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The influence of carbohydrate nature and drying methods on the compaction properties and pore structure of new methyl methacrylate copolymers

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Abstract

Methyl methacrylate (MMA) copolymers have recently been proposed as an alternative in controlled-release matrix tablets. The aims of this study were to assess the potential value of these copolymers as direct compression excipients and to investigate relationships between the physical and structural properties of the polymers and the compression behaviour of the powders and the microstructural properties of the tablets. Copolymers were synthesised by free radical copolymerisation of MMA with starch or cellulose derivatives and were alternatively dried by oven or freeze-drying techniques. Thus, the present study focuses on the influence of the carbohydrate nature and the drying process on the mechanical and compaction properties of MMA copolymers. Particle size, shape and surface texture of the copolymers have been studied in detail and Heckel treatment has been chosen for discriminating the densification behaviour of powdered materials. Total pore volume and pore size distribution of MMA copolymer tablets were investigated with mercury porosimetry. Oven drying gave less porous particles with more homogenous surfaces than those freeze-dried. Differences in morphology between the MMA copolymers were demonstrated by increasing apparent particle densities, smaller flow rates and higher binding capacities for freeze-dried products. The porousness and mean pore radius of the tablets obtained from freeze-dried copolymers were higher than those of tablets obtained from oven-dried ones.

Keywords: Controlled-release; Matrix tablets; Methyl methacrylate (MMA) copolymers; Heckel analysis; Compression properties; Porosity

1. Introduction

Among the different approaches for oral controlled-release dosage forms, matrix tablets have been gaining increasing attention because of the simple and low-cost manufacturing process (Artalejo et al., 1988; Marín et al., 1988). For these systems, the polymer nature has been shown as an essential parameter influencing the swelling rate in the case of hydrophilic matrices (Buri and Doelker, 1980; Artalejo et al., 1988; Marín et al., 1988) as well as the porosity, tortuosity and water

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uptake capacity in the case of inert matrices (Salomon and Doelker, 1980; Artalejo et al., 1988). So, the prior knowledge of the physico-mechanical properties of polymers becomes absolutely necessary for the successful formulation of tablets.

Recently, a new generation of copolymers combining semi-synthetic (cellulose and starch derivatives) and synthetic (methacrylates) polymers (Castellano, 1997) have been introduced as excipients for oral controlled-release matrices. The monomer (methyl methacrylate (MMA)) was grafted on starch or cellulose derivatives by free radical polymerisation, using Ce(IV) as an initiator. The products obtained were alternatively dried by two different methods: drying in a vacuum oven (5–10 mmHg) at 50 °C until constant weight or freeze-drying (freezing process at −20 °C for 24 h and sublimation process at 100 mTorrs and −50 °C) until powdered product was got.

These polymers have been characterised by NMR-techniques to determine the structure of the organic compounds and by IR spectrophotometry to identify the functional groups (Castellano, 1997). The amorphous nature of the graft copolymers has also been confirmed using X-ray diffraction (Ferrero et al., 1997). Surface area measurements and thermal analysis studies (Ferrero et al., 1999) allowed the determination of the specific surface area and glass transition temperature of these copolymers, that appeared to be dependent on polymer composition and drying method used.

Since the compaction characteristics of polymers are dominant factors in choosing a polymer for sustained release (Nokhodchi et al., 1995), the purpose of the present work was to reach a better understanding of this group of copolymers to support its utility in direct compression. The paper discusses the effect of the carbohydrate nature and drying process on the compressional characteristics of the powdered materials and the porous structure of the tablets obtained from these copolymers. Knowledge of particle properties, such as particle size distribution and particle morphology, can give a deeper insight into the mechanism of void formation and packing behaviour.

The compression behaviour of MMA copolymers was evaluated using Heckel equation, which is based on the assumption that the densification of the bulk powder column follows the first order kinetics (Heckel, 1961a,b). Although the Heckel function has its limitations in describing densification at low and very high compression pressures (Roberts and Rowe, 1985; Sonnergaard, 1999; Krumme et al., 2000), this equation is nevertheless rather useful for obtaining practical data concerning the densification behaviour of materials compressed.

Finally, total pore volume and pore size distribution of MMA copolymer tablets were investigated with mercury porosimetry.

2. Materials and methods

2.1. Materials

Copolymers (batches SS01) synthesised by free radical copolymerisation of MMA and different carbohydrates (hydroxypropylstarch HS, carboxymethylstarch CS, hydroxypropylcellulose HC) were selected for the study. The products were dried either in a vacuum oven (OD copolymers) or freeze-dried (FD copolymers) (Castellano, 1997). The OD products were crushed in a knives mill (Retsch, Haan, Germany) to obtain powdery samples.

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

2.2. Methods

2.2.1. Powder and particle characterisation

2.2.1.1. Particle size analysis. Particle size analysis was carried out on a vibratory sieve shaker (Retsch Vibro, Haan, Germany) using 500, 450, 400, 350, 300, 250, 200, 150, 100, 50, 25 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 (S.D.) and kurtosis and skewness coefficients (Gutiérrez-Cabria, 1978).

2.2.1.2. Scanning electron microscopy (SEM). Scanning electron microphotographs of the particulate samples were taken using a scanning electron microscope (Philips XL-30, Eindhoren, Holland), after coating the samples on an Edwards AUTO-306 sputter coater. Microphotographs were obtained at a magnification appropriate for particle size.

The particle shape factor (Sf) was determined using an image analysis system (SoftImage GmBH), by dividing the actual projected area of a particle, A, by the area of a circle whose circumference was equivalent to the perimeter of the projected image, P:

$$\mathrm{Sf} = \frac{4\pi A}{P^2}$$

(Exner and Linck, 1977).

