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RESEARCH ARTICLE

A comparison of chitosan-silica and sodium starch glycolate as disintegrants for spheronized extruded microcrystalline cellulose pellets

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Abstract

Chitosan-silica coprecipitate (C-S) has recently been proposed as a tablet disintegrant. In this study we compared it with a 1:1 physical mixture of chitosan and silica (C/S) at the same composition as the coprecipitate, and with the widely used commercial disintegrant sodium starch glycolate (SSG), as regards to its behavior in spheronized extruded pellets of microcrystalline cellulose (MCC) containing hydrochlorothiazide as a typical poorly water-soluble drug. In all three cases, possible synergism between the disintegrant (0–5%) and sorbitol (0–50%) was also evaluated. All the formulations examined exhibited appropriate morphology and had satisfactory mechanical and flow properties. Drug release depended mainly on sorbitol content, however C-S accelerated drug release at all sorbitol levels (the fastest release was from 50% sorbitol pellets with C-S, which disintegrated), whereas C/S did not vary drug release from pellets, and SSG depressed drug release, especially from 50% sorbitol pellets.

Keywords: Chitosan-silica, sodium starch glycolate, pellet, MCC, disintegrant, drug release

Introduction

Due to the plasticity and cohesiveness of wet microcrystalline cellulose (MCC)[1,2], this is the most widely used excipient for the production of pellets by extrusion-spheronization[3]. However, the reluctance of MCC pellets to disintegrate in aqueous media results in slow drug release, especially in the case of poorly water-soluble drugs[4]. Therefore, various alternatives to MCC have been put forward for extrusion-spheronization pellets[5,6]. A possible solution to the problem, which has so far received little attention, is the incorporation of disintegrants in MCC-based pellets[7–11].

Currently, the most widely used disintegrants, especially for tablets, are sodium starch glycolate (SSG), crosslinked sodium carboxymethyl cellulose and crosslinked polyvinylpyrrolidone. These agents are sometimes referred to as "superdisintegrants" due to the relatively low concentrations at which they are effective in solid dosage forms[12] and to their ability to bring about disintegration in very low volumes of liquid, thus they have commonly been used in so-called "flash-melt" orodispersible tablets[13]. In spite of these properties, they seem to be less effective in multi-particle dosage forms, although the available data are relatively scant and somewhat contradictory[7–9]. In particular, they have been reported not to achieve the disintegration of spheronized extruded MCC pellets[10,11], apparently because they hinder the uptake of water in formulations produced by wet granulation[14].

It has recently been reported that a novel tablet disintegrant formed by co-precipitation of chitosan and silica is superior to the "superdisintegrants" mentioned above[15]. In the work described here we compared chitosan-silica (C-S) with SSG with regards to their behavior in MCC-based pellets formed by extrusion-spheronization; We evaluated the behavior of coprecipitated chitosan-silica with that of a 1:1 w/w physical mixture of chitosan and silica (C/S); and

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we investigated the effect of adding the water-soluble excipient sorbitol[16]. Evaluation was in terms of the morphology, microstructure and mechanical properties of the pellets, and release of the poorly water-soluble drug hydrochlorothiazide.

Materials and methods

Materials

Excipients

Microcrystalline cellulose (Avicel® PH 101, lot 912050001; FMC BioPolymer, Philadelphia, PA) sorbitol (Neosorb® P60, lot E834A; Roquette Laisa España S.A., Valencia, Spain); SSG (Explotab®, lot E4814X; JRS Pharma, Rosenberg, Germany) chitosan 150,000 Da, 95% deacetylated (Qingdao Milestone Biotech Co. Ltd., Qingdao, China); colloidal silica (Aerosil® 200 VV Pharma, lot 1323102; Evonik Industries, Essen, Germany).

Active principle

Hydrochlorothiazide (lot 939190004; Guinama, Valencia, Spain).

Methods

Formulations

The formulations containing each disintegrant (SSG, C-S or C/S) conformed to a 3×3 factorial design, being 0%, 2.5% or 5% disintegrant, 0%, 20% or 50% sorbitol, 10% hydrochlorothiazide, and the rest MCC (Tables 1–3).

Preparation of chitosan-silica

Following El-Barghouthi et al.[15], 500 g of chitosan was suspended in 1 L of 2 M HCl, and 500 g of colloidal silica in 1 L of 2 M NaOH. To the latter suspension were added, under stirring, 1 L of distilled water, followed, over 1 h, by the chitosan suspension and, simultaneously, concentrated HCl solution (to keep pH below 6.5). The resulting coprecipitate was filtered out, washed with distilled water, dried in an oven at 90°C, and passed through a sieve with 0.5 mm meshes.

