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Research paper

Graft copolymers of ethyl methacrylate on waxy maize starch derivatives as novel excipients for matrix tablets: Physicochemical and technological characterisation

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ABSTRACT

Nowadays, graft copolymers are being used as an interesting option when developing a direct compression excipient for controlled release matrix tablets. New graft copolymers of ethyl methacrylate (EMA) on waxy maize starch (MS) and hydroxypropylstarch (MHS) were synthesised by free radical polymerization and alternatively dried in a vacuum oven (OD) or freeze-dried (FD). This paper evaluates the performance of these new macromolecules and discusses the effect of the carbohydrate nature and drying process on their physicochemical and technological properties. Grafting of EMA on the carbohydrate backbone was confirmed by IR and NMR spectroscopy, and the grafting yields revealed that graft copolymers present mainly a hydrophobic character. The graft copolymerization also leads to more amorphous materials with larger particle size and lower apparent density and water content than carbohydrates (MS, MHS). All the products show a lack of flow, except MHSEMA derivatives. MSEMA copolymers underwent much plastic flow and less elastic recovery than MHSEMA copolymers. Concerning the effect of drying method, FD derivatives were characterised by higher plastic deformation and less elasticity than OD derivatives. Tablets obtained from graft copolymers showed higher crushing strength and disintegration time than tablets obtained from raw starches. This behaviour suggests that these copolymers could be used as excipients in matrix tablets obtained by direct compression and with a potential use in controlled release.

1. Introduction

New classes of excipients are currently available, derived from old and new materials, alone or in combination, adapted to the manufacture of high-performance pharmaceutical dosage forms [1]. In this sense, polymers are playing an important role in the development of new materials with different properties and several uses, and are being synthesised by different methods [2–4]. Like other excipients, polymers cannot be considered as mere inert supports for the active principles, but as essential functional components of modern pharmaceutical formulations [1].

Among the current approaches in the development of new polymeric systems, the synthesis of graft copolymers is an easy method for modifying the properties of native polymers such as starch. The low cost, non-toxicity, biodegradability and biocompatibility of this carbohydrate [5] make starch-based graft copolymers a focus of increasing attention [6]. Moreover, the use of tetravalent cerium species to initiate such synthesis attracts great interest because of ease of polymerization [7–9]. In this sense, copolymers obtained from potato starch derivatives and methacrylates have shown a potential value as direct compression excipients for controlled release matrices [10–12]. However, both the chemical composition of the starch and the modification techniques have a considerable influence on the physical properties of the modified starches [13,14].

Starch is a natural biopolymer composed principally of two polysaccharides: the linear amylose and the heavily branched amylopectin. Whereas amylopectin has stabilizing effects, amylose forms gels and has a strong tendency to form complexes with lipids and other components [13]. Waxy maize starch, with amylose content less than 1% [15], could be a candidate for tablet adjuvants, with one of its main advantages being increased storage stability [13]. Moreover, waxy maize starch has been shown to be more effective with regard to swelling and drug release retardation than are normal starches [16,17]. Nevertheless, like other starches, it is generally chemically modified to fulfil the demands of pharmaceutical industry. One common modification is the hydroxypropylation of starch that increases the hydrophilic character of the starch granules leading to higher swelling power [17].

Chemical modification of starch via vinyl graft copolymerization is an important technique to combine the good performances of starch and synthetic polymers. Grafting is preferred to physical blending as the grafted polymer chains are linked covalently with the backbone polymer, having beneficial effects on the properties of the composite [8]. Among vinyl monomers, ethyl methacrylate

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was chosen for the present study because of its known biocompatibility and non-toxic behaviour, together with its hydrophobic character and ease of polymerization [18,19].

Then, the purpose of the present work was to synthesise new graft copolymers of ethyl methacrylate (EMA) on waxy maize starch (MS) and hydroxypropylstarch (MHS) and to reach a better understanding of this group of copolymers, in order to evaluate its utility in direct compression in comparison with the raw starches. This paper discusses the effect of the carbohydrate nature and drying process on the physicochemical and mechanical properties of the powdered materials as well as the porous structure of the tablets obtained from these new macromolecules.

NMR, IR and X-ray diffraction techniques were used to obtain information on copolymers structure. Particle size, shape and surface morphology were also taken into consideration when evaluating the flow properties and consolidation characteristics of the new materials, due to the implications of these parameters in the manufacturing of solid dosage forms. Finally, compressed porous tablet structures were evaluated using mercury porosimetry.

2. Materials and methods

2.1. Materials

Waxy maize starch (Amioca powder TF, batch MCH 308) and waxy maize hydroxypropylstarch (N-Lite L, batch KCK 3649) were kindly supplied by National Starch & Chemical (Manchester, UK).

Ethyl methacrylate (Merck, Hohenbrunn, Germany) was used as monomer.

All the reagents used for the synthetic process were of analytical grade.

Before use, the materials were stored at constant relative humidity (40%) and room temperature (20 °C).

2.2. Methods

2.2.1. Synthesis of graft copolymers and grafting yields

Copolymers were synthesised by free radical copolymerization of EMA and different starches (waxy maize starch (MS) and waxy maize hydroxypropylstarch (MHS)) following the procedure described by Echeverria et al. [12]. The carbohydrate (40 g) was dispersed in 550 mL of bidistilled water at 30 °C under a nitrogen atmosphere. Next, 118 mL of EMA was added, followed by the addition of 50 mL of the initiator solution (0.1 M ceric ammonium nitrate in 1 N nitric acid) 15 min later. Grafting was allowed to proceed for 4 h under a constant light source. The products obtained were filtered, and the solid was exhaustively washed with diluted nitric acid and bidistilled water until neutral pH was reached. A noteworthy aspect to mention is that the use of water as a reaction solvent guarantees not only the solubility of all the reactants and reagents, but also the absence of toxic substances in the final product [12].

The products obtained (waxy maize starch-ethyl methacrylate, MSEMA and waxy maize hydroxypropylstarch-ethyl methacrylate, MHSEMA) were alternatively dried by two different methods: drying in a vacuum oven (0.5 Pa) at 50 °C until constant weight (OD copolymers) or freeze-drying (freezing process at −80 °C for 48 h and sublimation process at 0.1 Pa) (FD copolymers). The starch-based copolymers (MSEMA) were crushed at 10,000 rpm in a knives mill (Retsch ZM 200, Haan, Germany) to obtain powdery samples.