2.2.1.3. Apparent particle density. The apparent particle densities of the powders were determined, in triplicate, by means of an air comparison pycnometer (Quantachrome SPY-3, 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 (Viana et al., 2002).

2.2.1.4. Flow properties. An automated flowmeter system developed by Muñoz-Ruiz and Jiménez-Castellanos (1993) 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. 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 six replicates.

2.2.2. Compression behaviour

To allow direct comparison of all copolymers, the amount of material 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 (Mettler LJ16 Balance, Zürich, Switzerland) and manually placed into the die. Tablets were obtained using an instrumented (Muñoz-Ruiz et al., 1995) single-punch tablet machine (Bonals AMT 300, Barcelona, Spain) with 12 mm flat-faced punches at a speed of 30 cycles per min. 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 (Heckel, 1961a,b), 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 3 mm was chosen. The linear portion was determined mathematically using 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 more appropriate for each derivative (generally, 25–200 MPa).

2.2.3. Preparation of tablets

The different copolymers were compacted into tablets employing the machine described previously. A quantity of powder (500 mg) was manually fed into the die (12 mm) and flat-faced compacts were prepared at a fixed breaking force (70–80 N). No additives were included in order to get information, which were intrinsic to the poly-

Table 1
Physical and technological properties of MMA copolymers: mean particle diameter (μm), kurtosis and skewness coefficients, shape factor, apparent particle density (g/cm^3), flow rate (g/s)

Copolymer	Mean particle diameter (μm)	Kurtosis coefficient	Skewness coefficient	Shape factor	Apparent particle density (g/cm^3)	Flow rate (g/s)
OD-HSMMA	112 (120)	4.44	2.27	0.680 (0.153)	1.308 (0.013)	18.49 (2.79)
FD-HSMMA	161 (143)	−0.41	1.03	0.718 (0.183)	1.283 (0.015)	15.05 (2.41)
OD-CSMMA	157 (112)	0.58	1.00	0.725 (0.157)	1.258 (0.010)	18.28 (2.19)
FD-CSMMA	269 (126)	−1.09	−0.01	0.713 (0.215)	1.380 (0.023)	5.14 (0.35)
OD-HCMMA	171 (140)	0.57	1.19	0.702 (0.195)	1.208 (0.008)	18.48 (0.87)
FD-HCMMA	282 (131)	−1.09	−0.13	0.691 (0.175)	1.251 (0.017)	5.37 (0.11)

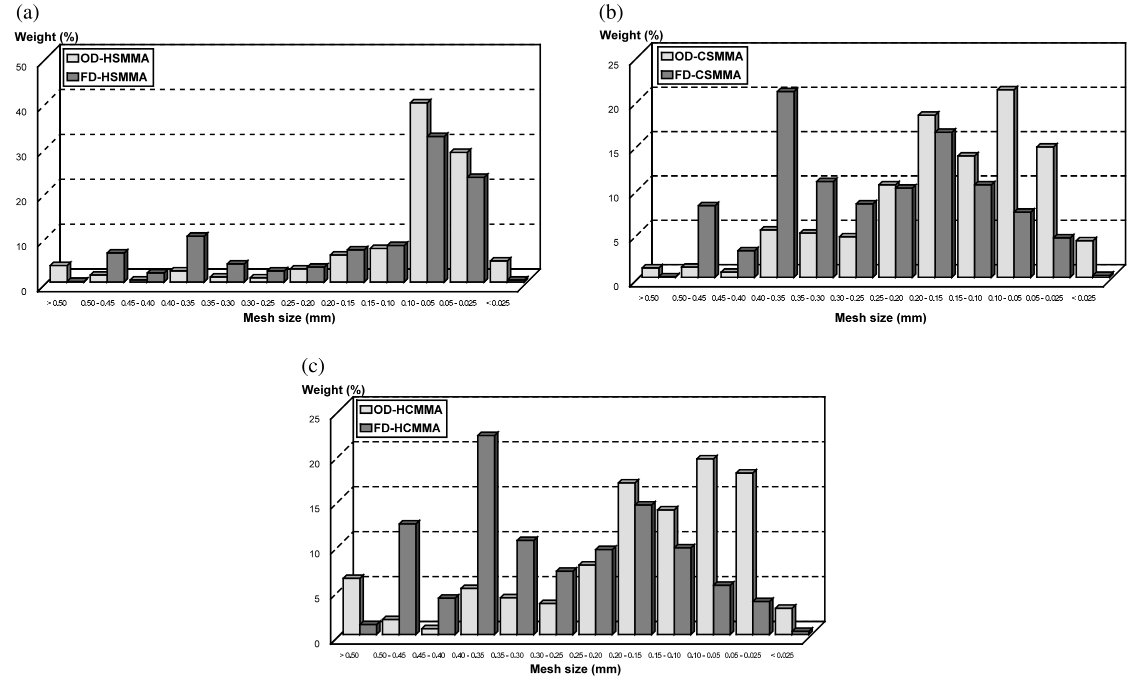

Fig. 1. Particle size distribution of MMA copolymers: (a) HSMMA products; (b) CSMMA products; (c) HCMMA products.

meric material itself. Compression data were collected from three tableting cycles.

In order to produce a sufficient number of tablets for evaluating their properties, the machine was equipped with a forced feeding system and the materials were tableted in the same conditions outlined before.

2.2.4. 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, the standard deviation (S.D.) and relative standard deviation (R.S.D.) were obtained from 20 individually weighed (Mettler LJ16 analytical balance, Zürich, Switzerland) tablets according to European Pharmacopeia (1997).

