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Research paper

Influence of moisture content on the mechanical properties of methyl methacrylate–starch copolymers

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Abstract

The water vapour sorption–desorption behaviour of graft copolymers (hydroxypropylstarch–methyl methacrylate -HSMMA- and carboxymethylstarch–methyl methacrylate -CSMMA-) synthetised by free-radical polymerisation and alternatively dried by oven (OD) or freeze-drying (FD) techniques was investigated in a previous paper. The aim of the present study was to analyse the influence of the amount and distribution of water molecules on the flow and compaction characteristics of this family of methyl methacrylate–starch copolymers. Products were stored at constant temperature (25 °C) and different relative humidity conditions (RH). Flow properties of the powdered materials were evaluated using glass and stainless-steel funnels and the densification behaviour was studied in detail by means of Heckel treatment and compression parameters. Results revealed that the storage at 25–50% RH was the optimum condition relating flowability for HSMMA and OD-CSMMA copolymers. At higher RH values, the flow characteristics worsened, due to an increment in cohesive forces. Compaction experiments showed that the 25–50% RH range improved also the compression performance of the copolymers, due to increasing powder compressibility and reduced compact relaxation. Under these circumstances, absorbed water might act as plasticiser and adsorbed water as lubricant.

Keywords: Methyl methacrylate–starch copolymers; Flow properties; Heckel analysis; Compression behaviour; Moisture content

1. Introduction

Pharmaceutical powders generally show certain residual moisture, originated during their elaboration and/or by exposition at environmental humidity conditions. In this situation, the presence of water molecules may promote deep changes in their technological properties that will depend on the water amount and distribution of water molecules in the solid.

In this regard, internally absorbed water promotes an increase in polymer chains mobility, which is known as plasticising effect [1–5]. This phenomenon should negatively affect powder flowability because of the increase in both cohesive and adhesive particle forces but, on the other hand, should have a positive effect on particles consolidation under compression.

In case of externally adsorbed water, the effect on technological parameters is clearly influenced by its amount, so lower percentages of adsorbed water onto the particles might have a very positive effect on both powder flowability and compression because of its lubricating effect which improves the particle slippage by elimination of particle surface microirregularities, electrostatic charges, etc. [2,6]. However, if the adsorbed water content increases, the formation of agglomerates because of the presence of liquid bridges could clearly worsen the flow properties of the solid. Concerning compression, although this increase in cohesion could promote the formation of interparticulate unions under pressure, the surfacial contaminant effect that adsorbed water shows at this condition [1,7] should

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overcome this phenomenon, leading to a global negative effect of an excess of adsorbed water onto the particles. Finally, if the presence of absorbed or adsorbed water is excessively high, its hydrodynamic effect should significantly limit the particles compression ability.

Among the current approaches in the development of new polymeric systems, the synthesis of graft copolymers is an easy method for modifying the structure of natural polymers [8]. Hydrophobic and hydrophilic components can be combined in order to diminish the important hygroscopic character of some natural products such as starch, improving their technological properties. In this sense, a new generation of copolymers combining semi-synthetic (starch derivatives) and synthetic (methyl methacrylate) polymers have been synthetised by free-radical polymerisation. The products obtained (hydroxypropylstarch–methyl methacrylate, HSMMA and carboxymethylstarch–methyl methacrylate, CSMMA) were alternatively dried by two different methods: drying in a vacuum oven (6.67–13.33 hPa) at 50 °C until constant weight (OD copolymers) or freeze drying (freezing process at −20 °C for 24 h and sublimation process at 0.13 hPa and −50 °C) until a powdered product was obtained (FD copolymers) [9]. These polymers were thoroughly characterised at room conditions and their potential value as direct compression excipients for controlled-release matrices was assessed [10,11]. Both copolymer composition and drying method used were demonstrated to have an important influence on copolymer properties. However, knowing the effect that moisture content may have on the technological parameters, a complete characterisation of these excipients under different humidity conditions is necessary in order to establish the best storage conditions.

With this purpose, the water vapour sorption and desorption behaviour of these copolymers was investigated, compared with the original carbohydrates, in order to identify the water uptake mechanisms and determine the effect of the hydrophobic component and the drying method used on the water–copolymer interaction. Some mathematical models broadly applied in the characterisation of solids–water interactions such as Guggenheim–Anderson–deBoer (GAB) and Young–Nelson models were used. Results demonstrated that the presence of a high percentage of acrylic component grafted limited the direct hydration of the carbohydrate chains in HSMMA products; thus, the water molecules were absorbed into the material by water–water interactions, promoting its plasticising effect. However, CSMMA derivatives adsorbed more water molecules directly onto the hydrophilic sites, due to their higher hydrophilicity and also to the fact that the carbohydrate backbone structure was altered less than in case of HSMMA [12].