The reproducibility of the synthetic and drying processes was demonstrated for three batches of each copolymer (data not shown).

In order to evaluate the composition of the solids obtained, the PEMA (poly-ethyl methacrylate) homopolymer was removed from the total reaction product, with tetrahydrofuran (THF), by soxhlet extraction for 72 h. Afterwards the grafted PEMA was isolated from the carbohydrate chains by acid hydrolysis with perchloric acid (60%) in a glacial acetic acid medium [20]. The following parameters were calculated:

- Percent grafting efficiency (%GE) Eq. (1) to quantify the amount of homopolymer formed during the grafting reaction [21]

$$\%\mathrm{GE} = \frac{\text{Graft copolymer weight}}{\text{Total product weight}} \times 100 \quad (1)$$

- Percentage grafting (%G) Eq. (2) to assess the methacrylic-carbohydrate ratio in the copolymer [21]

$$\%\mathrm{G} = \frac{\text{Grafted methacrylic polymer weight}}{\text{Grafted carbohydrate weight}} \times 100 \quad (2)$$

The results are shown as the mean value of two replicates.

2.2.2. Spectroscopy characterisation

2.2.2.1. IR spectroscopy. Fourier-transform infrared (FT-IR) spectra were recorded with a FT-IR spectrometer Nicolet 510 (California, USA). One hundred scans were collected for each sample at a resolution of 4 cm^{-1} over the wavenumber region 4000–400 cm^{-1}. Samples were prepared in KBr discs.

2.2.2.2. NMR spectroscopy. Materials were dissolved in a mixture of d_6-DMSO and d_5-pyridine solvents (1/1) to give a concentration of 3% w/v. ^{13}C NMR spectra measurements were recorded at 30 °C on a FT-NMR Bruker Avance 500 (Wissembourg, France) for each product. Chemical shifts are quoted in ppm relative to tetramethylsilane as internal reference.

2.2.2.3. X-ray powder diffraction measurements. X-ray diffraction patterns were recorded using a Siemens Kristalloflex D-5000 (Haan, Germany) diffractometer. The sample was exposed to Ni-filtered CuKα radiation with the X-ray generator running at 36 kV and 26 mA. The scan rate employed was 1° (2θ)/min.

2.2.3. Powder and particle characterisation

2.2.3.1. Particle size analysis. Particle size analysis was carried out on a vibratory sieve shaker (Retsch Vibro, Haan, Germany) using 500, 355, 250, 180, 125, 90, 63, 45, 38 μm calibrated sieves (Cisa, Barcelona, Spain). From plots of powder weight (%) versus size (mm), typical parameters from a particle size distribution were determined: mean particle diameter, standard deviation (SD) and kurtosis and skewness coefficients [22].

2.2.3.2. Scanning electron microscopy (SEM). The particulate samples were sputter coated with a thin layer of gold (Edwards Pirani 501 Scan-Coat Six, Crawley, West Sussex, UK) under high vacuum and were examined using a scanning electron microscope (Philips XL-30, Eindhoven, Holland). Microphotographs were obtained at 4000× magnification.

2.2.3.3. Apparent particle density. The apparent particle densities of the powders were determined [23], in triplicate, by means of an air comparison Ultrapycnometer 1000 (Quantachrome, Boyton Beach, FL, USA), using helium as an inert gas. Due to the high diffusivity of helium, this method was considered to give the closest approximation to the true density [24].

2.2.3.4. IR balance moisture determination. The moisture content of the samples was determined by means of an infrared balance (Mettler Toledo LJ16, Zürich, Switzerland). Samples (500 mg) were tested at 50 °C until constant weight (weight variation less than 0.2 mg/s) was achieved. The results are shown as the mean value of three replicates.

2.2.3.5. Flow properties. An automated flowmeter system developed by Muñoz-Ruiz and Jiménez-Castellanos [25] was used to estimate the flow rate of the different samples. A glass funnel with an internal diameter of 10 mm and an angle of 30° with respect to the vertical was selected as vessel [23]. Weight data were acquired by means of a balance (Mettler AE50, Zürich, Switzerland) connected to a personal computer, using adequate software. The results are shown as the mean value (g/s) of three replicates.

2.2.4. Compression behaviour

To allow direct comparison of all materials, the amount of sample required to produce a 3 mm thick compact at theoretical zero porosity was calculated from the apparent particle densities. The quantities of powder (mg) were accurately weighed (Sartorius CP224S, Göttingen, Germany) and manually placed into the die. Tablets were obtained using an instrumented [26] single-punch tablet machine (Bonals AMT 300, Barcelona, Spain) with 12 mm flat-faced punches at a speed of 30 cycles per minute. Powders were compressed at 25, 50, 100, 150, 200, 300 MPa of applied pressure, and four tablets per pressure were manufactured. The die was lubricated with a chloroformic suspension of magnesium stearate (5% w/v) before each compression cycle.

Evaluation of the consolidation mechanism of powders was made on the basis of Heckel equation [27,28], using both the tablet-in-die and ejected-tablet methods. In the case of the tablet-in-die method, the compression cycle corresponding to tablets with the thickness closest to 3 mm was chosen. The linear portion was determined mathematically using a suitable software, which calculated the first derivative of the plot to give an evaluation of the pressure range where constant slope started and ended. The least-squares method was used to obtain accurate slope and intercept values, and the criterion to estimate the fit was the correlation coefficient. The relative precompression density (D_0) was determined as the relative density of the powder bed at the point where a measurable force is applied. In the case of the ejected-tablet method, the packing fractions at each maximum applied pressure were determined by measuring the dimensions of the tablets 24 h after ejection from the die. The least-squares method was also employed, taking into account the pressure range that is more appropriate for each derivative (generally, 25–150 MPa).

2.2.5. Preparation of tablets

The different powders were compacted into tablets by employing the machine described previously. A quantity of powder (500 mg) was manually fed into the die (12 mm), and the copolymer compacts were prepared at a fixed crushing force of 140–150 N. In the case of the carbohydrates, tablets could not be prepared at this crushing force, so powders were compressed in a pressure interval similar to that used for the copolymers (120–130 MPa). No additives were included in order to get intrinsic information of the polymeric material itself.