The thickness of ten tablets was measured individually placing them in and parallel to the face of an electronic micrometer (Mitutoyo MDC-M293, Tokyo, Japan).

The breaking force (European Pharmacopeia, 1997) of ten tablets was determined by diametral loading with a Schleuninger-2E tester (Greifensee, Switzerland).

Tablet friability (European Pharmacopeia, 1997) was calculated as the percentage weight loss of 20 tablets after 4 min at 25 r.p.m. in an Erweka TA (Heusenstamm, Germany) friability tester.

Disintegration testing (European Pharmacopeia, 1997) was performed at 37 °C in distilled water (800 ml), using an Erweka ZT3 (Heusenstamm, Germany) apparatus without disks. The disintegration times reported are averages of six determinations.

2.2.5. Mercury porosimetry measurements

Mercury porosimetry runs were undertaken using a Quantachrome Autoscan 33 (Boyton Beach, FL, USA) porosimeter with a 3 cm^3 penetrometer. The volume of sample was roughly 1/3 that of the penetrometer capacity. Working pressures covered the range 1–33 000 psi and the mercury solid contact angle and surface tension were considered to be 140° and 480 erg/cm^2, respectively. Total porosity and pore size distributions were determined, in duplicate, for each tablet tested.

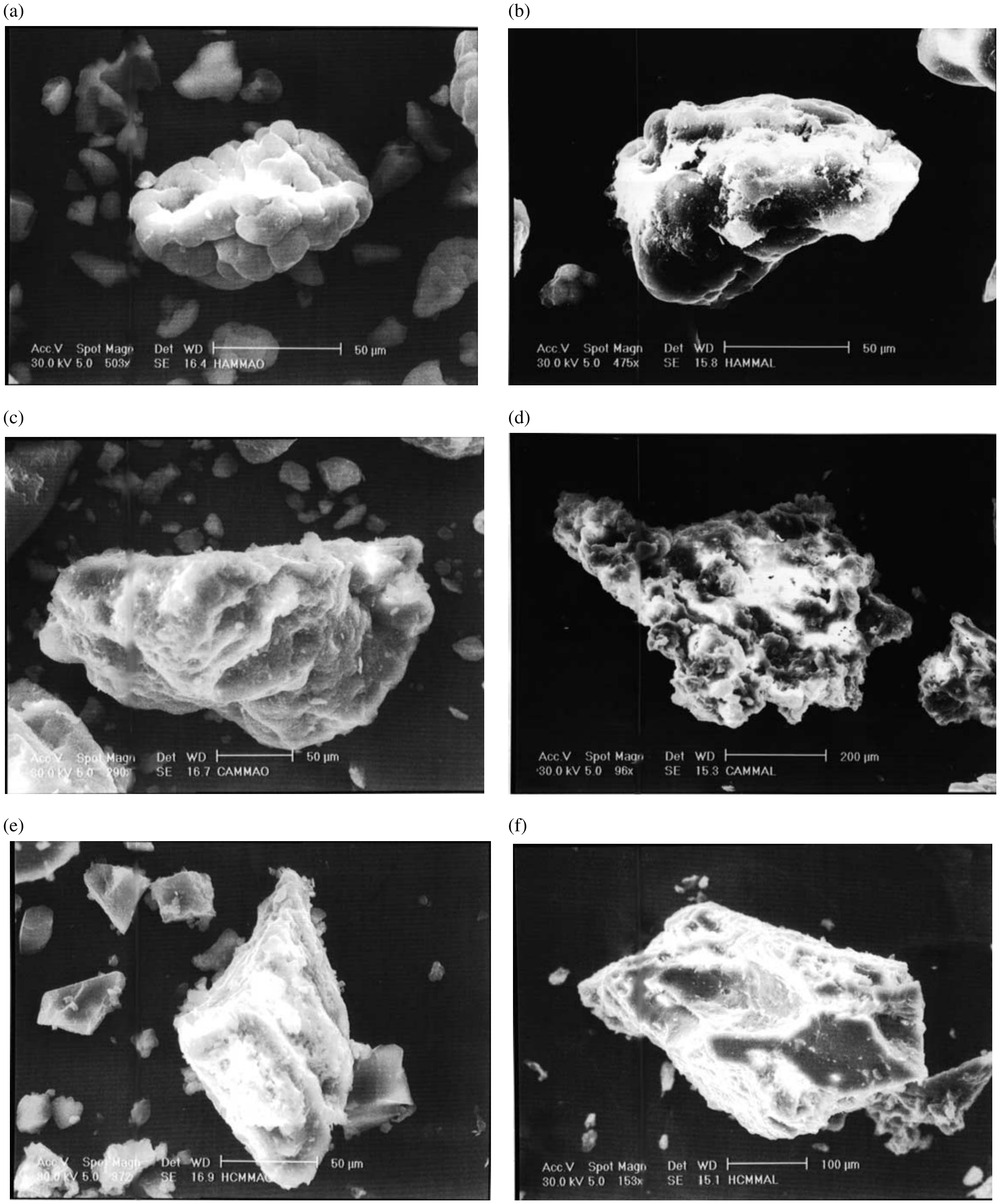

Fig. 2. Microphotographs corresponding to: (a) OD-HSMMA; (b) FD-HSMMA; (c) OD-CSMMA; (d) FD-CSMMA; (e) OD-HCMMA; (f) FD-HCMMA.