Preparation of pellets

MCC, disintegrants and active principle were mixed dry in a Turbula® T2C mixer (15 min, 30 rpm, Muttenz, Switzerland). The mixture was moistened with water in a Kenwood® planetary mixer (10 min, 44 rpm (Havant, UK) for wetting volumes see Tables 1–3) and the wet mass was extruded through 1 mm meshes in a Caleva® 25 extruder (60 rpm, Dorset, UK), and then spheronized in a Caleva® 120 apparatus using a friction plate 12 cm in diameter with grooves 1 mm deep (10 min, 1200 rpm). The resulting pellets were dried for 24 h in a forced air oven at 40°C. The wetting volumes were optimized to maximize the yield of pellets sized 0.75–1.25 mm.

Table 1. Characteristics of MCC-based pellets containing sodium starch glycolate (SSG) and/or sorbitol (Sorb).

% Sorb	% SSG	% MCC	Wetting agent volume (mL/g)	Pellet size* (μm)	Circularity	Compressibility (%)	Micropore volume (cm^3/g)	Drug released in 60 min (%)
0	0	90	1	782 ± 112	0.969 (2.2×10^{-2})	3.01 (1.42)	0.0629 (6.3×10^{-3})	34.04
0	2.5	87.5	1	885 ± 165	0.971 (2.6×10^{-2})	2.13 (0.17)	0.1506 (7.8×10^{-4})	34.54
0	5	85	1	900 ± 182	0.955 (3.9×10^{-2})	3.95 (1.28)	0.2012 (1.4×10^{-3})	40.22
20	0	70	0.60	796 ± 132	0.954 (2.7×10^{-2})	3.50 (0.78)	0.0621 (3.1×10^{-3})	56.25
20	2.5	67.5	0.60	836 ± 175	0.962 (3.1×10^{-2})	2.79 (1.06)	0.1124 (1.8×10^{-3})	55.8
20	5	65	0.60	1013 ± 206	0.953 (3.9×10^{-2})	10.58 (0.58)	0.2060 (2.3×10^{-2})	52.12
50	0	40	0.15	945 ± 276	0.949 (3.7×10^{-2})	5.37 (0.39)	0.1936 (2.7×10^{-2})	90.2
50	2.5	37.5	0.15	1037 ± 346	0.935 (4.5×10^{-2})	6.61 (1.27)	0.2586 (1.1×10^{-2})	83.72
50	5	35	0.15	1106 ± 293	0.929 (4.4×10^{-2})	5.76 (0.30)	0.2550 (2.1×10^{-2})	82.28

All formulations included 10% hydrochlorothiazide. Standard deviations are shown in parentheses.
MCC, microcrystalline cellulose; Sorb, sorbitol; SSG, sodium starch glycolate.
*Mean diameter ± estimated standard deviation of the fitted normal distribution.

Table 2. Characteristics of microcrystalline cellulose (MCC)-based pellets containing coprecipitated chitosan-silica (C-S) and/or sorbitol (Sorb).

% Sorb	% C-S	% MCC	Wetting agent volume (mL/g)	Pellet size* (μm)	Circularity	Compressibility (%)	Micropore volume (cm^3/g)	Drug released in 60 min (%)
0	0	90	1	782 ± 112	0.969 (2.2×10^{-2})	3.01 (1.42)	0.0629 (6.3×10^{-3})	34.04
0	2.5	87.5	0.95	600 ± 120	0.959 (4.0×10^{-2})	2.71 (0.47)	0.0849 (1.2×10^{-3})	46.15
0	5	85	0.95	688 ± 123	0.975 (2.4×10^{-2})	4.78 (0.58)	0.0983 (1.4×10^{-4})	45.37
20	0	70	0.60	796 ± 132	0.954 (2.7×10^{-2})	3.50 (0.78)	0.0621 (3.1×10^{-3})	56.25
20	2.5	67.5	0.60	694 ± 163	0.963 (3.1×10^{-2})	3.36 (2.65)	0.0788 (3.2×10^{-3})	69.36
20	5	65	0.60	727 ± 166	0.971 (3.0×10^{-2})	2.92 (1.79)	0.0813 (6.0×10^{-4})	78.43
50	0	40	0.15	945 ± 276	0.949 (3.7×10^{-2})	5.37 (0.39)	0.1936 (2.7×10^{-2})	90.2
50	2.5	37.5	0.15	835 ± 261	0.942 (4.3×10^{-2})	5.68 (0.12)	0.2164 (9.1×10^{-3})	97.74
50	5	35	0.15	913 ± 273	0.937 (4.1×10^{-2})	5.25 (0.03)	0.2223 (2.0×10^{-3})	97.69

All formulations included 10% hydrochlorothiazide. Standard deviations are shown in parentheses.
C-S, chitosan-silica coprecipitate; MCC, microcrystalline cellulose; Sorb, sorbitol.
*Mean diameter ± estimated standard deviation of the fitted normal distribution.

