig. 6) showed that for most formulations the aspect ratio was between 1.12 and 1.20, which complied with the range defined by Chopra et al. [38] for acceptable pellet sphericity. The significant interaction between water and spheronisation speed indicated that a low spheronisation speed and

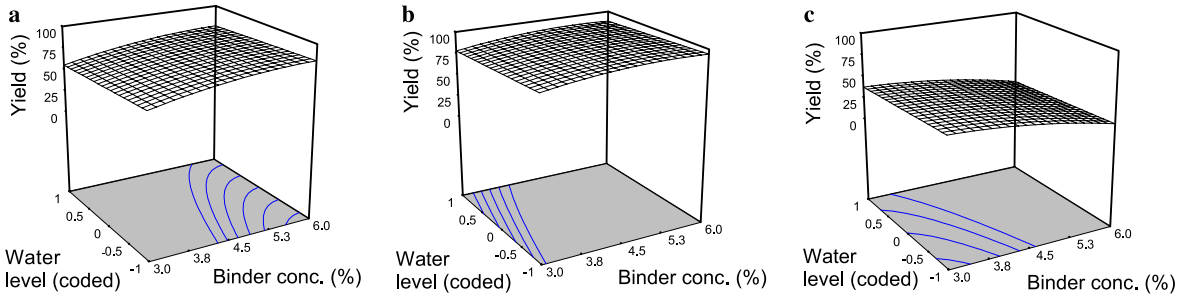

Fig. 5. 3D surface response diagrams of pellet yield as a function of water and binder level at fixed spheronisation speed (medium) and sorbitol level: (a). 0% (low), (b) 11.25% (medium), and (c) 20% (high).

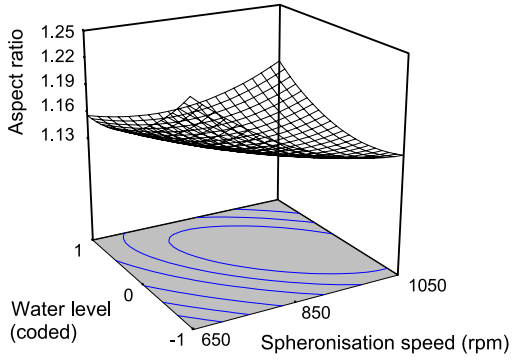

Fig. 6. 3D surface response diagram of pellet aspect ratio as a function of water level (coded) and spheronisation speed at fixed binder and sorbitol level (medium).

water level decreased the sphericity of the end product, confirming the importance of energy input during spheronisation as well as of an adequate water level for successful spheronisation. Sphericity improved at higher spheronisation speeds, but the influence of water was less pronounced, suggesting that a wider water range could be used to obtain acceptable sphericity. The binder concentration and its interactions were not significant, indicating that the concentration range (3–6%, w/w, dry mass) selected during preliminary study was optimal. Agrawal, et al. [18] employed HPMC as a binder in a higher concentration range (5–10%, w/w) in pellet formulations containing chitosan and reported significant interactions between binder concentration and spheronisation speed.

ANOVA of shape factor (e_R) resulted in similar significant factors compared to aspect ratio as a response parameters, with sorbitol as an additional significant factor ($P = 0.0493$). The shape factor was lower at high sorbitol level due to an increase of pellet surface roughness, since the shape factor combined by definition pellet geometry and surface roughness [29]. Due to the low mechanical strength of extrudates at this sorbitol concentration, fine particles were sticking to the surface of larger pellets during spheronisation, thus increasing surface roughness (Fig. 9d).

The ANOVA of pellet size (mean Feret diameter) is presented in Table 3. Significant linear model ($P < 0.05$), insignificant lack-of-fit test ($P > 0.05$) and agreement of predicted and adjusted R^2 values allow data modelling. Only linear functions of spheronisation speed, water and sorbitol concentration were significant ($P < 0.05$). The regression equation (Eq. 8) in terms of the coded factor values is:

$$\text{Feret diameter} = 1056.6 - 60.5 * B - 55.6 * C + 39.4 * D \quad (8)$$

3D surface response diagrams of pellet size (Fig. 7) showed that for all batches the mean pellet diameter was between 900 and 1200 μm. Furthermore, a higher water concentration generated larger pellets due to particle agglomeration during spheronisation. Additionally, at higher spheronisation speed excessive fragmentation of the extrudates occurred at the beginning of the spheronisation phase, yielding smaller pellets. Furthermore, the

