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Research paper

# Co-processed MCC-Eudragit® E excipients for extrusion–spheronization

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ABSTRACT

This study investigates the extrusion–spheronization performance of some mixtures of co-processed microcrystalline cellulose and Eudragit® E (as excipients) and sorbitol (as soluble filler-disintegrant). Attention is focused on the dissolution rate of low water solubility drugs (hydrochlorothiazide is used as a model drug) from pellets prepared with these mixtures. All pellet formulations studied presented adequate morphological, flow and mechanical properties. The pellets prepared with co-processed MCC-Eudragit® E and sorbitol show a drug dissolution rate dependent on the content of Eudragit® E in the co-processed excipient and on the proportion of sorbitol incorporated. Furthermore, the pellets made with co-processed MCC-Eudragit® E incorporating the higher proportion of sorbitol (50%) show a very high dissolution rate of hydrochlorothiazide (HCT) and undergo rapid disintegration in the dissolution medium.



## 1. Introduction

Microcrystalline cellulose (MCC) is the most widely used excipient for the production of pellets by extrusion–spheronization, due to unique characteristics of plasticity and cohesiveness of their wet masses [1,2], making it an excellent base excipient for extrusion–spheronization. However, it does have certain limitations, among which include the slow release rate of low water solubility drugs [3] owing to the non-disintegration of the MCC pellets [4,5].

With this limitation in mind, various technological alternatives have been proposed and evaluated, among which include wetting the mass with water–alcohol mixtures instead of water alone [6,7] or the addition to the pellets of different excipients as disintegrant [7,8], tensoactive agents [9] or water-soluble diluents [10,11]. Another alternative that has been used is the replacement, completely or partially, of microcrystalline cellulose by other diluents [12], such as microfine cellulose [13–15]; pectinic acid [16], carrageenan [17], modified starch [18], crospovidone [19] and mixture of polyethylene oxides and methoxypolyethyleneglycol [20]. Although these substitutes may have resolved certain disadvantages of using microcrystalline cellulose, none has the unique characteristics of microcrystalline cellulose in extrusion–spheronization [12].

The co-processed cellulose based excipients are multifunctional products that, in theory, maintain the advantages of microcrystalline cellulose combined with functional qualities that provide the additional components to the cellulose. Several co-processed cellulose excipients have allowed the number of stages and the number of excipients needed in the process of developing different formulations to be reduced and, thus, have simplified the production processes, reduced costs and improved the dosage form properties. Therefore, the high functionality can be in terms of the improved processability, such as flow properties, compressibility, content uniformity, dilution potential and lubricant sensitivity, or improved performance such as the disintegration and dissolution profile [21].

Among co-processed cellulose based excipients are as follows: the co-processed excipient with microcrystalline cellulose and colloidal silicon dioxide (Prosolv® SMCC), which improves flow properties and compaction; the one composed of microcrystalline cellulose, colloidal silicon dioxide, mannitol, fructose and crospovidone (Prosolv® ODT), which is an orally disintegrating excipient matrix that enhances tablet disintegration; another which contains microcrystalline cellulose, colloidal silicon dioxide, sodium starch glycolate and sodium stearyl fumarate (Prosolv® Easy Tab) for rapid tablet manufacture; and one more that contains MCC and sodium carboxymethylcellulose (Avicel® RC and CL) used for the incorporation of high doses of active ingredient in pellets [21–26].

The aim of this work is to evaluate co-processed excipients of MCC and Eudragit® E obtained by wet massing, with suitable properties for accelerating the dissolution of low solubility drugs in pellets produced by extrusion–spheronization. Eudragit® E is a cationic copolymer based on dimethylaminoethyl methacrylate,

*Abbreviations:* MCC, microcrystalline cellulose; HCT, hydrochlorothiazide; S, sorbitol content; E, Eudragit® content; $DE_{30}$, dissolution efficiency; MV, micropore volume.

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butyl methacrylate and methyl methacrylate, which is used as an active sensitive protector and for taste and odor masking. It is soluble in acidic medium up to pH 5, therefore soluble in gastric fluid [22]. For this study, we have selected hydrochlorothiazide (HCT) as the low water solubility model drug (HCT water solubility [27]: $60.9 \times 10^{-3}$ g/100 mL). In addition, we have incorporated sorbitol into the formulations as a diluent of marked water solubility, in order to assess the presence of any possible synergistic effects, between co-process excipient and sorbitol, which could affect the drug dissolution process. Additionally, a formulation that incorporates the commercial co-processed excipient Prosolv® ODT was included in the study as a reference formulation because of its claimed tablet disintegrating capacity. Morphological, mechanical, microstructural and drug-release properties of all pellet formulations under study were also determined.