Characterization of pellets

The pellets of the various formulations (Tables 1–3) were characterized as follows.

Morphology Pellet size and shape were evaluated using an Olympus SZ-CTV optical stereomicroscope connected to a JVC TK-S350 video camera. At least 600 pellets of each formulation were sized in terms of the mean of four Feret diameters measured in different directions, and their circularity was calculated as $4\pi A/p^2$, where A is the area of the projection of the pellet on the horizontal plane and p is the length of the perimeter of this area[17]. For each formulation, the size distribution was Gaussian. Photomicrographs were taken using a 435VP scanning electron microscope (LEO, Cambridge, UK).

Porosity Mercury intrusion porosimetry was performed over the pressure range 0.01–14.00 MPa using an Autopore IV 9500 apparatus (Micromeritics, Norcross, Georgia). Micropore volume was calculated as the total volume of pores larger than 0.1 μm in diameter. Two replicate determinations were carried out.

Compressibility Compressibility C was calculated from bulk densities measured before (d_i) and after (d_f) tapping in a PT-E powder tester (Hosokawa, Osaka, Japan) operated for 20 min at 50 taps/min, and was expressed as a percentage of final density: $C = 100(d_f - d_i)/d_f$[18,19]. Two replicate determinations were carried out.

Friability In each test, 20 g of pellets and 30 g of glass beads 4 mm in diameter were tumbled in a TAB apparatus

Table 3. Characteristics of MCC-based pellets containing sorbitol (Sorb) and/or 1:1 physical mixture of chitosan and silica (C/S).

% Sorb	% C/S	% MCC	Wetting agent volume (mL/g)	Pellet size* (μm)	Circularity	Compressibility (%)	Micropore volume (cm^3/g)	Drug released in 60 min (%)
0	0	90	1	782 ± 112	0.969 (2.2×10^{-2})	3.01 (1.42)	0.0629 (6.3×10^{-3})	34.04
0	2.5	87.5	0.95	797 ± 128	0.979 (2.4×10^{-2})	4.20 (0.20)	0.0773 (6.7×10^{-4})	32.93
0	5	85	0.95	747 ± 129	0.976 (2.6×10^{-2})	4.10 (1.50)	0.0900 (4.1×10^{-3})	34.68
20	0	70	0.60	796 ± 132	0.954 (2.7×10^{-2})	3.50 (0.78)	0.0621 (3.1×10^{-3})	56.25
20	2.5	67.5	0.60	882 ± 154	0.975 (2.3×10^{-2})	2.20 (0.74)	0.0641 (2.5×10^{-3})	50.62
20	5	65	0.60	1002 ± 167	0.965 (3.7×10^{-2})	2.36 (0.49)	0.0777 (4.2×10^{-3})	49.94
50	0	40	0.15	945 ± 276	0.949 (3.7×10^{-2})	5.37 (0.39)	0.1936 (2.7×10^{-2})	90.2
50	2.5	37.5	0.15	957 ± 335	0.932 (4.8×10^{-2})	3.19 (0.31)	0.1827 (8.5×10^{-3})	92.92
50	5	35	0.15	970 ± 272	0.930 (4.8×10^{-2})	3.41 (0.15)	0.1645 (1.8×10^{-2})	97.00

All formulations included 10% hydrochlorothiazide. Standard deviations are shown in parentheses.
C/S, mixture of chitosan and silica; MCC, microcrystalline cellulose; Sorb, sorbitol.
*Mean diameter ± estimated standard deviation of the fitted normal distribution.