2.2.6. Statistical analysis

Apparent particle density, flow rate and compression data were statistically analysed by one-way analysis of variance (ANOVA) using the SPSS program version 7.5. 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. Powder and particle characterisation

3.1.1. Particle size analysis

The results presented in Table 1 show higher mean particle diameters for the freeze-dried (FD) products as compared with oven-dried (OD) ones, being the smallest differences for HSMMA derivatives. The particle size distribution (Fig. 1), as well as the kurtosis and skewness coefficients (Table 1), revealed a broader and more symmetric distribution for FD products. The negative values obtained for kurtosis coefficient in the case of FD copolymers indicated a platicurtic distribution. The symmetry was also more significant in these samples, mainly for FD-CSMMA and FD-HCMMA, with skewness coefficients close to zero.

The milling process of the OD copolymers could be responsible for these results. As OD-HSMMA was obtained as a more powdery product, less milling was needed, so its particle size distribution was more similar to its corresponding FD derivative.

3.1.2. Scanning electron microscopy (SEM)

The microphotographs of the copolymers used in this study (Fig. 2) illustrate the differences in particle shape and surface texture. Powders were found to display quite different morphologies, depending on the carbohydrate nature and drying method employed. HSMMA derivatives were characterised by lobe masses with a smoother surface for the OD product. OD-CSMMA particles showed a spongy structure with some smooth faces. The spongy structure was clearer in FD-CSMMA particles, with significant hollow regions. In the case of HCMMA derivatives, the OD product consisted of less wrinkled surfaces than the FD one.

These results are consistent with the specific surface area values reported previously (Ferrero et al., 1999). HSMMA particles, similar in morphology, yielded close surface area values. In contrast, the other copolymers exhibited a more porous structure for FD samples, which could be related to the measurement of higher specific surface areas for these derivatives. The smoother surfaces and smaller surface areas detected for OD products might be due to the milling process carried out after drying.

Kleinebudde (1994) have also established remarkable differences between freeze-drying and oven-drying regarding MC and L-HPC pellet properties. Removing the water during the freeze-drying process leaves a skeleton of solid material so that these pellets are characterised by high porosities. Evaporation of water in an oven is accompanied by a shrinking and densification process, which leads to smaller porosities.

According to the particle shape factor (Table 1), no great differences could be detected among the different derivatives.

3.1.3. Apparent particle density

The differences in particle morphology between the FD and OD types of MMA copolymers were also apparent from density determinations (Table 1). Except for HSMMA samples, apparent particle density values were statistically ($P < 0.05$) higher for FD copolymers. Assuming that most open pores and cavities are able to helium access, these results lead to the hypothesis that FD particles (mainly FD-CSMMA) were practically open porous sponge structures, so the measured volume approximates more the solid real volume. OD particles could present partially closed pores (due to the oven drying and milling process) inaccessible to the gas that would lead to higher volumes and, hence, lower density values.

3.1.4. Flow properties

FD derivatives were characterised by a significant ($P < 0.05$) slower flow rate (Table 1) compared with OD products. Again, the smallest differences were seen for HSMMA copolymers,

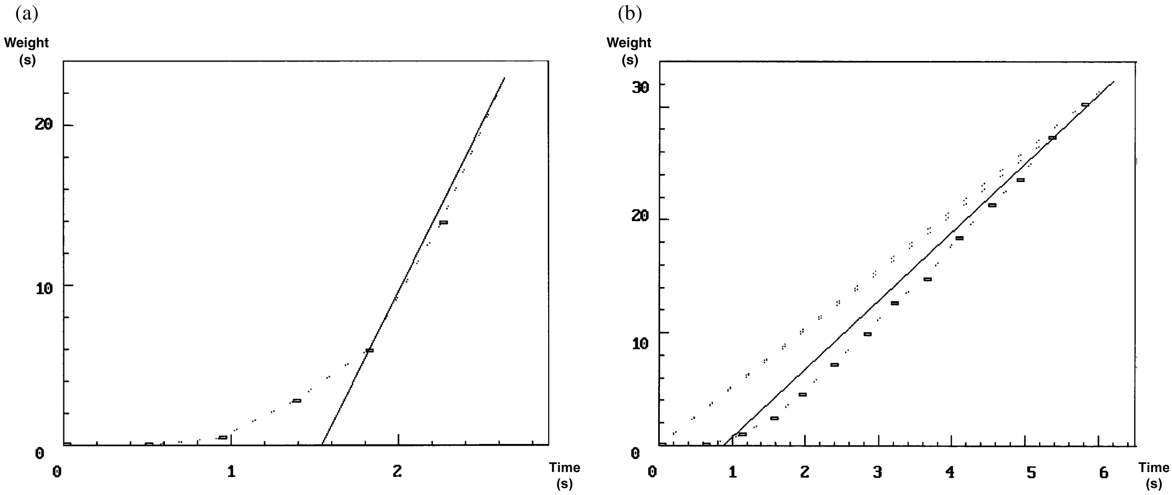

Fig. 3. Flow rate profiles: (a) two-slopes pattern (corresponding to OD-HSMMA); (b) linear pattern (corresponding to FD-CSMMA).

which could be explained by the similar particle size, shape and specific surface area values. Nevertheless, the drying method leads to important differences in CSMMA and HCMMA derivatives. So, the narrower particle size distribution (Fassihi and Kanfer, 1987), smoother texture and smaller surface areas resulted in better flow properties for OD products. Different authors (Fonner et al., 1966; Stamm, 1978) have pointed out the increase in friction and cohesion properties for rough particles.

The different behaviour is also noticed when evaluating the flow rate graphs (Fig. 3). OD derivatives and FD-HSMMA showed a graph with two different slopes, while FD-CSMMA and FD-HCMMA exhibited a straight line during the whole test.