## 2. Materials and methods

### 2.1. Materials

#### 2.1.1. Excipients

Microcrystalline cellulose (Avicel® PH 101, lot 912050001); sorbitol (Neosorb® P60, lot E834A, supplied by Roquette Laisa España S.A.); Aminoalkyl methacrylate copolymer (Eudragit® E 12.5, organic solution 12.5%, lot A090621050, supplied by Evonik Industries), Prosolv® ODT (lot Q1X090623, supplied by JRS Pharma, Germany).

#### 2.1.2. Active principle

Hydrochlorothiazide (from Guinama, Spain, lot 939190004).

### 2.2. Methods

#### 2.2.1. Preparation of co-processed MCC-Eudragit® E excipients

The method used for the preparation of the co-processed MCC-Eudragit® E was a kind of solvent evaporation technique by wet massing. MCC was blended with the acetone and isopropanol commercial solution of Eudragit® E 12.5, and the wet mass was mixed until the solvent evaporation in a Kenwood planetary mixer (44 rpm, approximately 1 h at room temperature). The resulting mass was additionally dried in an oven (24 h, 45 °C) and passed through a sieve with 0.5 mm meshes. Three co-processed excipients were prepared, at proportions of Eudragit® E of 5%, 10% and 15% (dried w/w).

#### 2.2.2. Characterization of co-processed MCC-Eudragit® E excipients

Samples of the co-processed MCC-Eudragit® E excipients were characterized by the following assays.

*2.2.2.1. X-ray powder diffraction.* The X-ray powder diffractograms were obtained in a Philips PW1710 diffractometer (Eindhoven, Holland) in Bragg–Brentano geometry, using glass tubing with a Cu anode and graphite monochromator. The intensity and voltage applied were 30 mA and 40 kV. Samples, all being a particle size of less than 250 μm, were randomly placed on a glass slide. The angular range of data acquisition was 5–65° $2\theta$, with a stepwise size of 0.02° every 3 s.

*2.2.2.2. IR spectroscopy.* The IR spectra for the samples were registered in a BRUKER IFS-66 V spectrometer (Ettlingen, Germany) using disks made with the sample and KBr (1% w/w). The data acquisition range was 4000–400 $cm^{-1}$, with a 4 $cm^{-1}$ resolution.

*2.2.2.3. Scanning electron microscopy.* Morphology of the co-processed excipients and of the MCC was evaluated by taking photomicrographs of samples coated with gold–palladium with a scanning electron microscope (Zeiss EVO LS 15, Germany).

#### 2.2.3. Preparation of pellets

Excipients and the drug were dry mixed in a Turbula T2C mixer (15 min, 30 rpm). The mixture was moistened with water in a Kenwood planetary mixer (10 min, 44 rpm), and the wet mass was extruded through 1 mm meshes in a Caleva 25 extruder (60 rpm) 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.

**Table 1**
Characteristics of co-processed MCC-Eudragit®E based pellets with various percentages of sorbitol and 10% hydrochlorothiazide.