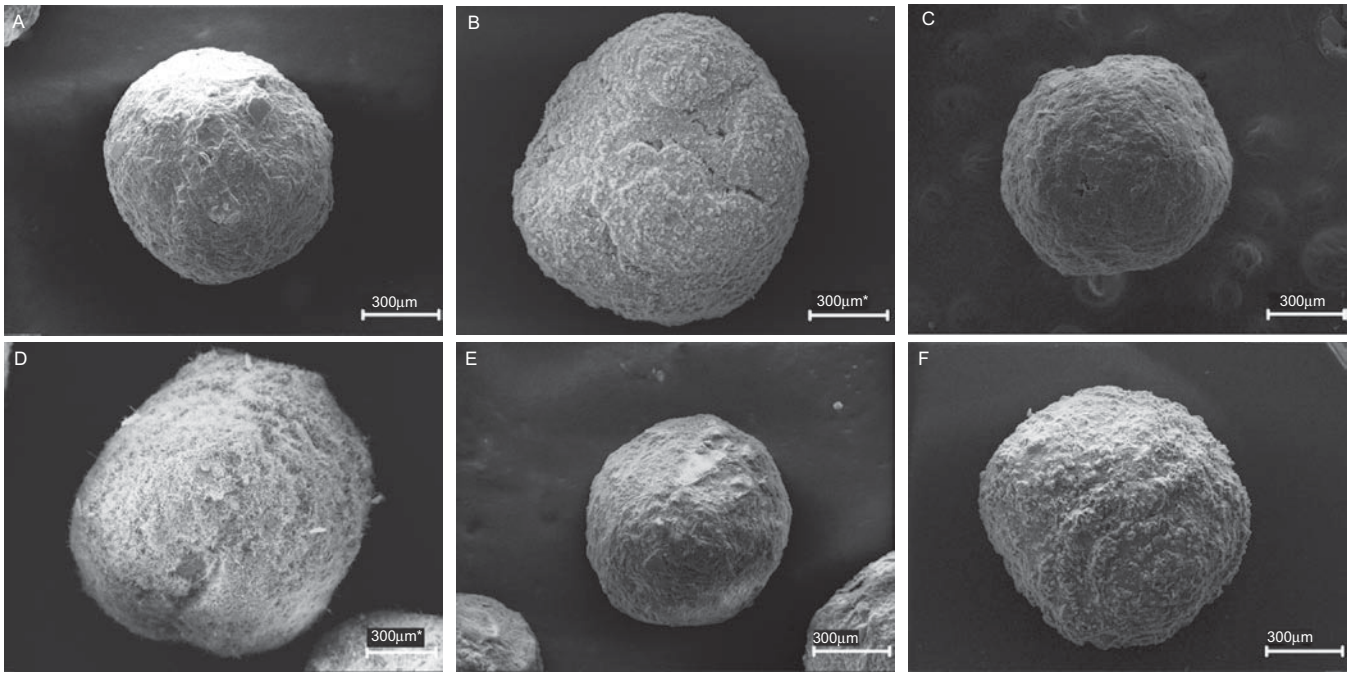

Figure 1. Scanning electron micrographs of formulations containing 5% of coprecipitated chitosan-silica (A, B), 5% of sodium starch glycolate (SSG) (C, D), or 5% of a 1:1 physical mixture of chitosan and silica (E, F). Formulations A, C and E had no sorbitol, and formulations B, D and F a sorbitol content of 50%.

(Erweka, Hensenstamm, Germany) operated for 30 min at 20 rpm. Friability was defined as the weight of pellet fragments sized less than 0.25 mm, expressed as a percentage of total pellet weight.

Dissolution rate Dissolution profiles were constructed in accordance with the USP protocol using a DT-6 USP 29 type II apparatus (Turu Grau, Barcelona, Spain). In each assay, a 200 mg sample of pellets was stirred at a paddle speed of 50 rpm in 900 mL of 0.1 N HCl at 37°C, and the hydrochlorothiazide content of the medium was determined periodically by measuring absorbance at 272 nm in an Agilent 8453 UV spectrophotometer. Profiles were characterized in terms of the percentage of drug released within 1 h (D_{60}). Six replicate profiles were constructed for each formulation.

Statistical analysis

For each disintegrant, the experimental assay was adapted to the structure of a two factorial experimental design-disintegrant content (D) and sorbitol content (S)- with three levels each. A stepwise multiple regression was used to quantify the effects of all variables under study on the properties of the pellets and to construct the corresponding response surfaces (SPSS, v.14)

Results and discussion

Tables 1–3 show the results obtained in the characterization of the formulations under study. Experimental data in the tables show that the optimal volume of wetting agent for extrusion decreased as sorbitol content rose (as in a previous study of sorbitol in MCC-based pellets)[20], but was unaffected by disintegrants except for a slight (5%) decrease in formulations with disintegrant but not with sorbitol. With these wetting volumes, no formulation suffered excessive aggregation or erosion during pellet spheronization, and all exhibited satisfactory morphological, mechanical and flow characteristics, with negligible friability (≤0.05% in all cases) and low compressibility. Within this general uniformity, it may be noted that mean Feret diameter increased slightly with sorbitol content and with SSG content; and that,