The aim of the present study was to analyse the influence of the amount and distribution of water on the mechanical properties of these copolymers, in order to establish the best storage conditions for these products. Flow rate measurements and Heckel equation were selected to evaluate, respectively, the flowability and compression performance of these copolymers stored under different RH conditions. The results are discussed taking into account the role of the carbohydrate nature and the drying method variables.

2. Materials and methods

2.1. Materials

Copolymers (batches SS02) were prepared by free-radical polymerisation of methyl methacrylate (MMA) with hydroxypropylstarch (HS) – Perfectamyl, Avebe, Holland or carboxymethylstarch (CS) – Quicksolan, Avebe, Holland. The products obtained (hydroxypropylstarch–methyl methacrylate, HSMMA and carboxymethylstarch–methyl methacrylate, CSMMA) were either dried in a vacuum oven (OD copolymers) or freeze-dried (FD copolymers) [9]. OD-CSMMA was crushed in a knives mill (Retsch, Haan, Germany) to obtain powdery samples. Sieve fractions of 25–500 μm were selected for all copolymers.

2.2. Methods

2.2.1. Samples preparation

The copolymers were stored in vacuum desiccators using silica-gel as desiccant to obtain products dried to constant weight. The materials were then transferred to room-temperature (25 °C) desiccators with a series of relative humidities (25%, 50%, 75%, and 100%) obtained with sulphuric acid solutions [12]. The samples were regularly weighed on an analytical balance (Mettler Toledo LJ16, Zürich, Switzerland) until constant weight was reached. The equilibrium moisture content was determined on a dry weight basis of the material and the results are shown as mean value of three replicates.

2.2.2. Powder and particle characterisation

2.2.2.1. Scanning electron microscopy (SEM). The stored 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 examined using a scanning electron microscope (Philips XL-30, Eidhoven, Holland). Microphotographs were obtained at a magnification appropriate for particle size.

2.2.2.2. Apparent particle density. The apparent particle density of powders equilibrated at the different RHs was determined, in triplicate, by means of an air comparison pycnometer (Quantachrome SPY-3, Boyton Beach, FL, USA), using helium as inert gas. The volume occupied by the material was directly determined without degassing the sample. By this procedure, changes in moisture content of the material during the measurement procedure were minimised [13].

2.2.2.3. Flow properties. An automated flowmeter system developed by Muñoz-Ruiz and Jiménez-Castellanos [14] was used to estimate the flow rate of the different samples. Standard funnels as described in European Pharmacopeia [18] were selected as vessels: a glass funnel with an internal diameter of 10 mm and an angle of 30° with respect to the vertical and a stainless-steel funnel with a semiangle of 20° and hole sizes of 5, 10, 15 and 20 mm. Weight data were acquired by means of a balance (Mettler LJ16, Zürich, Switzerland) connected to a personal computer, using adequate software. Results are shown as mean value (g/s) of three replicates.

2.2.3. Compression behaviour

To allow direct comparison of all copolymers at each RH, the amount of material required to produce a 3-mm thick compact at theoretical zero porosity was calculated from the apparent particle density values. The quantity of powder (mg) was accurately weighed (Mettler LJ16 balance, Zürich, Switzerland) and manually poured into the die. Tablets were prepared using an instrumented [15] single-punch tablet machine (Bonals AMT 300, Barcelona, Spain) with 12 mm flat-faced punches at a speed of 30 cycles/min. Powders were compressed at 25, 50, 100, 150, 200, and 300 MPa of maximum 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 [16,17], using both 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 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).

2.2.4. Preparation of tablets

The copolymers stored at the different RHs were compacted into tablets employing the tablet machine described previously. The powders were manually fed into the die (12 mm) to obtain flat-faced compacts of 500 mg weight at a fixed crushing force (70–80 N). No additives were included in order to get intrinsic information of the polymeric material itself. Compression data were collected from four tableting cycles.

2.2.5. Standard physical test of tablets

The physical testing of tablets was performed after a relaxation period of at least 24 h stored at the same RH conditions than powders. The tablet average weight, the standard deviation (S.D.) and relative standard deviation (R.S.D.) were obtained from 20 individually weighed (Mettler LJ16 balance, Zürich, Switzerland) tablets according to European Pharmacopeia [18].