Compression data were collected from four tableting cycles.

2.2.6. Standard physical test of tablets

The physical testing of tablets was performed after a relaxation period of at least 24 h.

The tablet average weight and the standard deviation (SD) were obtained from 20 individually weighed (Sartorius CP224S, Göttingen, Germany) tablets according to European Pharmacopoeia [23].

The thickness and diameter of 10 tablets were measured individually using an electronic micrometer (Mitutoyo MDC-M293, Tokyo, Japan).

The crushing force [23] of 10 tablets was determined by diametral loading with a Schleuninger-2E tester (Greifensee, Switzerland).

Tablet friability [23] was calculated as the percentage weight loss of 20 tablets after 4 min at 25 rpm in an Erweka TA (Heusenstamm, Germany) friability tester.

Disintegration testing [23] was performed at 37 °C in distilled water (800 mL), using an Erweka ZT3 (Heusenstamm, Germany) apparatus without discs. The disintegration times reported are averages of six determinations.

2.2.7. Mercury porosimetry measurements

Mercury porosimetry runs were undertaken using an Autopore IV 9510 (Micromeritics, Madrid, Spain) porosimeter with a 3 cm^3 penetrometer. A quantity of sample was included in order to obtain 20–90% of mercury intrusion. Working pressures covered the range 0.1–60,000 psi, and the mercury solid contact angle and surface tension were considered to be 130° and 485 mN m^{-1}, respectively. Total porosity and pore size distribution were determined, in duplicate, for each tablet tested.

2.2.8. Statistical analysis

Moisture content and compression data were statistically analysed by one-way analysis of variance (ANOVA) using the SPSS® program version 14.0. Post-ANOVA analysis was carried out according to Bonferroni's multiple comparison tests. Results were quoted as significant when $p < 0.05$.

3. Results and discussion

3.1. Synthesis of graft copolymers and grafting yields

The results presented in Table 1 show the reaction yields obtained after graft copolymerization of ethyl methacrylate on waxy maize starch or waxy maize hydroxypropylstarch. The low relative standard deviations collected in Table 1 ensure the reproducibility of the synthesis and, as would be expected, the similar yields for OD and FD products confirm the absence of influence of the drying method used [2]. The copolymers show very high values of %GE, which indicate a high reactivity of these carbohydrates with EMA and a low fraction of homopolymer PEMA.

MHSEMA products are characterised by higher %GE and %G values than MSEMA products. These results agree with those obtained by Echeverria et al. [12] for potato starch derivatives, so we can conclude that the presence of the hydroxypropyl group in the starch molecule favours the graft copolymerization. This can be attributed to the fact that the etherification of the starch weakens the internal bond structure [17,29] and has an activating effect on the carbohydrate [30], resulting in that more active sites are formed allowing the fixation of more polymethacrylic chains.

Table 1
Grafting yields of EMA on waxy maize starch (MS) and waxy maize hydroxypropylstarch (MHS). Values in parentheses represent the standard deviation, and RSD represents the relative standard deviation ($n = 2$).

Copolymer	OD-MSEMA	FD-MSEMA	OD-MHSEMA	FD-MHSEMA
%GE	93.5 (0.7) RSD = 0.8%	89.3 (0.0) RSD = 0.0%	99.0 (0.7) RSD = 0.7%	98.6 (0.4) RSD = 0.4%
%G	152.1 (1.1) RSD = 0.7%	156.0 (1.7) RSD = 1.1%	208.7 (3.3) RSD = 1.6%	197.4 (5.8) RSD = 2.9%

Combining the %GE and %G yields, the composition of the synthesised products can be estimated (Table 2). The quantity of homopolymer (non-grafted PEMA) is ⩽10%, so the final product is composed mostly of graft copolymer, mainly in the case of MHSEMA derivatives. The percentage of grafted PEMA in the graft copolymers is higher than the percentage of grafted carbohydrate, so copolymers present mainly a hydrophobic character. In summary, the synthesised products are composed of 30–40% carbohydrate and 60–70% PEMA, mostly grafted for MHSEMA products. A prevalence of the hydrophobic component has also been reported by Echeverria et al. [12] for potato starch graft-based copolymers.

Table 2
Weight percentages of the different components in the synthesised products. Values in parentheses represent the standard deviation ($n = 2$).

Product	Non-grafted PEMA	Graft copolymer	Grafted carbohydrate	Grafted PEMA
OD-MSEMA	6.5 (0.7)	93.5 (0.7)	37.1 (0.4)	56.4 (0.3)
FD-MSEMA	10.7 (0.0)	89.3 (0.0)	34.9 (0.2)	54.4 (0.2)
OD-MHSEMA	1.0 (0.7)	99.0 (0.7)	32.1 (0.1)	66.9 (0.8)
FD-MHSEMA	1.4 (0.4)	98.6 (0.4)	33.1 (0.5)	65.4 (0.9)

3.2. Spectroscopy characterisation

3.2.1. IR spectroscopy

To analyse modifications on the initial structure of a material, IR is a useful technique [31,32]. Fig. 1 presents an example of the FT-IR spectra from OD- and FD-MHSEMA and their respective carbohydrates. The band absorbances in starch have been assigned and matched with the vibrational modes of the chemical bands reported by many researchers [31–34]. It is interesting to mention the absorbance at 1750–1735 cm^{-1} for the copolymers due to C=O bonds from ester aliphatic stretching vibrations. This intense band testifies that EMA is grafted in the glucose moiety. Moreover, the typical stress (=C–H) and flexion (C=C) bands of α,β unsaturated carbonyl compounds at approximately 3040–3010 cm^{-1} (medium intensity) and 1690–1635 cm^{-1} (variable intensity) are not evident, confirming the absence of unreacted EMA. Finally, it is possible to see the relative decrease in intensity of the stretching O–H band (3500–3400 cm^{-1}) from the glucopyranose rings in the copolymers compared to the raw starch.

3.2.2. NMR spectroscopy

Furthermore, the graft copolymers and their respective carbohydrates were characterised by ^{13}C NMR spectroscopy. Fig. 2 shows the ^{13}C NMR spectrum of copolymer FD-MHSEMA, where the peaks attributed to the carbons of the glucose unit and those described in the literature for PEMA can be distinguished [35]. This technique confirms the results obtained by IR spectroscopy; moreover, it is a useful tool to identify C7, C8 and C9 of hydroxypropyl group.