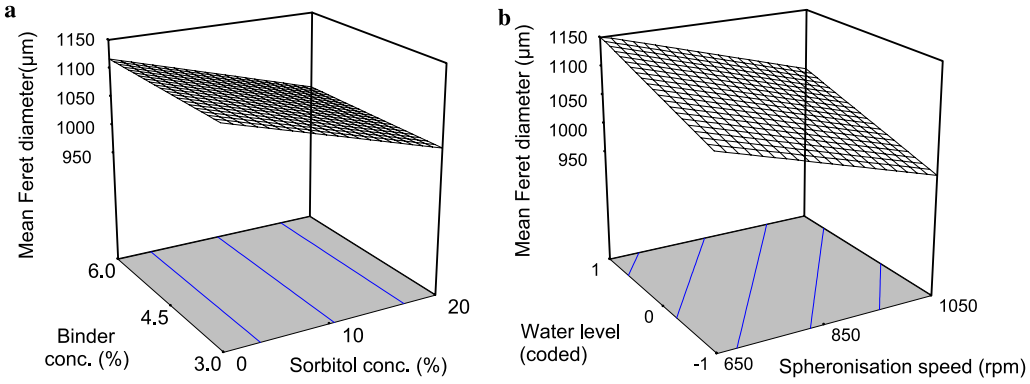

Fig. 7. 3D surface response diagrams of pellet size (mean Feret diameter) as a function of: (a) sorbitol and binder level at fixed spheronisation speed and water level (medium), and (b) spheronisation speed and water level at fixed sorbitol and binder level (medium).

results revealed that increasing sorbitol concentrations reduced pellet size. The addition of sorbitol provided a more uniform breaking of the extrudates at the beginning of the spheronisation phase. Formulations with the highest sorbitol concentration had the lowest pellet size due to insufficient mechanical strength of extrudates.

The regression equations of pellet yield and aspect ratio were used to determine the levels of all variables resulting in an optimal process in terms of maximal yield and minimal aspect ratio. For example, Fig. 8 presents the spheronisation speed and sorbitol concentration providing a pellet yield above 85% and an aspect ratio below 1.15 for medium binder and water level. It can be observed that an acceptable yield and sphericity is to be expected at a spheronisation speed between 750 and 950 rpm combined with sorbitol concentrations up to about 10% (w/w). To test the validity of the model, one point of the model was selected and the good agreement between the predicted and actual values (Table 5) indicated that the proposed statistical models can be used as a tool for successful process optimisation.

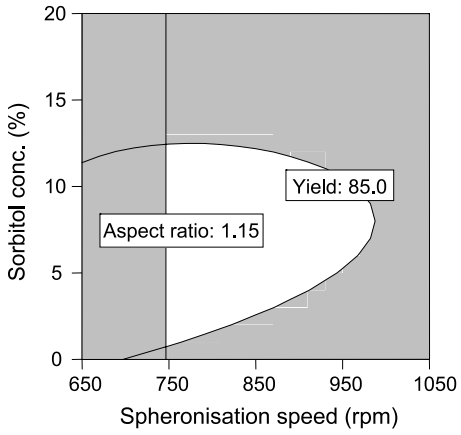

Fig. 8. Graphical presentation of process optimisation (yield > 85% and AR < 1.15) at medium water and binder level.

SEM pictures showed that sorbitol had a significant effect on surface morphology (Fig. 9): pellets without sorbitol had a cracked surface, whereas pellets containing sorbitol had a smoother surface. Since the presence of cracks is not a preferred feature for pellets intended for coating, the addition of sorbitol to the formulation is crucial for obtaining a successful sustained release coat. Friability measurements showed that starch-based pellets had high mechanical strength (friability of less than 0.01%), indicating that these pellets are able to withstand the shear forces during fluid bed coating.

Disintegration tests showed that pellets containing starch as the main excipient disintegrated, the disintegration time being determined by the sorbitol level: pellets with 20% sorbitol disintegrated within 2 min, whereas the

Table 5
Predicted and actual response values for a formulation consisting of 25% theophylline, 5.8% binder, 9.7% sorbitol and UNIPURE®EX starch

Response	Prediction value	SE Mean	95% CI low	95% CI high	Obtained value
Yield (%)	91.36	0.97	89.27	93.45	91.80
Aspect ratio	1.134	0.005	1.123	1.144	1.125
Shape factor	0.541	0.007	0.527	0.556	0.552

Spheronisation speed, 846 rpm; water level, 0.33 (coded value).