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

The resistance to crushing [18] of 10 tablets was determined by diametral loading with a texture analyser (TA-XT2i Stable Micro Systems, Surrey, UK).

Tablet friability [18] 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 [18] 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.

2.2.6. Statistical analysis

Apparent particle density and flow rate data were statistically analysed by one-way analysis of variance (ANOVA) using the SPSS program version 10. Post-ANOVA 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. Samples preparation

Moisture content of equilibrated samples at each RH level is compiled in Table 1 and varied between 1% and 20%. CSMMA products showed higher water uptake than HSMMA ones, which might be related with the higher hydrophilicity of the former [12]. With regard to drying methods, a slightly higher water uptake capacity was observed for OD products compared with FD ones. According to Bravo-Osuna et al. [12], almost all water molecules present in HSMMA copolymers were absorbed into the particles and only a few percentage formed solid–water bindings (monolayer adsorbed water), detecting a practical absence of multilayer adsorbed water. On the other hand, CSMMA showed both absorbed and adsorbed water, being the multilayer adsorbed water especially important at RH $\geqslant$ 75%.

3.2. Powder and particle characterisation

3.2.1. Scanning electron microscopy (SEM)

The microphotographs obtained (Fig. 1) illustrate the differences in particle shape and surface texture previously reported by Ferrero and Jiménez-Castellanos [10]. While OD-HSMMA and FD-HSMMA copolymers showed round and lobe particles without important differences

Table 1
Equilibrium moisture content (%) of the copolymers at different relative humidities (RH)

RH (%)	OD-HSMMA	FD-HSMMA	OD-CSMMA	FD-CSMMA
0	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
25	1.25 (0.02)	1.28 (0.03)	2.30 (0.01)	2.03 (0.03)
50	2.46 (0.03)	2.19 (0.04)	4.66 (0.02)	3.86 (0.03)
75	6.94 (0.05)	5.96 (0.05)	9.14 (0.05)	7.63 (0.05)
100	15.83 (0.06)	14.39 (0.04)	19.60 (0.04)	17.23 (0.06)

Values in brackets represent the standard deviation ($n = 3$).