3.2.3. X-ray diffraction

The X-ray patterns of starches are modified by graft copolymerization (Fig. 3). In agreement with Xie et al. [31], Chi et al. [32] and Athawale and Rathi [34], the native starch had sharp diffraction peaks at 15°, 17°, 18° and 23° (2θ), which indicated low crystallinity and typical A pattern of cereal starch [36]. Furthermore, these peaks become smaller in hydroxypropylstarch as has been mentioned by Xie et al. [31] after the addition of citrate groups. After graft polymerizations, the four peaks merged, suggesting that the crystal phase was also involved along with the amorphous phase during the grafting reaction [34,37]. The main reason is the presence of the new PEMA chains grafted in the carbohydrate backbone, which makes the effective packing of the copolymer chains difficult. In addition, Hancock and Zografi [38] indicate that pharmaceutical solids as polymers and products submitted to freeze-drying present amorphous structure.

3.3. Powder and particle characterisation

3.3.1. Particle size analysis

Compared with raw starches, larger mean particle sizes were observed for graft copolymers (Table 3), especially for MHSEMA derivatives. This can be attributed to the fact that the grafted synthetic polymer chains surround and agglomerate the individual

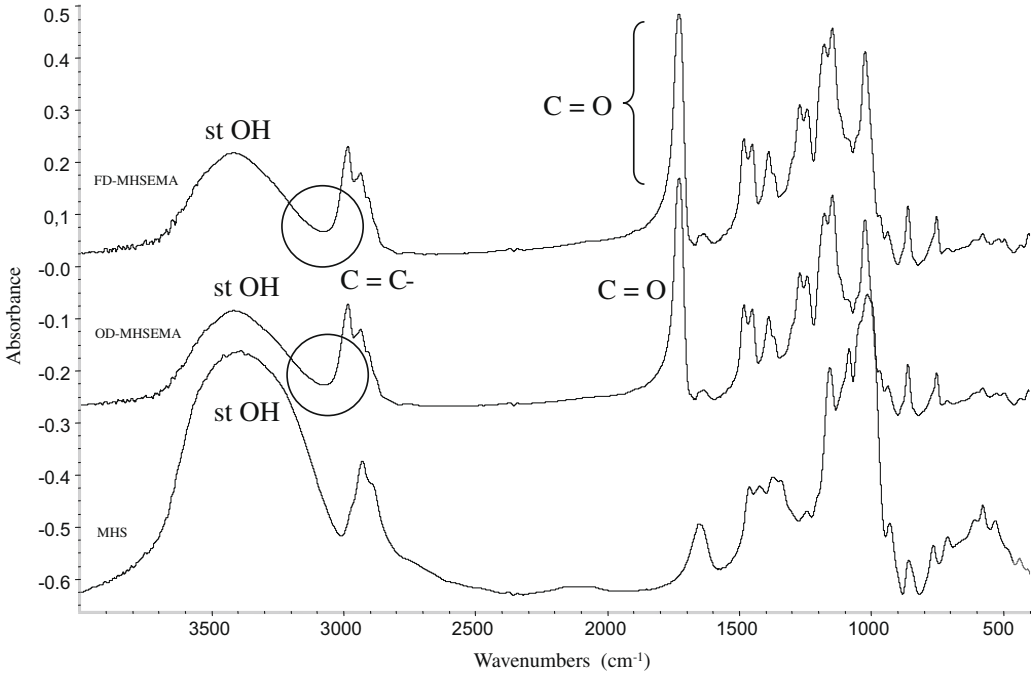

Fig. 1. IR spectra of waxy maize hydroxypropylstarch (MHS) and copolymers OD-MHSEMA and FD-MHSEMA.

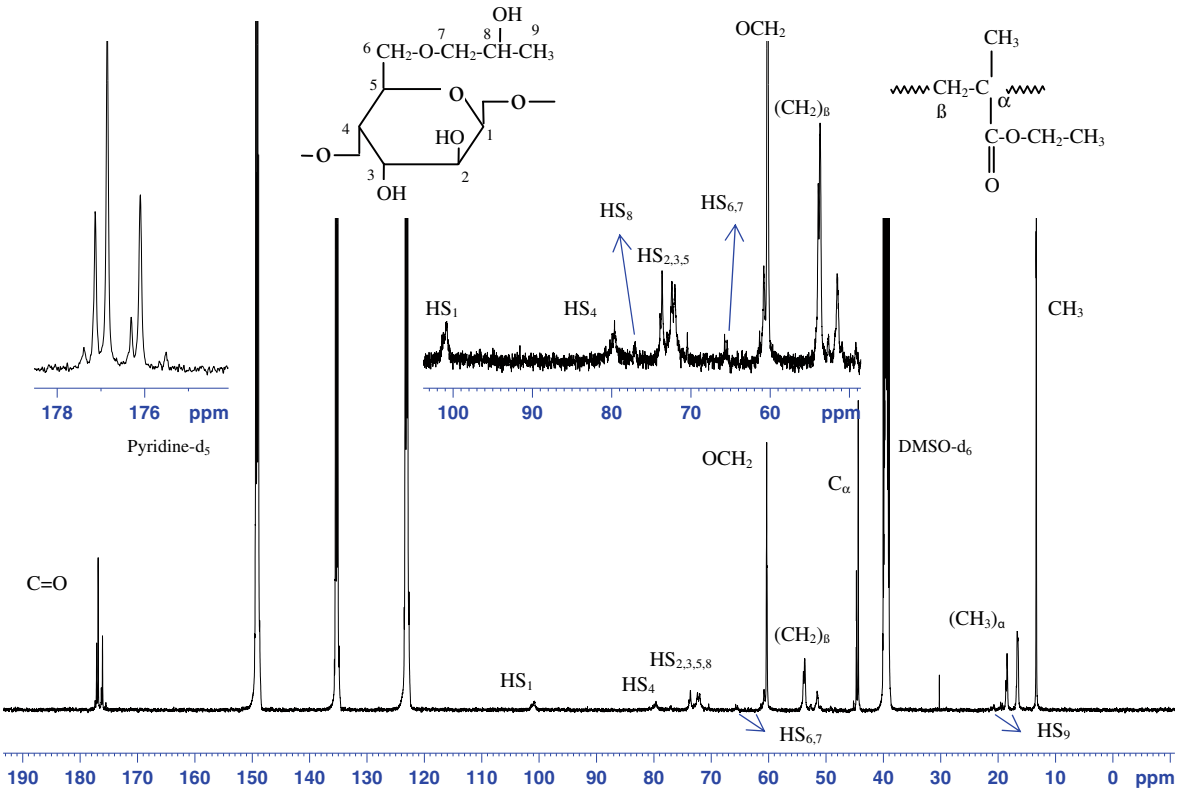

Fig. 2. NMR spectrum of FD-MHSEMA.