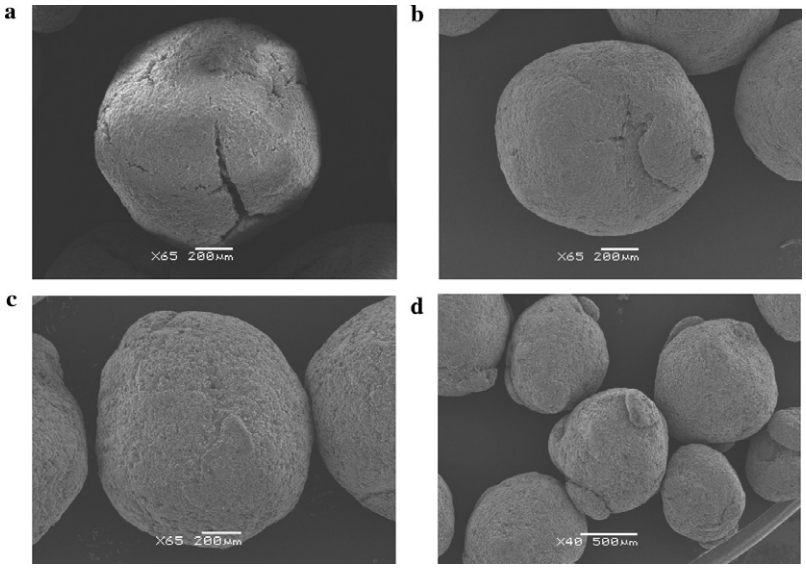

Fig. 9. SEM pictures of pellets containing different amounts of sorbitol (w/w, dry mass): (a) 0%, (b) 11.25%, (c) 20%, and (d) 20%.

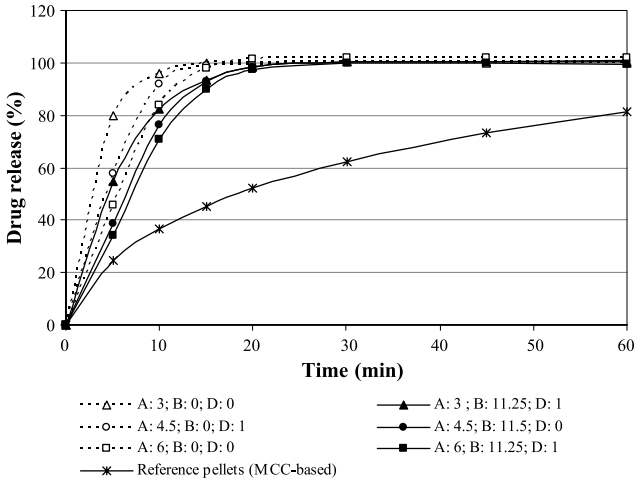

Fig. 10. Dissolution profiles of pellets containing different amounts of a binder (A: 3, 4.5 or 6% w/w, dry mass) and sorbitol (B: 0 or 11.25% w/w, dry mass). Water level (D) is presented in coded values.

other batches (irrespective of sorbitol level) had a similar disintegration time (between 5 and 7 min). The other variables of the experimental design did not have a significant influence on disintegration time.

Drug release profiles (Fig. 10) showed that all starch-based pellets completely released theophylline in less than 20 min, which is significantly faster than MCC-based pellets (only 50% drug was released within the same time interval), mainly due to the ability of starch-based pellets to disintegrate. The binder and sorbitol concentration only determined drug release during the initial 10 min of the test: pellets containing a high amount of binder or sorbitol at medium level had a slightly slower drug release. In contrast, formulations without sorbitol had slightly faster drug release, possibly due to surface irregularities (cracks). Nevertheless, immediate drug release was obtained for all batches, irrespective of formulation and process parameters.