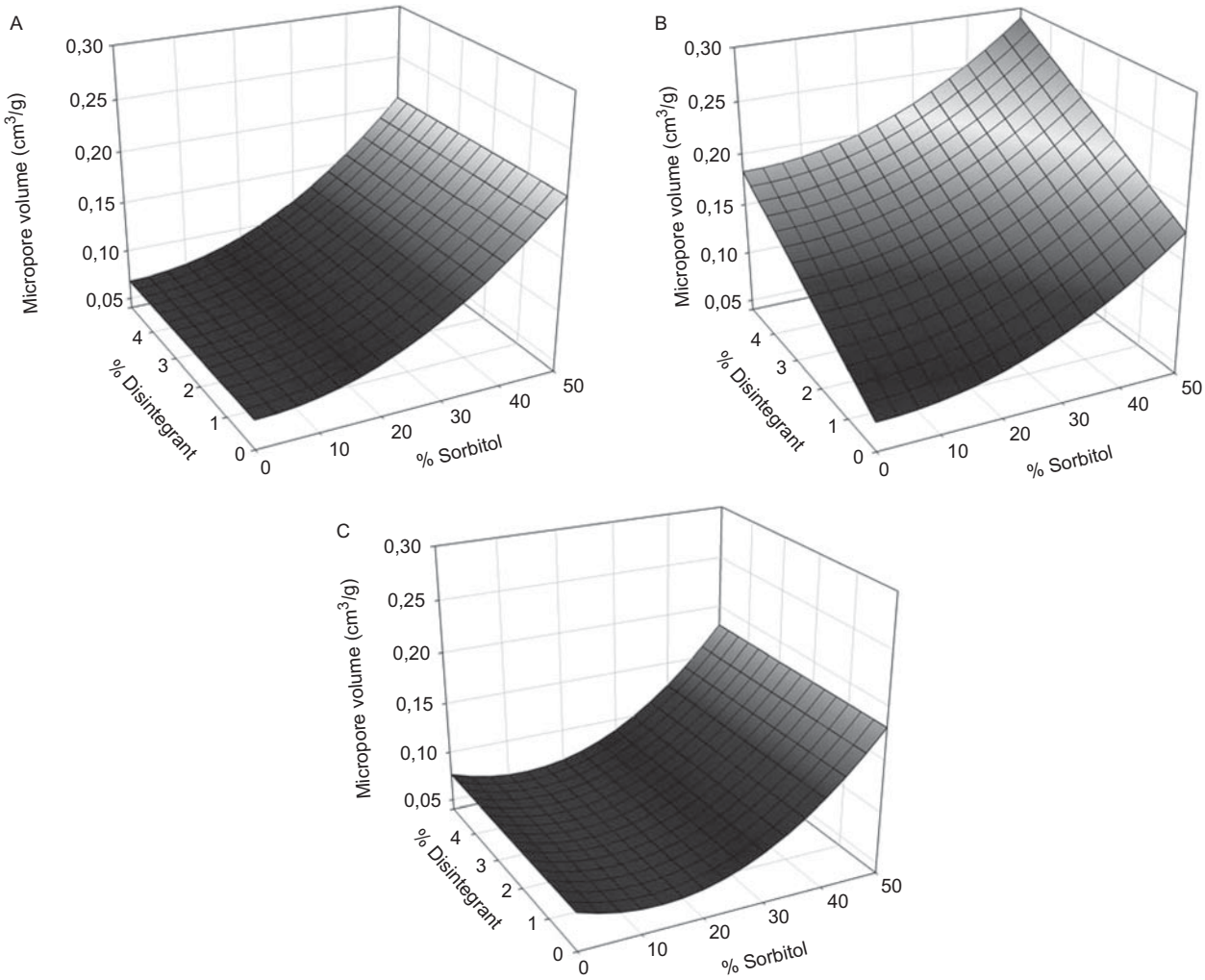

Figure 2. Response surfaces for pellet micropore volume (cm³/g) as a function of sorbitol content and disintegrant content for microcrystalline cellulose (MCC)-based pellets containing coprecipitated chitosan-silica (A), sodium starch glycolate (SSG) (B) or 1:1 physical mixture of chitosan and silica(C).

in keeping with the findings of Goyanes et al.[20], sorbitol also slightly decreased circularity and increased the surface roughness visible in photomicrographs (Figure 1). On the other hand neither of these properties was significantly affected by the presence of C-S or C/S. The aforesaid increase in pellet roughness may possibly explain the slight increase in compressibility—with the corresponding decline in the flow properties—which accompanies increasing sorbitol content in the absence of disintegrants.