granules of starch [39,40]. The milling process of the MSEMA copolymers could explain their lower particle diameter. The particle size distribution (Fig. 4), as well as the kurtosis and skewness coefficients (Table 3), reveals a broader and more symmetric distribution for copolymers, especially for MHSEMA products. This fact could play an important effect on the mechanical and technological properties [41]. The negative values obtained for kurtosis coefficient in the case of MHSEMA copolymers indicate a platykurtic distribution. The symmetry was also more significant in these samples, with skewness coefficients close to zero. Again, the milling process of MSEMA copolymers could be responsible for more similar skewness and kurtosis coefficients of OD and FD copolymers.

3.3.2. Scanning electron microscopy (SEM)

The microphotographs of the materials used in this study (Fig. S1) illustrate the differences in particle shape and surface texture. Waxy maize starch granules show oval and regular granule shape (Fig. S1), with a smooth surface and no obvious fissures or cavities. This morphology has also been detected by other authors [42–44] using different techniques. On the other hand, the hydroxypropylstarch particles show polygon, irregular and granule shape with fissures on their surfaces (Fig. S1).

MSEMA derivatives (Fig. S1) are characterised by irregular outline and significant hollow regions, as consequence of the milling process carried out. Doughnut-shaped particles are observed for MHSEMA (Fig. S1), which could be due to granular swelling followed by collapse [31]. No remarkable differences between freeze-drying and oven-drying are found for both copolymers.

3.3.3. Apparent particle density

MHS shows lower apparent particle density than MS (Table 3), in agreement with the chemical modification of starch by the introduction of the hydroxypropyl group.

Copolymers have lower apparent particle densities than the carbohydrates, due to the EMA component. Taking into account that the variation in pycnometric density due to operating parameters can affect the accuracy of the result to the nearest 0.01 g/cm^3 [24], no differences can be found in relation with the drying method effect.

3.3.4. IR balance moisture determination

Hydroxypropylstarch shows higher moisture content than starch ($p < 0.05$) (Table 3), which is in agreement with its more open structure as a result of a decrease hydrogen bonding between starch chains because of the bulky hydroxypropyl groups [45]. The copolymers show lower moisture content than carbohydrates ($p < 0.05$), which might be related with the higher hydrophobic character conferred by the introduction of PEMA [46].

The drying methods do not affect the moisture content ($p > 0.05$), probably because of the presence of a high percentage of methacrylic graft, which reduces the water uptake.

3.3.5. Flow properties

Materials are characterised by a complete lack of flow, with the exception of MHSEMA, FD-MHSEMA being the one with the best properties (Table 3). The particle size distribution and smaller particle size of raw starches and MSEMA products could be the reason for these results. Abdullah and Geldart [47] indicated that when powders are dominated by fine particles, the interparticle forces, as the Van der Waals forces, would hinder the flow of these materials. A slightly higher symmetry of FD-MHSEMA particle distribution could justify its better flow when compared with OD-MHSEMA [47].

3.4. Compression behaviour

Data from Heckel treatment are indicated in Table 4. From the tablet-in-die method, relative density values (D_a or total densifica-