4. Conclusion

This study illustrated the potential of UNI-PURE®EX starch as the main excipient in formulations intended for extrusion/spheronisation. Based on the high process yield, good pellet sphericity and immediate release properties of the pellets, UNI-PURE®EX starch can be proposed as an alternative to microcrystalline cellulose during processing of formulations (containing 25% drug) via extrusion/spheronisation. Future experiments will evaluate the opportunities offered by this modified starch for the preparation of pellets containing higher drug loads and will focus on the influence of drug load and drug solubility on drug release kinetics.

References

[1] R.E. O'Connor, J.B. Schwartz, Spheronization II: drug release from drug-diluent mixtures, Drug Dev. Ind. Pharm. 11 (1985) 1837–1857.
[2] A.W. Basit, J.M. Newton, L.F. Lacey, Formulation of ranitidine pellets by extrusion–spheronization with little or no microcrystalline cellulose, Pharm. Dev. Tech. 4 (1999) 499–505.
[3] S. Okada, H. Nakahara, H. Isaka, Adsorption of drugs on microcrystalline cellulose suspended in aqueous solutions, Chem. Pharm. Bull. 35 (1987) 761–768.
[4] S.L. Rivera, S. Ghodbane, In vitro adsorption–desorption of famotidine on microcrystalline cellulose, Int. J. Pharm. 108 (1994) 31–38.
[5] S.S. Al-Nimry, S.M. Assaf, I.M. Jalal, N.M. Najib, Adsorption of ketofifen onto some pharmaceutical excipients, Int. J. Pharm. 149 (1997) 115–121.
[6] J.F. Pinto, G. Buckton, J.M. Newton, The influence of four selected processing and formulation factors on the production of spheres by extrusion and spheronisation, Int. J. Pharm. 83 (1982) 187–196.
[7] C. Vervaet, L. Baert, J.P. Remon, Enhancement of in-vitro drug-release by using polyethylene-glycol-400 and peg-40 hydrogenated castor-oil in pellets made by extrusion/spheronisation, Int. J. Pharm. 108 (1994) 207–212.
[8] C. Souto, A. Rodriguez, S. Parajes, R. Martinez-Pacheco, A comparative study of the utility of two superdisintegrants in microcrystalline cellulose pellets prepared by extrusion–spheronization, Eur. J. Pharm. Biopharm. 61 (2005) 94–99.
[9] L. Baert, J.P. Remon, Influence of amount of granulation liquid on the drug release rate from pellets made by extrusion spheronisation, Int. J. Pharm. 95 (1993) 135–141.
[10] G.P. Millili, J.B. Schwartz, The strength of microcrystalline cellulose pellets – the effect of granulating with water ethanol mixtures, Drug Dev. Ind. Pharm. 16 (1990) 1411–1426.
[11] M. Schroeder, P. Kleinebudde, Structure of disintegrating pellets with regard to fractal geometry, Pharm. Res. 12 (1995) 1694–1700.
[12] H. Lindner, P. Kleinebudde, Use of powdered cellulose for the production of pellets by extrusion/spheronisation, J. Pharm. Pharmacol. 46 (1994) 2–7.
[13] L. Alvarez, A. Concheiro, J.L. Gomez-Amoza, C. Souto, R. Martinez-Pacheco, Powdered cellulose as excipient for extrusion–spheronization pellets of a cohesive hydrophobic drug, Eur. J. Pharm. Biopharm. 55 (2003) 291–295.
[14] P. Kleinebudde, Application of low substituted hydroxypropylcellulose (L-HPC) in the production of pellets using extrusion/spheronisation, Int. J. Pharm. 96 (1993) 119–128.
[15] R. Chatlapalli, B.D. Rohera, Physical characterization of HPMC and HEC and investigation of their use as pelletization aids, Int. J. Pharm. 161 (1998) 179–193.
[16] I. Tho, S.A. Sande, P. Kleinebudde, Pectinic acid, a novel excipient for production of pellets by extrusion/spheronisation: preliminary studies, Eur. J. Pharm. Biopharm. 54 (2002) 95–99.
[17] I. Tho, S.A. Sande, P. Kleinebudde, Disintegrating pellets from a water-insoluble pectin derivative produced by extrusion/spheronisation, Eur. J. Pharm. Biopharm. 56 (2003) 371–380.
[18] A.M. Agrawal, M.A. Howard, S.H. Neau, Extruded and spheronized beads containing no microcrystalline cellulose: influence of formulation and process variables, Pharm. Dev. Tech. 9 (2004) 197–217.
[19] M. Bornhoft, M. Thommes, P. Kleinebudde, Preliminary assessment of carrageenan as excipient for extrusion/spheronisation, Eur. J. Pharm. Biopharm. 59 (2005) 127–131.
[20] C.V. Liew, L. Gu, J.L.P. Soh, P.W.S. Heng, Functionality of cross-linked polyvinylpyrrolidone as a spheronization aid: a promising alternative to microcrystalline cellulose, Pharm. Res. 22 (2005) 1387–1398.
[21] M.A. Howard, S.H. Neau, J.S. Sack, PEO and MPEG in high drug load extruded and spheronised beads that are devoid of MCC, Int. J. Pharm. 307 (2006) 66–76.
[22] R.E. O'Connor, J. Holinej, J.B. Schwartz, Spheronization I: processing and evaluation of spheres prepared of commercially available excipients, Am. J. Pharm. 156 (1984) 80–87.
[23] R. Junnila, J. Heinamaki, J. Yliruusi, Effects of surface-active agent on the size, shape and hardness of microcrystalline cellulose/maize