The observation of the response surfaces for the micropore volume parameter allows us to conclude that the micropore volume (MV) increases in all formulations with increasing the sorbitol content (see Tables 1–3 and Figure 2). This aspect has already been observed in a previous study[20]. Regarding the influence of the disintegrants evaluated in the micropore volume it has been observed that the presence of C-S or C/S does not affect the porosity. The equations adjusted by stepwise multiple regression for formulations incorporating the coprecipitate C-S [$MV\,(\mathrm{cm^3/g}) = 0.068 + 5.6 \times 10^{-5}\,S^2$; $R^2 = 0.926$] or the physical mixture C/S [$MV\,(\mathrm{cm^3/g}) = 0.077 + 2.1 \times 10^{-3}\,S + 8.36 \times 10^{-5}\,S^2$; $R^2 = 0.961$] indicate that the micropore volume increases quadratically with the sorbitol content, but was unaffected by the disintegrant content. Only the presence of the disintegrant SSG significantly affected the porosity of the pellets [$MV\,(\mathrm{cm^3/g}) = 0.069 + 4.32 \times 10^{-5}\,S^2 + 0.023\,D$; $R^2 = 0.894$], increasing linearly with its content.

The average cumulative curves of hydrochlorothiazide (HCT) dissolution (Figure 3) showed a wide range of drug release profiles obtained from the different formulations. The aforementioned diversity of the dissolution profile is reflected in the different values of D_{60} (Tables 1–3).

The response surfaces (Figure 4) reveal several important facts from the point of view of the effects of the variables under study (disintegrant and sorbitol content) on the parameter D_{60}. Therefore, it should be noted first that the presence of C-S increased the drug dissolution rate in all formulations of which it forms part. Furthermore, in formulations that incorporated 50% of sorbitol the presence of the disintegrant C-S allows a rapid and complete disintegration of the pellets. The effectiveness of disintegrant is not hampered by the presence of sorbitol. The equation [$D_{60} = 36.92 + 1.05\,S + 2.73\,D$; $R^2 = 0.969$] also highlights the lack of interaction between the two variables, i.e., the additivity, without synergies or antagonisms, of the effects of the disintegrant and sorbitol content on the dissolution of HCT. These results for the sorbitol agree with those obtained in a previous study[20], in which significant increases were observed on the effectiveness of drug dissolution with increasing the sorbitol content in the pellets.