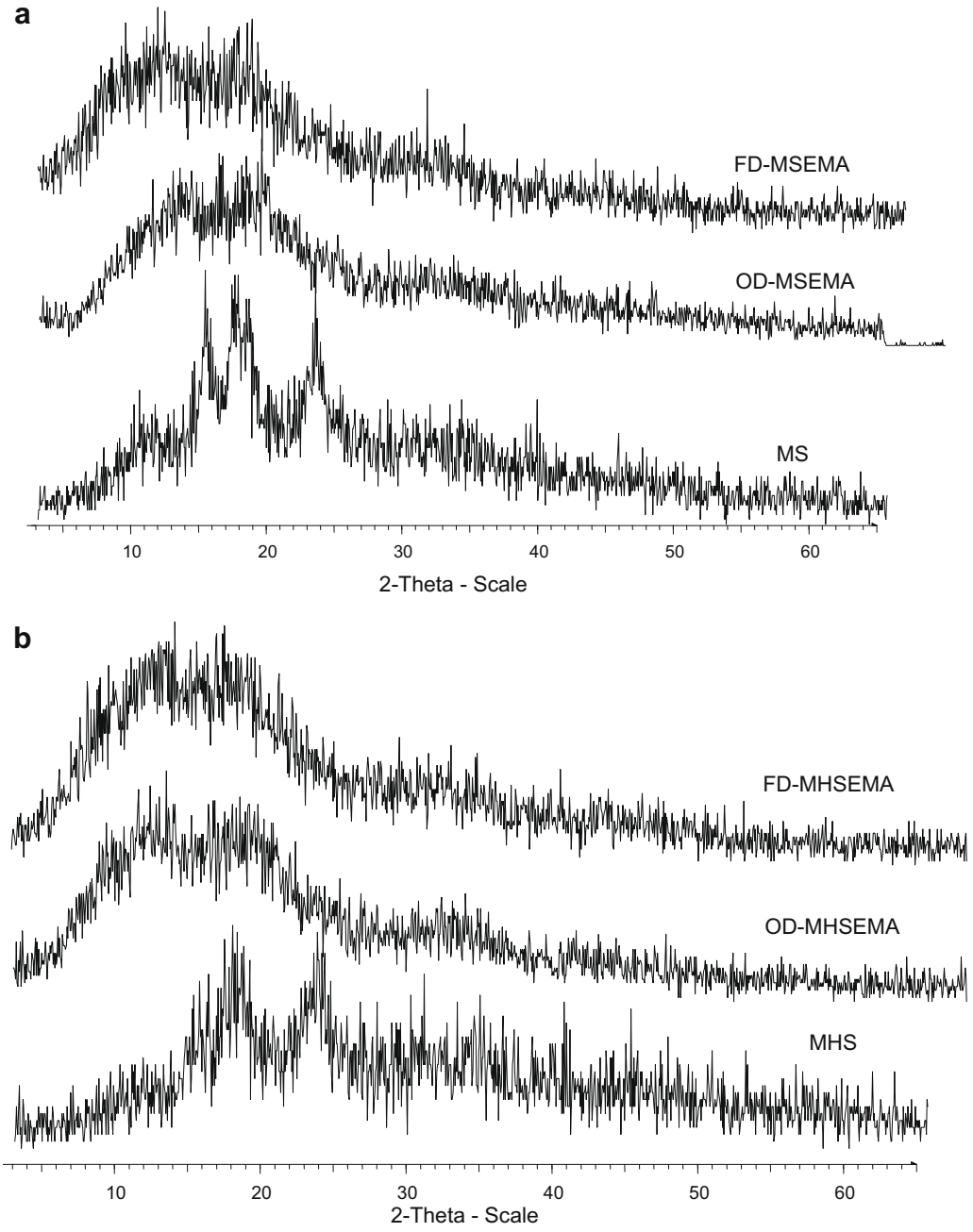

Fig. 3. X-ray diffraction patterns of (a) waxy maize starch (MS) and MSEMA copolymers; and (b) waxy maize hydroxypropylstarch (MHS) and MHSEMA copolymers.

Table 3
Physical and technological properties of the carbohydrates and copolymers: mean particle size (μm), skewness and kurtosis coefficients, apparent particle density (g/cm^3), moisture content (%) and flow rate (g/s). Values in parentheses represent the standard deviation.

Polymer	Mean particle size (μm)	Skewness coefficient	Kurtosis coefficient	Apparent particle density (g/cm^3)	Moisture content (%)	Flow rate (g/s)
MS	95 (101)	3.35	13.31	1.500 (0.002)	2.80 (0.02)	–
OD-MSEMA	144 (140)	1.62	2.19	1.236 (0.002)	0.96 (0.03)	–
FD-MSEMA	144 (138)	1.60	2.25	1.229 (0.001)	0.96 (0.02)	–
MHS	82 (74)	4.90	30.38	1.478 (0.003)	3.50 (0.03)	–
OD-MHSEMA	416 (221)	−0.69	−1.10	1.234 (0.001)	0.96 (0.03)	6.56 (1.52)
FD-MHSEMA	300 (243)	0.10	−1.67	1.225 (0.002)	0.97 (0.01)	12.30 (2.17)

tion, D_0 or densification by die filling, D_b or densification by particle rearrangement and fragmentation) were obtained. The tendency of the material to total deformation and fast elastic deformation could also be evaluated from the mean yield pressures K_d and K_{ef}, respectively. The ability of the material to deform plastically was shown by K_p, obtained using the ejected-tablet method. K_{et}

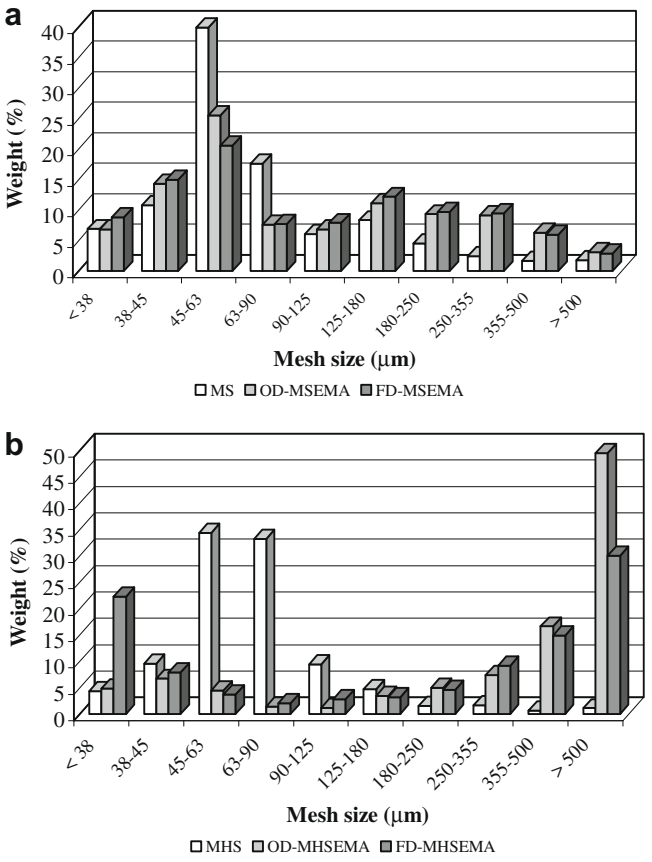

Fig. 4. Particle size distribution of materials: (a) MS and MSEMA copolymers; (b) MHS and MHSEMA copolymers.

has been regarded as a constant that describes the tendency of the material to deform elastically, and was obtained from the two methods mentioned above [48]. The higher the mean yield pressure values (K), the smaller the tendency to deform by one or another mechanism.

Higher D_b and smaller D_0 values are observed for raw starches than for copolymers. The predominance of small particles in the formers that promote the presence of mechanical and electrostatic forces could prevent the packing of their particles in the bulk state [49]. The values of D_b support the findings of Paronen and Juslin [49], Huffine and Bonilla [50], Fell and Newton [51] and York [52] on the higher rearrangement in the presence of smaller particles.

Paronen and Juslin [49] related that corn starch underwent much plastic flow and only little elastic recovery, this being the most favourable among the starches studied. This behaviour is also described for the waxy maize starch derivatives (MS, MHS) under study. The extremely low tendency of total elastic deformation (K_{et}) for MS and MHS could be related with the high pressure used for K_d analysis in the tablet-in-die method. So, Antikainen and Yliruusi [53] observed that for maize starch and low compression levels, the amount of air trapped inside the tablets is high, which increases the elasticity values. However, at higher compression pressures, as those used to calculate K_d, the trapped air becomes less significant, as it has already been removed from the tablet, leading to a decrease in elastic deformation.