| Excipients | Excipient (%) | Sorbitol (%) | Wetting agent volume (mL/g) | Pellet size[a] (μm) | Circularity | Compressibility (%) | Micropore volume ($cm^3$/g) | $DE_{30}$[b] |
|---|---|---|---|---|---|---|---|---|
| MCC | 90 | 0 | 1 | 782 ± 112 | 0.969 ($2.2 \times 10^{-2}$) | 3.01 (1.42) | 0.0629 ($6.3 \times 10^{-3}$) | 15.6 |
| | 70 | 20 | 0.6 | 796 ± 132 | 0.954 ($2.7 \times 10^{-2}$) | 3.50 (0.78) | 0.0621 ($3.1 \times 10^{-3}$) | 25.7 |
| | 40 | 50 | 0.15 | 945 ± 276 | 0.949 ($3.7 \times 10^{-2}$) | 5.37 (0.39) | 0.1936 ($2.7 \times 10^{-2}$) | 45.7 |
| Co-processed MCC–5% Eudragit® E | 90 | 0 | 0.95 | 656 ± 104 | 0.981 ($2.2 \times 10^{-2}$) | 4.82 (1.89) | 0.1093 ($1.7 \times 10^{-3}$) | 22.1 |
| | 70 | 20 | 0.55 | 745 ± 187 | 0.979 ($2.2 \times 10^{-2}$) | 4.24 (0.43) | 0.1060 ($2.7 \times 10^{-4}$) | 29.9 |
| | 40 | 50 | 0.14 | 1129 ± 320 | 0.935 ($4.4 \times 10^{-2}$) | 3.42 (0.20) | 0.2324 ($3.1 \times 10^{-4}$) | 72.5 |
| Co-processed MCC–10% Eudragit® E | 90 | 0 | 0.95 | 652 ± 109 | 0.986 ($2.2 \times 10^{-2}$) | 3.98 (0.48) | 0.0921 ($3.1 \times 10^{-4}$) | 28.0 |
| | 70 | 20 | 0.52 | 724 ± 230 | 0.974 ($3.8 \times 10^{-2}$) | 5.37 (0.93) | 0.1029 ($1.1 \times 10^{-3}$) | 31.1 |
| | 40 | 50 | 0.12 | 1150 ± 316 | 0.933 ($4.8 \times 10^{-2}$) | 4.96 (0.60) | 0.2417 ($2.4 \times 10^{-3}$) | 80.0 |
| Prosolv® ODT | 70 | 20% MCC | 0.18 | 1039 ± 268 | 0.940 ($5.0 \times 10^{-2}$) | 2.67 (0.68) | 0.0482 ($3.2 \times 10^{-3}$) | 39.7 |

[a] Mean diameter ± estimated standard deviation of the fitted normal distribution.
[b] 0–30 min Dissolution efficiency. Standard deviations are shown in parentheses.

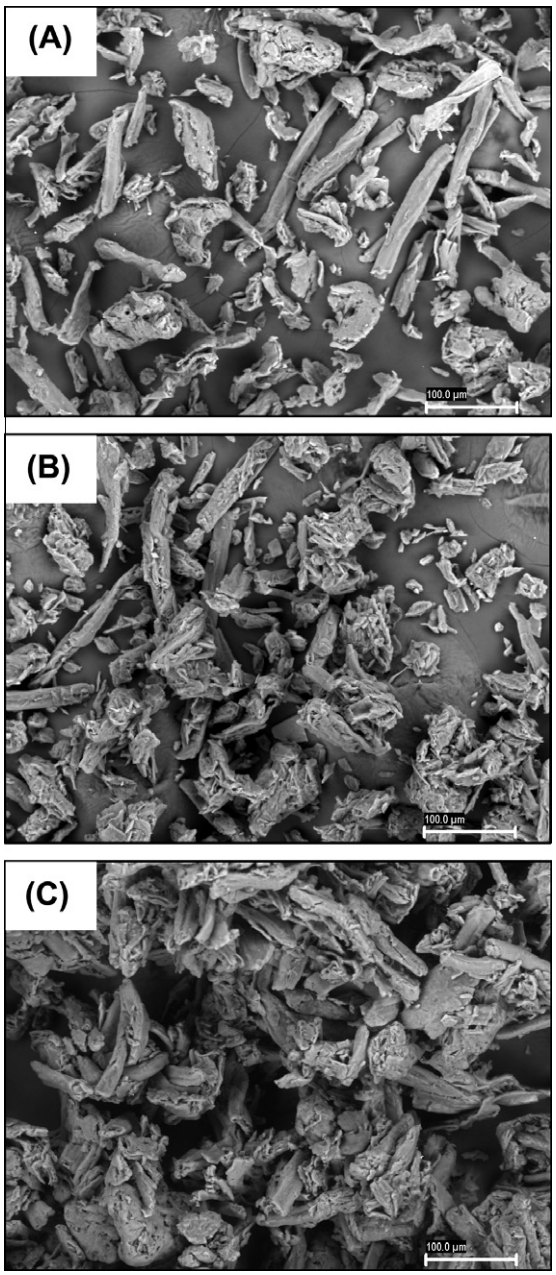


**Fig. 1.** Scanning electron photomicrographs of the particles of MCC (A), co-processed MCC-5% Eudragit® E (B) and co-processed MCC-10% Eudragit® E (C).