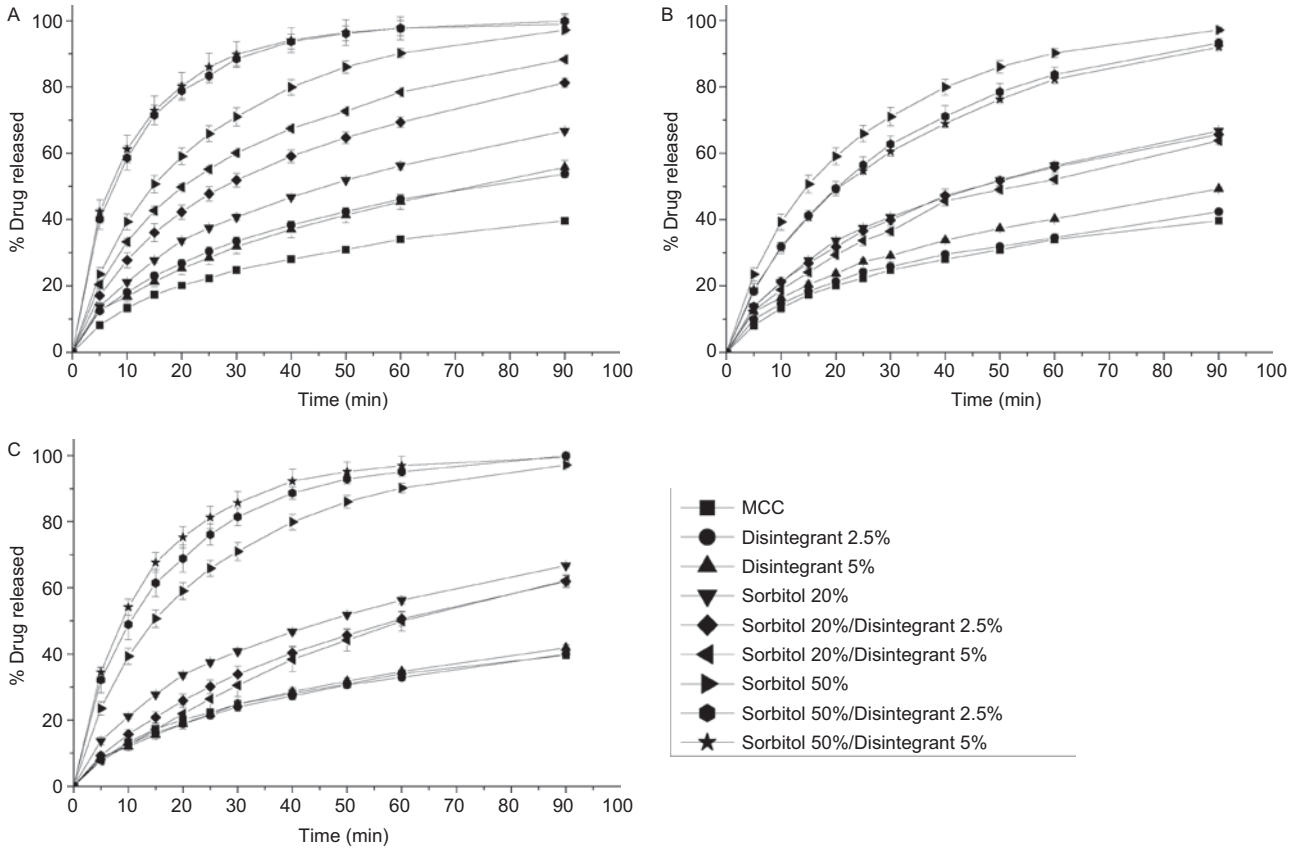

Figure 3. Dissolution profiles for the release of hydrochlorothiazide from microcrystalline cellulose (MCC)-based pellets containing coprecipitated chitosan-silica (A), sodium starch glycolate (SSG) (B) or 1:1 physical mixture of chitosan and silica (C). Means of six replicate experiments for each formulation; SDs are indicated by whiskers.