The tendency to total deformation (K_d) is higher for the copolymers, mainly due to the increase in the elastic component (K_{et}). A dependence between K_d and particle size has been described by different authors [49,51,52], indicating that the smaller the particle size is, the greater the K_d value is obtained.

Furthermore, the K_d values obtained for the copolymers compare well with those of some widely used commercial direct compression excipients, being similar to pregelatinized starches such as Starch 1500® [48] and being even lower than the exhibited by Avicel PH® series [48,54], microcrystalline celluloses which are known to deform easily by plastic flow.

MSEMA copolymers show slightly better compression properties than MHSEMA copolymers, those being more plastic and less elastic. The shape of MSEMA particles, more prone to plastic flow, could explain these results. Paronen and Juslin [49] indicated that the shape of particles affects the tendency of the starches to deform plastically. Similar behaviour was found for FD products related to OD products, which is in agreement with the results obtained by Ferrero and Jiménez-Castellanos [10] for potato starch-methyl methacrylate copolymers.

3.5. Preparation of tablets

In order to obtain a deeper understanding of the compression physics, various works or energy terms involved in compression have been determined. These typical compression parameters [55,56] are summarised in Table 5.

Copolymer tablets were compacted at a fixed crushing force of 140–150 N. However, the carbohydrates were not able to form tablets at this crushing force, probably due to a decrease in the plastic component when increasing compression pressure [53]. Thus, for comparison purposes, MS and MHS tablets were compressed in a pressure range (120–130 MPa) similar to that used for the copolymers.

The maximum applied pressures (P) (Table 5) are larger for OD than FD derivatives, although these differences are only significant ($p < 0.05$) for MSEMA copolymers. This is in agreement with the different plastic deformation values (Table 4) obtained using Heckel equation.

The lubrication ratio values (R) obtained (0.6–0.7) do not fulfil the requirements proposed by Bolhuis and Lerk [57] for direct compression excipients, and no significant differences ($p > 0.05$) are found between the copolymers. The low values observed for this parameter make us think about the need of adding a lubricant when using these copolymers as tablet excipients.

In spite of the poor R measurements, the values found for the ejection force (F_e) (Table 5) are smaller than 750 N, the limit for direct compression excipients [57]. No statistical differences between the copolymers are detected for F_e and W_f values. FD-MSEMA shows larger expansion work values (W_e) than OD-MSEMA ($p < 0.05$). These results do not agree with the tendency to fast elastic deformation (K_{ef}) noticed in Heckel compression cycles (Table 4). This could be attributed to the different measuring conditions: K_{ef} values (with high SD) are obtained from a linear phase of Heckel compression cycles [48], while the expansion work takes into account the whole process of elastic expansion during decompression.

MHSEMA derivatives were characterised by higher apparent network (W_{an}) values than MSEMA derivatives ($p < 0.05$), which are in agreement with K_p values in Heckel analysis (Table 4). The plasticity (Pl) values are statistically similar for all copolymers, except for FD-MSEMA ($p < 0.05$) that shows a slightly lower value due to its higher expansion work.

3.6. Standard physical test of tablets

Results from the physical testing of tablets obtained from the different materials are compiled in Table 6.

All tablets fulfil the guidelines specified in European Pharmacopoeia [23] related to weight uniformity test. In spite of the flow data obtained (Table 3), tablets from the different copolymers show good weight reproducibility.

Table 4
Typical parameters from Heckel treatment for the different materials under study: tablet-in-die method (total densification, D_a; densification due to die filling, D_0; densification due to particle rearrangement and fragmentation, D_b; mean yield pressure of total deformation, K_d; and mean yield pressure of fast elastic deformation, K_{ef}), ejected-tablet method (mean yield pressure of plastic deformation, K_p) and both methods (mean yield pressure of total elastic deformation, K_{et}). Values in parentheses represent the standard deviation ($n = 4$).

Materials	Tablet-in-die method[a]					Ejected-tablet method[b]	Both methods
	D_a	D_0	D_b	K_d (MPa)	K_{ef} (MPa)	K_p (MPa)	K_{et} (MPa)
MS	0.472	0.165	0.307	108.6	689.5		
	(0.003)	(0.003)	(0.002)	(4.1)	(62.8)	114.9	1960.7
OD-MSEMA	0.434	0.275	0.159	69.9	311.6		
	(0.008)	(0.003)	(0.009)	(3.2)	(53.2)	140.9	138.6
FD-MSEMA	0.398	0.256	0.142	75.3	577.1		
	(0.007)	(0.005)	(0.007)	(2.8)	(97.3)	128.2	182.1
MHS	0.476	0.188	0.288	127.8	863.7		
	(0.004)	(0.004)	(0.006)	(4.1)	(192.1)	156.3	703.9
OD-MHSEMA	0.332	0.209	0.122	71.2	263.0		
	(0.013)	(0.000)	(0.014)	(3.7)	(45.0)	149.3	136.1
FD-MHSEMA	0.356	0.225	0.132	75.3	463.2		
	(0.007)	(0.006)	(0.004)	(2.2)	(123.8)	144.9	156.6

[a] Correlation coefficients of tablet-in-die method: compression (0.990–0.999) and decompression (0.799–0.975) phases.
[b] Correlation coefficients of ejected-tablet method: 0.975–0.990.

Table 5
Main compression parameters for the carbohydrates and copolymers: maximum applied upper punch pressure (P), lubrication ratio (R), maximum ejection force (F_e), Juslin's friction work (W_f), expansion work (W_e), Juslin's apparent network (W_{an}), and plasticity (Pl). Values in parentheses represent the standard deviation ($n = 4$).