*2.2.4. Formulations*

The evaluated formulations in this study contain invariably 10% Hydrochlorothiazide (HCT) (w/w). Non co-processed MCC, co-processed MCC-5% Eudragit® E, co-processed MCC-10% Eudragit® E or co-processed MCC-15% Eudragit® E was employed as the base excipient, and sorbitol (S) was added as a high soluble excipient (see Table 1). In addition, a formulation was prepared using a mixture of HCT (10%), Prosolv® ODT (70%) and MCC (20%) under the conditions described in the previous section.

*2.2.5. Characterization of pellets*

The pellets of the various formulations (Table 1) were characterized as follows.

*2.2.5.1. Morphology.* The 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 [28]. For each formulation, the size distribution was Gaussian. Photomicrographs of the pellets coated with gold–palladium were taken using a scanning electron microscope (Zeiss EVO LS 15, Germany).

*2.2.5.2. 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.

*2.2.5.3. 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: $C = (d_f - d_i)100/d_f$ [29,30]. Two replicate determinations were carried out.

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

*2.2.5.5. 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 0–30 min dissolution efficiency, $DE_{30}$ [31].

*2.3. Statistical analysis*

The experimental assay was adapted to the structure of a two factorial experimental design—based on excipient and sorbitol content—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).

## 3. Results and discussion

As a first stage of the study, the preparation of the three co-processed excipients evaluated in this study was carried out (MCC-5% Eudragit® E, MCC-10% Eudragit® E and MCC-15% Eudragit® E), by wet massing of MCC with the acetone and isopropanol commercial solution of Eudragit® E 12.5.

The photomicrographs of scanning electron microscopy (SEM) obtained for the three excipients (Fig.1) allow observing the cellulose particles and the effects produced by the presence of copolymer Eudragit® E. In the first image, MCC fibers are free and unconnected. The cellulose fibers appear thicker as the percentage of Eugragit® E increases in the exipient, due to the presence of the copolymer on its surface, and partially agglomerated due to binding effect of Eudragit® E.

To characterize the co-processed excipients, the IR spectroscopy and X-ray powder diffraction techniques were employed. The

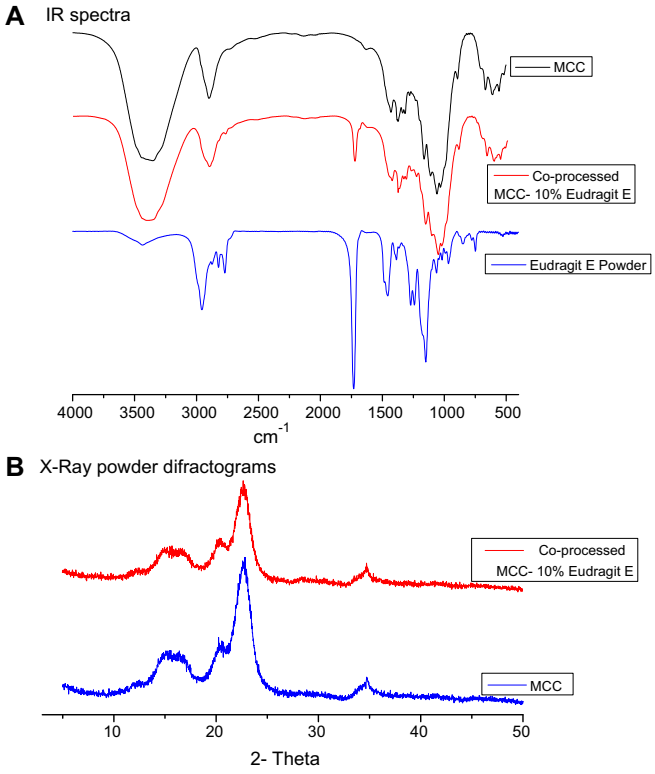


**Fig. 2.** IR Spectra (A) and X-ray powder diffractograms (B) of MCC and co-processed MCC-10% Eudragit® E. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

observation of the IR spectra shows that the process of wet massing does not induce any kind of chemical reaction, since the IR spectra of those co-processed MCC-Eudragit® E are predictable on the basis of the IR spectra of MCC and Eudragit® E Powder, as an example co-processed MCC-10% Eudragit® E IR spectrum is shown (Fig. 2). Furthermore, the X-ray powder diffractograms reveal that the wet massing process remains unchanged the crystallinity characteristics of MCC (Fig. 2). Therefore, one of the requirements of the co-processed excipients is fulfilled, such as the absence of chemical change [21].