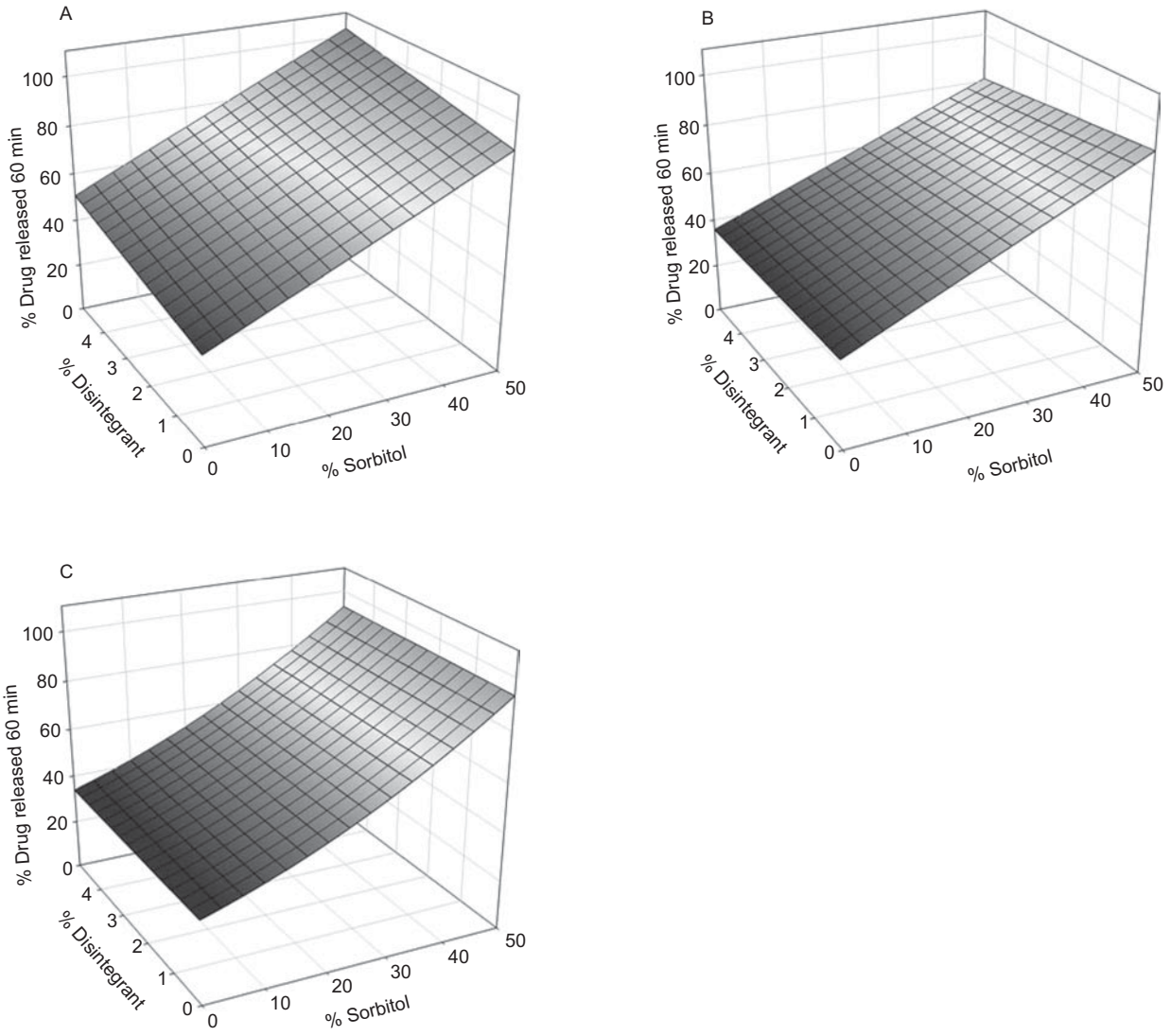

Figure 4. Response surfaces for D_{60} (percentage of drug released within 60 minutes in dissolution experiments) as a function of sorbitol content and disintegrant content for microcrystalline cellulose (MCC)-based pellets containing coprecipitated chitosan-silica (A), sodium starch glycolate (SSG) (B) or a 1:1 physical mixture of chitosan and silica (C).

The analysis of the effects of the incorporation of the physical mixture of C/S on D_{60} allows us to come to the conclusion that it has no significant effect on the HCT dissolution rate. Accordingly, the equation of the response surface for C/S [$D_{60} = 33.88 + 0.74\ S + 9.01 \times 10^{-3}\ S^2$; $R^2 = 0.991$] indicates only a quadratic effect of the sorbitol content. This highlights the importance of the co-precipitation process on the disintegrant efficiency of C-S, El-Barghouthi et al.[15] attributed it to a physical coating of chitosan particles by silica.

The effectiveness of the commercial disintegrant SSG is very limited in whatever formulation of which it forms part. In fact, the effect of the incorporation of SSG on the parameter D_{60} is negative in formulations that include a sorbitol composition. The equation [$D_{60} = 35.79 + 1.07\ S – 3.30 \times 10^{-2}\ SD$; $R^2 = 0.991$) resulting in the corresponding response surface (Figure 4) leads us to the conclusion that the incorporation of SSG into sorbitol pellets during their composition, reduces the HCT dissolution rate because of an antagonistic effect, and the greater the sorbitol content incorporated to pellets is the more negative it is.

One possible explanation is that this net negative influence of SSG on the dissolution rate in the presence of sorbitol, in spite of the increasing micropore volume, could be attributed partly to the competition between the disintegrant and sorbitol for water[9,12,16], and partly to the hydration of SSG at the pellet surface forming a gel that hinders the penetration of water to more internal regions of the pellet[21]. This latter problem may not occur for C-S, which does not gel so readily as SSG[15]. On the contrary, the high hygroscopicity of C-S, together with its resistance to forming gel layers, favors the penetration of water within capillaries[15]. In formulations which contain sorbitol this release-promoting effect of the disintegrant C-S would be improved by facilitating the dissolution of sorbitol and the consequent weakening of the pellet structure[22]. This would explain why in the present study

the formulations containing C-S and sorbitol favored faster drug release (Figure 3) and the pellet disintegration when the sorbitol content is high.

In conclusion, all the formulations had adequate values of size and shape as well as high mechanical resistance and very good flow properties. The incorporation of any of the evaluated disintegrants to the pellet composition did not appreciably deteriorate these properties. In respect to the microstructural properties, only the addition of one of the disintegrants—SSG—is accompanied by significant increases on the pellets micropore volume. The release of hydrochlorothiazide from MCC-based pellets was accelerated by inclusion of 20–50% of sorbitol and was also slightly increased (additively with respect to sorbitol) by inclusion of 2.5–5.0% of coprecipitated chitosan-silica (C-S). In addition, pellets with C-S and 50% of sorbitol did disintegrate. The incorporation of the physical mixture of chitosan and silica had null effects on the drug dissolution rate. Finally, incorporation of sodium starch glycolate to pellets that include sorbitol in composition reduces the HTC dissolution rate.

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Declaration of interest

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