Materials	P (MPa)	R	F_e (N)	W_f (J)	W_e (J)	W_{an} (J)	Pl (%)
MS	126.64	0.794	278.9	2.3	0.4	11.4	96.3
	(1.15)	(0.029)	(182.6)	(0.6)	(0.0)	(0.1)	(0.2)
OD-MSEMA	133.43	0.660	571.6	3.7	0.4	15.1	97.3
	(6.54)	(0.033)	(152.4)	(0.5)	(0.0)	(0.4)	(0.3)
FD-MSEMA	114.67	0.744	278.4	2.9	0.6	15.3	96.1
	(3.84)	(0.033)	(33.1)	(0.4)	(0.1)	(0.2)	(0.4)
MHS	126.65	0.653	1183.0	3.1	0.2	11.4	97.9
	(2.61)	(0.002)	(25.4)	(0.1)	(0.0)	(0.3)	(0.2)
OD-MHSEMA	131.69	0.671	459.9	4.3	0.5	18.1	97.1
	(2.52)	(0.029)	(116.5)	(0.5)	(0.0)	(0.1)	(0.3)
FD-MHSEMA	121.25	0.698	288.7	4.1	0.5	16.9	97.2
	(4.25)	(0.041)	(68.0)	(0.7)	(0.0)	(0.2)	(0.2)

The tablet thickness varies between 3.5 and 4.9 mm, and the diameter varies between 12.2 and 12.3 mm. MS and MHS products present the smallest values, which might be related to a greater axial and radial expansion of copolymers than of carbohydrates.

The crushing force test [23] confirms the values of 140–150 N for all the tablets, except for carbohydrate tablets that show lower values.

Copolymer tablets are characterised by lower friability than the tablets obtained from the carbohydrates, although only FD-MSEMA shows values lower than 1% [23]. The rough texture of MSEMA derivatives could be associated to higher binding capacity and, in consequence, to lower friability than that of MHSEMA derivatives [41,49,58].

It is remarkable to note that only the copolymer tablets show disintegration times larger than 30 min, similar to Preflo® modified starches, a commercial direct compression diluent for sustained release formulations [59]. This behaviour suggests that the copolymers under study could be used as compressed non-disintegrating matrix tablets.

3.7. Mercury porosimetry measurements

The microstructure of the matrices was evaluated by mercury intrusion–extrusion porosimetry (Table 7) and, according to IUPAC guidelines definitions [60], the systems under study contain mesopores.

Carbohydrate tablets show smaller porosities than copolymer tablets, which are in agreement with the thickness data compiled in Table 6. Tablets compacted from OD copolymers are characterised by slightly higher porosities, mean and median pore diameter than those obtained from FD derivatives (Table 7). These results are consistent with the larger elastic expansion observed for OD products (Table 4).

The pore size distribution profiles (Fig. 5) show a unimodal profile for all materials under study. This behaviour was also found by Carli et al. [61] for matrices obtained with acrylic polymers and by Ferrero and Jiménez-Castellanos [10] for potato hydroxypropylstarch and methyl methacrylate copolymers.

4. Conclusions

It can be concluded that grafting of EMA on the carbohydrate backbone cause several modifications on the physicochemical and technological properties of waxy maize starch and hydroxypropylstarch.

The amorphization and changes in particle size and morphology affect the densification behaviour of the copolymers compared with the original carbohydrates. Graft copolymers are found to be less prone to particle fragmentation and exhibit a higher tendency to deformation. However, their compression behaviour could be considered a mixture of plastic and elastic deformations. The relative importance of these two mechanisms depends on carbohydrate nature and drying method used.

Although carbohydrates are characterised by lower elasticity, the graft copolymerization improves the compactibility of native starches, as tablets of acceptable crushing strength can be obtained. Interparticulate bonds formed in copolymer tablets are strong enough to allow stress relaxation without breakage of the tablets.

The higher mechanical resistance and hydrophobic character of graft copolymers make only these tablets show disintegration times larger than 30 min. This behaviour suggests that these copolymers could be used as compressed non-disintegrating matrix tablets with potential application for controlled drug delivery.

The next step, which will be reported in a future publication, is to ascertain the mechanism governing drug release from matrix systems made with these excipients.

Table 6
Tablet test results for the carbohydrates and copolymers: average weight, thickness, diameter, crushing force (CF), friability (F), and disintegration time (t_d). Values in parentheses represent the standard deviation.

Materials	Average weight (mg)	Thickness (mm)	Diameter (mm)	CF (N)	F (%)	t_d (min)
MS	504 (14)	3.519 (0.039)	12.198 (0.019)	95 (15)	4.45	2
OD-MSEMA	499 (2)	4.608 (0.008)	12.274 (0.022)	150 (9)	1.11	>30
FD-MSEMA	501 (2)	4.647 (0.027)	12.248 (0.020)	150 (9)	0.91	>30
MHS	502 (8)	3.882 (0.010)	12.145 (0.018)	55 (8)	5.59	3
OD-MHSEMA	500 (1)	4.825 (0.005)	12.300 (0.029)	150 (7)	1.21	>30
FD-MHSEMA	501 (2)	4.815 (0.008)	12.270 (0.023)	146 (5)	1.36	>30

Table 7
Parameters characterising the porous structure of materials, calculated by mercury intrusion–extrusion porosimetry. Values in parentheses represent the standard deviation ($n = 2$).

Materials	Porosity (%)	Mean pore diameter (nm)	Median pore diameter (nm)
MS	19.1 (0.1)	35.5 (0.0)	1049.2 (7.1)
OD-MSEMA	27.0 (0.7)	38.9 (12.7)	991.9 (47.7)
FD-MSEMA	26.2 (0.2)	31.6 (2.1)	775.9 (0.4)
MHS	23.9 (0.7)	44.2 (18.4)	1673.3 (53.3)
OD-MHSEMA	29.2 (0.0)	40.1 (2.1)	1215.8 (17.8)
FD-MHSEMA	28.9 (0.3)	37.8 (5.7)	1124.9 (3.0)

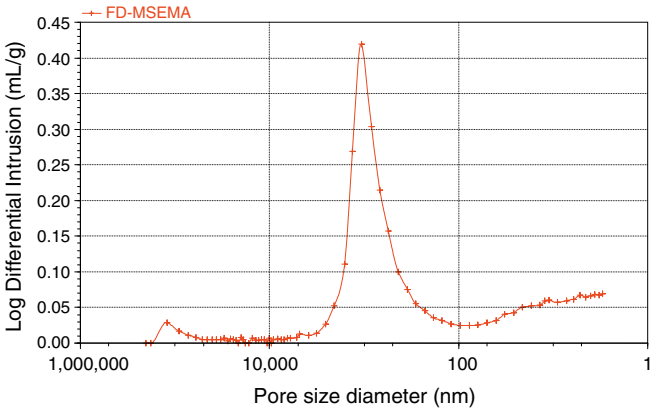

Fig. 5. Pore size distribution profiles for FD-MSEMA tablets.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejpb.2008.12.008.

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