Table 1 presents the results obtained in the evaluation of different formulations of pellets under study. Although the elaboration of the pellets was possible with co-processed MCC-15% Eudragit® E, they were very small due to erosion experienced in the process of spheronization and had an excessively wide size distribution; thus, they were not considered suitable as a formulation.

The wetting agent volumes indicated in Table 1 are the optimum in order to obtain the most out of the pellet in the size range between 750 and 1250 μm. As can be seen, a progressive reduction is produced on the wetting agent volume requirements as the proportion of water-soluble diluent (sorbitol) incorporated into the pellets increases [10]. The use of co-processed excipients also changes the volume requirements of wetting agent slightly; thus, to avoid the agglomeration of the pellets in the spheronization stage, a small reduction in the water volume is required when the proportion of Eudragit® E increases in the co-processed excipient. This reduction suggests that Eudragit® E does not retain water during the wetting, since the water/MCC ratio remains constant (≈1.1 ml/g) in all co-processed excipients.

Regarding Prosolv® ODT, it was not possible to produce pellets by extrusion–spheronization using only the commercial co-processed excipient and HCT, due to the strong agglomeration observed in the spheronization stage. It is necessary to incorporate at least 20% of MCC to the mixture to obtain pellets of suitable size.

All the formulations present satisfactory morphological, mechanical and flow characteristics (Tables 1). No process effects of agglomeration or of erosion were observed in the spheronization stage. In addition, the incorporation of increasing proportions of sorbitol produces slight increases in the average size of the pellets, a phenomenon already observed in previous studies [8,10]. In regard to the shape of pellets, the values for the circularity parameter allowed us to complete an acceptable sphericity of the pellets with whichever formulation. However, the use of higher sorbitol proportions led to less spherical pellets and increased surface roughness [8,10]. The photomicrographs by scanning electron microscope obtained for pellets of several of the most representative formulations (Fig. 3) reaffirm these results. On the surface, no differences in size can be observed between the pellets prepared from different co-processed MCC-Eudragit® E with respect to those

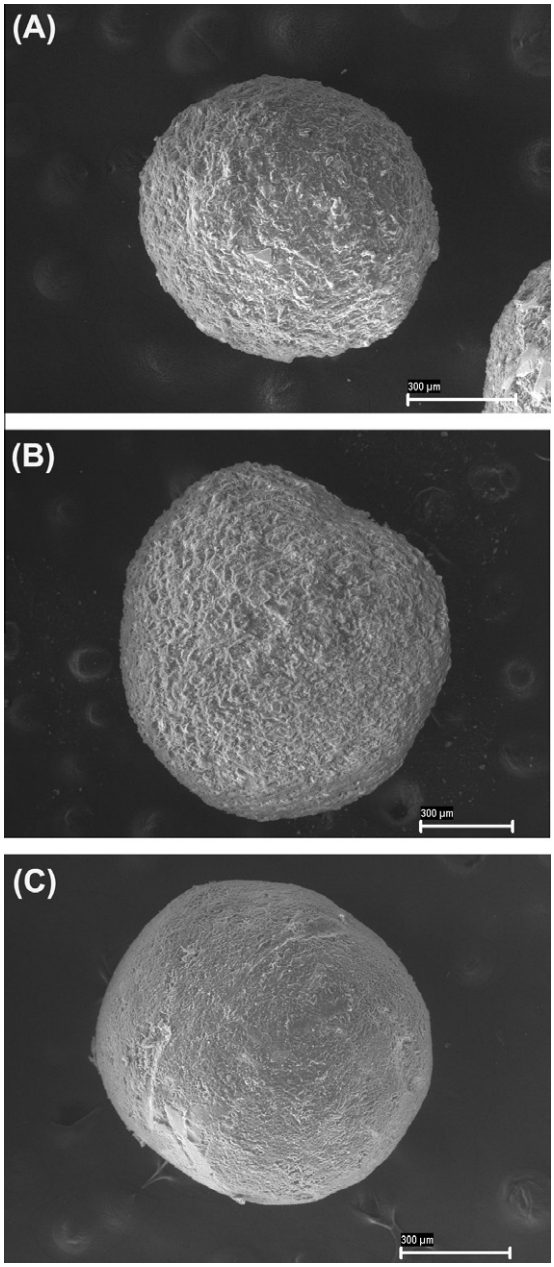


**Fig. 3.** Scanning electron photomicrographs of formulations containing MCC/Sorbitol 50% (A), co-processed MCC-10% Eudragit® E/ Sorbitol 50% (B) and Prosolv® ODT (C).