starch pellets prepared by an extrusion–spheronization technique, STP Pharma Sci. 8 (1998) 221–226.
[24] R. Junnila, P. Palviainen, J. Heinämäki, P. Myllärinen, P. Forssell, J. Yliruusi, Waxy corn starch: a potent cofiller in pellets produced by extrusion–spheronisation, Pharm. Dev. Techn. 5 (2000) 67–76.
[25] S. Almeida Prieto, J. Blanco Mendez, F.J. Otero Espinar, Starch–dextrin mixtures as base excipients for extrusion–spheronization pellets, Eur. J. Pharm. Biopharm. 59 (2005) 511–521.
[26] US Patent No. 5281276.
[27] M.D. Parker, R.C. Rowe, N.G. Upjohn, Mixer torque rheometry: a method for quantifying the consistency of wet granulations, Pharm. Tech. Int. 2 (1990) 50–62.
[28] R.C. Rowe, M.D. Parker, Mixer torque rheometry – An update, Pharm. Tech. Eur. 6 (1994) 24–27.
[29] F. Podczeck, J.M. Newton, A shape factor to characterize the quality of spheroids, J. Pharm. Pharmacol. 46 (1994) 82–85.
[30] S. Gaudin, D. Lourdin, D. Le Botlan, J.L. Ilari, P. Colonna, Plasticisation and mobility in starch–sorbitol films, J. Cereal Sci. 29 (1999) 273–284.
[31] L. Baert, D. Fanara, P. Debaets, J.P. Remon, Instrumentation of a gravity feed extruder and the influence of the composition of binary and ternary mixtures on the extrusion forces, J. Pharm. Pharmacol. 43 (1991) 745–749.
[32] G.A. Hileman, S.M. Upadrashta, S.H. Neau, Drug solubility effects on predicting optimum conditions for extrusion and spheronisation of pellets, Pharm. Dev. Tech. 2 (1997) 43–52.
[33] C. Lustig-Gustafsson, H.K. Johal, F. Podczeck, J.M. Newton, The influence of water content and drug solubility on the formulation of pellets by extrusion and spheronisation, Eur. J. Pharm. Sci. 8 (1999) 147–152.
[34] GP. Millili, R.J. Wigent, J.B. Schwartz, Autohesion in pharmaceutical solids, Drug Dev. Ind. Pharm. 16 (1990) 2383–2407.
[35] L. Baert, H. Vermeersch, J.P. Remon, J. Smeyers-Verbeke, D.L. Massart, Study of parameters important in the spheronisation process, Int. J. Pharm. 96 (1993) 225–229.
[36] L. Hellen, J. Poutanen, J. Yliruusi, P. Merkku, E. Kristoffersson, Changes in size and size distribution of pellets during spheronisation, Part I. Boll. Chim. Farm. 133 (1994) 80–87.
[37] L.C.S. Wan, P.W.S. Heng, C.V. Liew, Spheronization conditions on spheroid shape and size, Int. J. Pharm. 96 (1993) 59–65.
[38] R. Chopra, F. Podczeck, J.M. Newton, G. Alderborn, The influence of pellet shape and film coating on the filling of pellets into hard shell capsules, Eur. J. Pharm. Biopharm. 53 (2002) 327–333.