Velasco et al. (1995) distinguished two phases in graphics corresponding to the flow behaviour of different mixtures. In the first phase, the powder flows slowly because it has to overcome the wall effect, the static friction and the operator delay. This fact may be aggravated by the stickiness of the material as well as its low density. In the second phase, with a higher slope, the material has overcome all the friction force from the wall and starts to flow according to its own characteristics. In our study, the two phases were evident for OD copolymers and FD-HSMMA, which could be attributed to a major static friction in these derivatives. Nevertheless, once the first phase was overcome, they flowed at higher rate than FD-CSMMA and FD-HCMMA. OD derivatives and FD-HSMMA behaviour would be typical of funnel flow while FD-CSMMA and FD-HCMMA would be near of mass flow (Muñoz-Ruiz, 1992).

3.2. Compression behaviour

Data from Heckel treatment are compiled in Table 2. From the tablet-in-die method, relative density values (D_a or total densification, 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} has been regarded as a constant describing the tendency of the material to deform elastically and was obtained from the two methods mentioned above (Paronen, 1986). The higher the mean yield pressure values (K) the smaller the tendency to deform by one or another mechanism.

The similar particle characteristics of OD-HSMMA and FD-HSMMA were in agreement with the similar densification values. The smaller D_0 for the FD product could be due to the slightly

Table 2
Typical parameters from Heckel treatment for the different copolymers 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, 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})

Copolymer	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)
OD-HSMMA	0.436 (0.008)	0.393 (0.007)	0.043 (0.009)	105.76 (4.10)	437.51 (22.29)	164.21	297.12
FD-HSMMA	0.402 (0.018)	0.337 (0.009)	0.065 (0.011)	81.14 (2.47)	445.17 (69.28)	175.72	150.75
OD-CSMMA	0.511 (0.004)	0.481 (0.005)	0.030 (0.008)	110.85 (4.07)	341.41 (76.46)	174.30	304.51
FD-CSMMA	0.427 (0.004)	0.289 (0.005)	0.138 (0.002)	146.87 (5.35)	655.34 (102.50)	149.54	8225.82
OD-HCMMA	0.576 (0.006)	0.444 (0.035)	0.132 (0.040)	90.40 (2.50)	385.14 (56.53)	213.25	156.92
FD-HCMMA	0.556 (0.009)	0.385 (0.002)	0.171 (0.009)	102.95 (5.79)	304.87 (31.42)	107.64	2362.80

[a] Correlation coefficients of tablet-in-die method: compression (0.984–0.999) and decompression (0.896–0.997) phases.
[b] Correlation coefficients of ejected-tablet method (0.887–0.999).

higher particle size (Table 1). The total deformation ability (K_d) was more marked for the FD derivative, mainly due to an increase in the elasticity (K_{et}). This behaviour could be explained by the lower densification (D_a) and plasticity (K_p) of this copolymer.

A higher D_b value was observed for FD-CSMMA compared with the OD derivative, which might be explained by the broader particle size distribution detected for the FD product (Table 1 and Fig. 1). Pospěch and Schneider (1989) have pointed out that, in powders with wide size distribution, smaller particles can be partly accommodated in the voids between larger ones. FD-CSMMA was also characterised by a smaller tendency to total deformation (K_d), mainly due to an important decrease in the elastic component (K_{et}). This event might be explained by the more porous structure of particles from this derivative (Fig. 2), as the ability to absorb deformations is higher in a porous structure.

HCMMA copolymers showed a parallel behaviour to CSMMA ones. Again, the FD sample, with a wider particle size distribution (Table 1 and Fig. 1), was characterised by larger values of D_b. This derivative was also the one less prone to elastic deformation (K_{et}).

It is worthwhile to denote that the freeze-drying process in CSMMA and HCMMA derivatives induced an increase in the densification by fragmentation and plastic deformation as well as an important decrease in the tendency to elastic expansion. The larger specific surface areas measured for these powders (Ferrero et al., 1999) would increase the contact surfaces available for the formation of bridges between particles, ensuring particle cohesion (Pontier et al., 2001). On the other hand, it has been reported (Jetzer et al., 1983) that milling will increase the resistance to deformation for a material that plastically deforms.

From the above, it can be concluded that the compressional characteristics of powdered MMA copolymers, namely, the particle packing and deformation, are related with the drying method mainly due to the particle size and particle shape changes.

3.3. Preparation of tablets

In addition to Heckel equation, various work or energy terms involved in compression have been determined to improve our understanding of compression physics. These typical compression parameters (Doelker, 1978; Järvinen and Juslin, 1981) are summarised in Table 3.

The applied pressure (P) necessary to obtain tablets with a breaking force of 70–80 N was significantly ($P < 0.05$) larger for OD derivatives. This could be attributed to a lower specific surface area (Ferrero et al., 1999) and smoother surfaces (Fig. 2) in these products, which results in a

Table 3
Main compression parameters for the different 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 net work (W_{an}), plasticity (Pl), elastic recovery (ER)