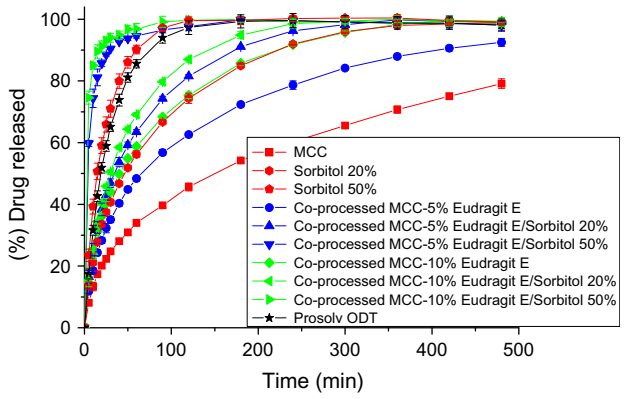


**Fig. 4.** Cumulative hydrochlorothiazide dissolution profiles from indicated formulations (means of six replicate experiments for each formulation; error bars indicate SDs). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

of MCC. Only the surface of the formulation that incorporates the commercial excipient Prosolv® ODT is noteworthy as remarkably smooth. On the other hand, it is important to stress that, in view of the compressibility values (Table 1), every one of the formulations should be considered as free-flowing products [32].

From the standpoint of mechanical strength of the pellets, all formulations are suitable in view of the low values (⩽0.25%, values not shown) obtained for friability.

With regard to the dissolution rate of HCT, there are marked differences in the average cumulative curves of HCT dissolution for the evaluated formulations (Fig. 4), which are reflected in the values of 0–30 min dissolution efficiency ($DE_{30}$) (Table 1). The response surface (Fig. 5) reveals several important facts of the effects of the variables under study, the percentage of Eudragit® E (**E**) in the evaluated co-processed excipients and the percentage of sorbitol (**S**) on the $DE_{30}$ parameter. Thus, it should be noted, first, that sorbitol markedly increases the dissolution of HCT in every formulation of which it forms part. The equation obtained by stepwise multiple regression [$DE_{30} = 20.11 + 1.12 \times 10^{-2}\,S^2 + 6.0 \times 10^{-2}$ SE; $R^2 = 0.953$] also indicates the existence of a synergistic effect between sorbitol and co-processed excipients which incorporate Eudragit® E, which significantly increased the value of $DE_{30}$. This effect is clearly dependant on the Eudragit® E content in the co-processed excipients. Furthermore, during the dissolution test, a rapid and complete disintegration (<5 min) of the pellets was observed in the formulations containing 50% of sorbitol, which may be the cause of the rapid dissolution of the drug (faster than dissolution of HCT powder in the same conditions, for which $DE_{30} = 51.5$).

The formulation prepared with Prosolv® ODT provided a HCT dissolution rate higher than that obtained with MCC pellets. However, it was less effective in terms of accelerating the HCT dissolution than any of the formulations which incorporated 50% sorbitol in its composition.

Furthermore, it may be noted that the use of any co-processed MCC-Eudragit® E provides formulations with faster HCT dissolution rate than those that incorporate 5% of the superdisintegrant sodium starch glycolate and even those containing the new disintegrant chitosan-silica [8].

Observing the response surface corresponding to the parameter micropore volume (MV) of the pellets (Fig. 6) allowed us to conclude that the increases in the HCT dissolution rate, observed by increasing the sorbitol content, can be attributed both to high solubility of the diluent and the increase in porosity produced by its presence in the formulations. This increase in the micropore volume has also been described in an earlier work [10]. The consideration of the equation of MV for the formulations [MV ($cm^3$/g) = $0.06 + 5.7 \times 10^{-5}\,S^2 + 3.9 \times 10^{-3}$ E; $R^2 = 0.951$] indicates that the presence of the co-processed MCC-Eudragit® E led to slight increases in MV, which is accompanied by increases in the HCT dissolution rate, the more pronounced the higher sorbitol content of the pellets. To justify the efficiency of the co-processed excipients, their possible action mechanism should be referred to. During the elaboration of the extrusion–spheronization of the pellets, the microcrystalline cellulose particles bond together to form pellets, and after drying, these bonds are difficult to break during the dissolution process. The co-processed excipients prepared by

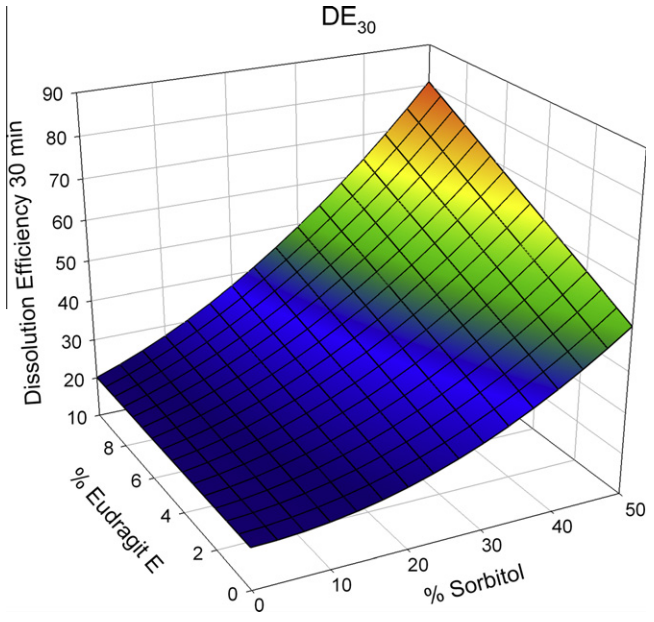


**Fig. 5.** Response surface for $D_{60}$ as a function of Eudragit® E content in co-processed excipient (0% for pure MCC) and of sorbitol content. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

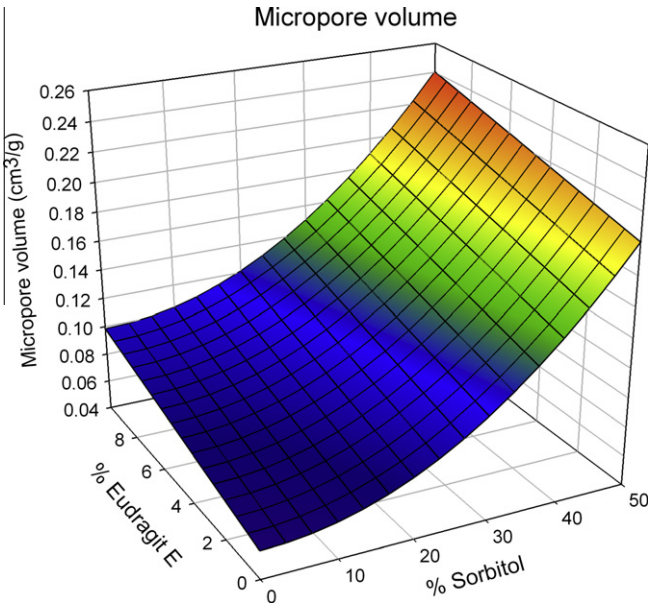


**Fig. 6.** Response surface for pellet micropore volume ($cm^3$/g) as a function of Eudragit® E content in co-processed excipient (0% for pure MCC) and of sorbitol content. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

massing MCC with Eudragit® E show deposits of acrylic polymer on the surface of the MCC particles. These deposits hinder the cellulose particles from establishing bonds over its entire surface, making joints of lower intensity. Between the MCC particles, there are portions of polymer Eudragit® E, soluble up to pH 5.0 that is rapidly dissolved in the acidic dissolution medium. During the dissolution process, the co-processed excipients favor the entry of water into the structure of the pellets and the dissolution of sorbitol, which would result in the formation of new pores and a weakening of the pellet structure. This would justify both the increased HCT dissolution rate and the disintegration of the pellets when the sorbitol proportion is at its highest.

To conclude, the incorporation of co-processed MCC-Eudragit® E allows the production of pellets by extrusion–spheronization of a suitable size and shape, with high mechanical strength and very good flow properties. With respect to the microstructural properties, the incorporation of co-processed excipients is accompanied by slight increases in micropore volume of pellets. The pellets prepared with co-processed MCC-Eudragit® E present a high drug dissolution efficiency whose value is clearly dependent on the Eudragit® E content in the co-processed excipient and on the incorporated sorbitol content. The hydrochlorothiazide release from the pellets is always accelerated by the addition of 20–50% of sorbitol; however, only pellets that incorporated a co-processed MCC-Eudragit® E and 50% of sorbitol content experience a fast and complete disintegration process.

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