Copolymer	P (MPa)	R	F_e (N)	W_f (J)	W_e (J)	W_{an} (J)	Pl (%)	ER
OD-HSMMA	114.59 (0.97)	0.618 (0.007)	429.05 (25.53)	3.644 (0.150)	0.693 (0.139)	12.231 (0.082)	94.64 (1.00)	0.392 (0.000)
FD-HSMMA	93.82 (2.09)	0.590 (0.007)	513.56 (13.74)	3.824 (0.133)	1.303 (0.138)	10.970 (0.332)	89.38 (1.22)	0.240 (0.007)
OD-CSMMA	105.53 (0.42)	0.651 (0.006)	572.07 (14.02)	2.305 (0.037)	0.619 (0.094)	8.447 (0.262)	93.17 (1.00)	0.099 (0.008)
FD-CSMMA	63.35 (1.27)	0.514 (0.003)	554.42 (23.64)	4.643 (0.010)	0.139 (0.023)	9.889 (0.102)	98.61 (0.24)	0.000 (0.000)
OD-HCMMA	150.23 (8.78)	0.638 (0.008)	722.51 (92.79)	2.609 (0.130)	0.342 (0.175)	9.847 (0.732)	96.60 (1.76)	0.232 (0.002)
FD-HCMMA	99.52 (4.55)	0.518 (0.006)	845.10 (48.04)	3.381(0.163)	1.730 (0.163)	6.955 (0.456)	80.08 (1.35)	0.133 (0.005)

smaller binding capacity (te Wierik et al., 1996). Moreover, Heckel study (Table 2) showed higher D_b values and higher tendency for plastic deformation for FD-CSMMA and FD-HCMMA copolymers compared with the corresponding OD derivatives.

The lubrication ratio (R) values obtained (0.5–0.6) did not fulfil the requirements proposed by Bolhuis and Lerk (1973) for direct compression excipients. As the tablet thickness was very high, the forces were poorly transmitted, which leads to an increase in R values. FD derivatives showed poorer values ($P < 0.05$), which might be related to their rough surfaces (Fig. 2). The low values observed for this parameter make us think about the need of adding a lubricant when using these copolymers as tablet excipients.

The values found for the ejection force (F_e) were upper 400 N, being FD-HCMMA the copolymer with the highest value, more than 750 N, limit for direct compression excipients (Bolhuis and Lerk, 1973). No statistical ($P > 0.05$) differences were seen concerning drying method. In the case of CSMMA and HCMMA copolymers, the FD samples ($P < 0.05$) were characterised by higher values of friction work (W_f).

FD hydroxypropyl derivatives showed larger expansion work (W_e) values than the OD ones ($P < 0.05$), whereas the opposite behaviour was seen for CSMMA products. These results did not agree too much with the tendency for fast elastic deformation (K_{ef}) noticed in Heckel compression cycles (Table 2). This could be attributed to the different measuring conditions: K_{ef} values (with high S.D.) are obtained from a linear phase of Heckel compression cycles (Paronen, 1986) while the expansion work takes into account the whole process of elastic expansion during decompression.

In contrast, the elastic recovery (ER) values (Armstrong and Haines-Nutt, 1972) were statistically ($P < 0.05$) higher for OD copolymers, in accordance to the tendency to total elastic deformation (K_{et}) (Table 2) described earlier. It is worthwhile to denote the absence of elastic recovery for FD-CSMMA. The flat surfaces observed for OD materials could diminish the interparticulate bonding, resulting in larger elastic recoveries (Garekani et al., 1999).

FD hydroxypropyl derivatives were also characterised by smaller apparent net work (W_{an}) and plasticity (% Pl) values and the opposite behaviour was detected for CSMMA products. Again, no correlation between these values and Heckel ones (K_p) (Table 2) could be seen for the conditions under study. In this sense, Nokhodchi et al. (1995) have pointed out that mean yield pressure values accounts for plasticity behaviour while plastic energy also takes into account differences in particle interactions, i.e. the number of contact points.

3.4. Standard physical test of tablets

Results from the physical testing of tablets obtained from the different copolymers are compiled in Table 4.

All tablets fulfilled the guidelines specified in European Pharmacopeia (1997) related to weight uniformity test. Tablet weight was between 489 and 501 mg and the R.S.D. was near 1, except for

Table 4
Tablet test results for the different copolymers: average weight and R.S.D., thickness, friability (F), disintegration time (t_d)

Copolymer	Average weight (mg)	Thickness (mm)	F (%)	t_d (min)
OD-HSMMA	501 (6), R.S.D. = 1.12%	4.666 (0.004)	1.93	> 30
FD-HSMMA	494 (13), R.S.D. = 2.55%	4.771 (0.015)	1.38	> 30
OD-CSMMA	497 (5), R.S.D. = 1.02%	4.561 (0.007)	2.85	> 30
FD-CSMMA	493 (11), R.S.D. = 2.15%	5.337 (0.009)	1.24	> 30
OD-HCMMA	493 (6), R.S.D. = 1.13%	4.276 (0.028)	2.27	> 30[a]
FD-HCMMA	489 (5), R.S.D. = 1.08%	4.465 (0.007)	1.44	> 30

[a] Tablets manufactured from the different copolymers remain nearly intact after 30 min, except those obtained from OD-HCMMA.

FD-HSMMA and FD-CSMMA. In spite of the flow data obtained (Table 1), tablets from the different copolymers showed a good weight reproducibility. No actual correlation could be seen between this parameter and flow properties, in accordance to the results found by Doelker (1993), for several types of microcrystalline celluloses.

The tablet thickness varied between 4 and 5 mm, being FD products the ones with higher values. This might be related to a more porous structure in these tablets.

The breaking force test (European Pharmacopeia, 1997) confirmed the values of 70–80 N for all tablets.

Although friability values, in all cases, were higher than 1% (European Pharmacopeia, 1997), FD copolymers resulted in tablets with lower friability. The rough texture of FD derivatives would be associated to higher binding capacity and, in consequence, lower friability.

All tablets showed disintegration times larger than 30 min. Tablets remained nearly intact after the test, although some attrition could be seen for OD-HCMMA tablets.

3.5. Mercury porosimetry measurements

In order to evaluate the microstructure of the matrices, their pore size distribution was measured by mercury intrusion–extrusion porosimetry.

Tablets compacted from FD copolymers were characterised by higher porosities and mean pore radius than those obtained from OD derivatives (Table 5). The smallest differences were seen for HSMMA derivatives, OD-HCMMA tablets were the least porous and FD-CSMMA were the most porous ones, which could be in agreement with their smallest and largest thickness, respectively (Table 4).

The higher intraparticle porous structure observed for particles from FD products (Fig. 2) could contribute to the larger porosities detected now in the tablets. The present results are consistent with the elastic recovery values (Table 3). The higher porous structure of tablets from FD derivatives would easily absorb deformations, leading to a reduction in elastic expansion.

According to IUPAC definitions, pores with a diameter between 40 and 1000 Å are mesopores and pores larger than 1000 Å are macropores (Juppo and Yliruusi, 1994). From the mean pore radius data obtained, the systems under study would contain mesopores, except the tablets from HSMMA, with macropores.

Several workers (Rootare and Nyce, 1971; Doelker, 1993) have reported reasonably good agreements between surface area determinations from mercury porosimetry and BET surface areas. A linear relationship could be distinguished (Fig. 4), in our case, between total surface area by mercury porosimetry (for the tablet) and specific surface area by nitrogen adsorption (for the powder). In spite of the limitations derived from applying the Washburn equation, which is based on cylindrical pore assumption (Ridgway et al., 1997), the relationship observed might show the

Table 5
Parameters characterising the porous structure of MMA polymeric matrices (calculated by mercury intrusion–extrusion porosimetry)

Copolymer	Total surface area (m^2/g)	Porosity (%)	Mean pore radius (Δ)	Median pore radius (Å)
OD-HSMMA	11.681 (0.290)	32.2 (0.6)[a]	597.0 (6.8)	12 050 (98)
FD-HSMMA	12.497 (0.219)	34.3 (0.7)[a]	614.6 (32.4)	9122 (330)
OD-CSMMA	17.514 (0.082)	24.8 (0.1)[b]	292.4 (1.3)	2927 (85)
FD-CSMMA	22.792 (0.546)	41.3 (2.1)[b]	438.5 (35.8)	2125 (470)
OD-HCMMA	13.090 (0.460)	14.6 (0.3)[c]	208.3 (5.1)	7731 (158)
FD-HCMMA	15.211 (0.020)	23.1 (1.0)[c]	291.9 (11.3)	7455 (1923)

[a] Unimodal distribution.
[b] Bimodal distribution.
[c] Intermediate behaviour.

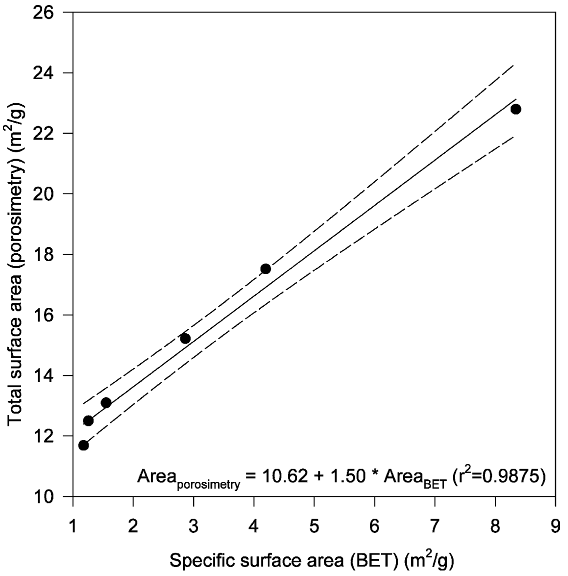

Fig. 4. Correlation between total surface area for the tablet (by mercury porosimetry) and specific surface area for the powder (by nitrogen adsorption).

contribution of two factors. The constant value of 11 m^2/g would be related to the interparticle porous structure, as all tablets have been prepared with the same breaking force (Nyström et al., 1993) and the cylindrical pore model is assumed. The second factor might be associated to the intraparticle porous structure and, therefore, is a function of the BET specific surface area. The prevalence of the interparticle area over the surrounding and intraparticle area yielded higher values for mercury porosimetry. Ciftcioglu et al. (1988) also observed higher surface area values by mercury porosimetry compared with BET measurements when evaluating compacts from ordered spheres.

The pore size distribution profiles (Fig. 5) showed a different behaviour for the copolymers under study. HSMMA derivatives showed a unimodal profile whereas CSMMA leaded to a bimodal pore size distribution and an intermediate behaviour could be found for HCMMA products. Carli et al. (1984) have also detected unimodal distributions for matrices prepared from acrylic polymers (Eudragit®). On the other hand, Juppo and Yliruusi (1994) observed a bimodal distribution for manitol granules and a unimodal one for glucose granules.

It can be concluded that pore size profiles depend basically on the chemical nature of copolymers, but drying method also modifies the total porosity and surface area values (Table 5). Although the tendency is the same for both parameters (higher values for FD products), there was no global correlation between them, which could be attributed to geometric factors that affect surface area measurements. So, HSMMA tablets would be characterised by macropores, which could result in higher median pore radius and smaller surface area values. For HCMMA tablets, the contribution of smaller pores shifted the median pore radius to lower values and increased the surface area. Finally, CSMMA tablets showed the highest contribution of smaller pores (the surface area increased and the median pore radius diminished) and the bimodal behaviour was clear.

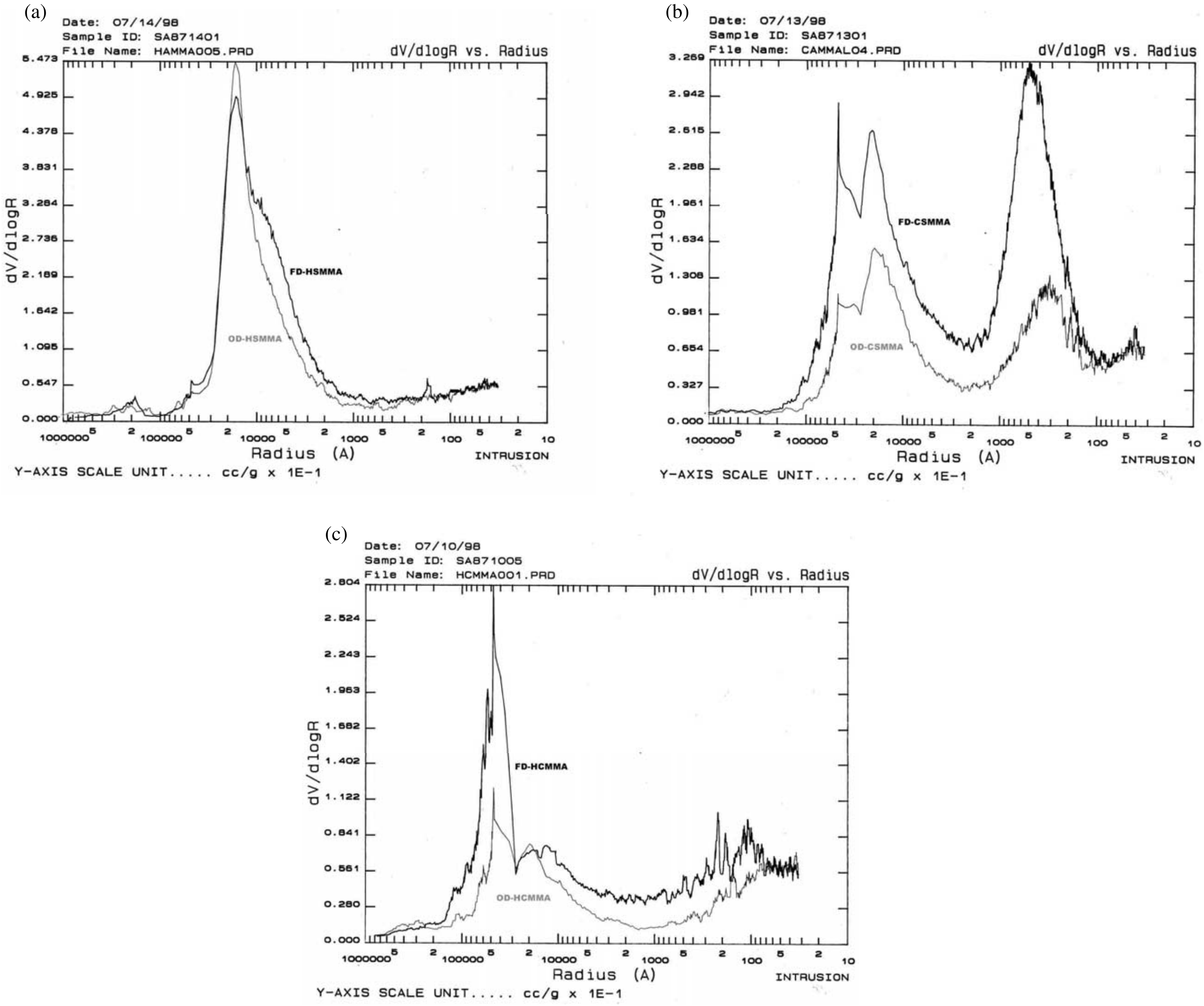

Fig. 5. Pore size distribution profiles of matrices of MMA copolymers: (a) HSMMA derivatives; (b) CSMMA derivatives; (c) HCMMA derivatives.

4. Conclusions

For MMA copolymers reported herein, this study verified that the carbohydrate nature and the drying process modify the physico-mechanical characteristics of the copolymer particles and the microstructural properties of tablets prepared thereof.

MMA copolymers have been extensively characterised, highlighting important differences in particle size range, appearance, surface area, apparent particle density, flow properties, compression behaviour and porosity.

In general, OD products consisted of smaller particles with rather regular shapes and smooth surfaces. In contrast, FD derivatives, mainly CSMMA and HCMMA ones, could be considered as larger aggregates with rough surfaces. The differences in particle morphology leaded to higher apparent particle density values and slower flow rates for FD materials.

Useful conclusions from the deformation properties of the compared materials were possible to make using Heckel function. From the data, it was clear that most materials showed a complex compression behaviour and could not simply be labelled as plastically deforming or brittle (undergoing fragmentation). The greater compactibility potentials of FD-CSMMA and FD-HCMMA, compared with the OD derivatives, could be the result of higher powder specific surface areas, larger plasticity and smaller elasticity values.

Finally, the method and conditions of drying also affected both interparticle and intraparticle pore structure, with higher values of porosity and mean pore radius for tablets prepared from FD products. The pore size distribution profile (unimodal, bimodal or intermediate behaviour) was clearly dependent on the carbohydrate nature and it was suggested that the tablet surface area was a function of the powder surface area and the pressure applied to the tablet.

For future studies, it would be interesting to correlate compaction properties and porous structure with dissolution rate data to verify if the copolymers most suited by their compression properties give the desired dissolution rate profiles.

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