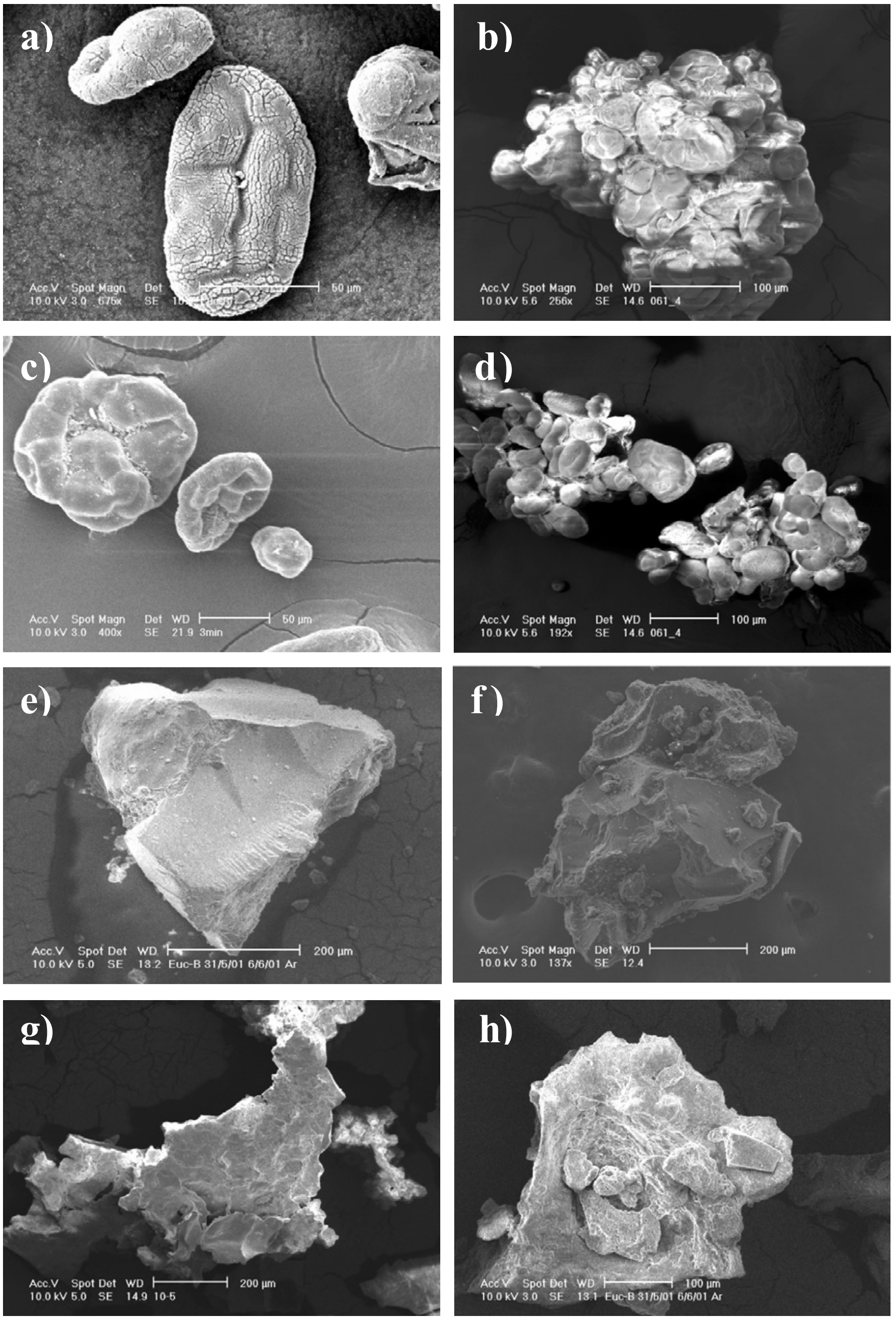

Fig. 1. SEM microphotographs corresponding to: OD-HSMMA 0% RH (a), OD-HSMMA 100% RH (b), FD-HSMMA 0% RH (c), FD-HSMMA 100% RH (d), OD-CSMMA 0% RH (e), OD-CSMMA 100% RH (f), FD-CSMMA 0% RH (g), and FD-CSMMA 100% RH (h).

between them, the milling necessary for OD-CSMMA particles created smooth faces, in contrast to the spongy structure of FD-CSMMA [10]. At macroscopic level all copolymers seemed to form aggregates at high levels of RH due to the water cohesive effect. The electron microscopic observations revealed that the aggregation was particularly significant for HSMMA copolymers (Fig. 1).

3.2.2. Apparent particle density

As can be observed in Table 2, the apparent particle density decreased with the increased moisture content. The statistical tests carried out showed a gradual change in OD-HSMMA, FD-HSMMA and OD-CSMMA products whereas, for FD-CSMMA ones, significant differences ($P < 0.05$) were found only at 100% RH.

Other amorphous products have also exhibited this relationship between apparent particle density and moisture content [13] as consequence of their swelling nature. However, this phenomenon was not detected in the copolymers under study (Fig. 1), so there may be another reason for this behaviour. In this sense, the presence of water in the particles might contribute to a decrease in the apparent particle density, as might be expected according to the density value (1 g/cm^3) of pure water. In addition, the particle aggregation observed with the RH (Fig. 1) could promote the creation of internal cavities inaccessible for helium, which would lead to higher volumes and hence, lower density values. The less pronounced effect of RH on FD-CSMMA samples would become consistent with this idea, revealing significant changes only in presence of an excess of adsorbed water which might not be stored in its porous structure and hence would increase particle cohesion [6,19].

3.2.3. Flow properties

The presence of water in the copolymers promoted significant changes in their flow capacity through the different funnels used.

When OD-HSMMA, FD-HSMMA and OD-CSMMA samples flowed through the glass funnel (Fig. 2), their flow rate was higher than 10 g/s, indicative of free flow [20]. Moreover, a rise in flow rate was observed from 0% to 25% RH ($P < 0.05$), especially for OD-HSMMA samples. According to Young–Nelson model results of water distribution in the copolymers [12], water in these products at 25% RH was only necessary to form a monolayer of adsorbed water, which might reduce the electrostatic charges that typically appear in small particles in dry conditions [19,21]. At RH > 25%, the cohesive forces increase worsened the flow behaviour ($P < 0.05$). The presence of absorbed water in HSMMA copolymers [12] would have a plasticising effect causing the particle deformation [22] and therefore improving the contact area [2,13] and the particle cohesion. In case of OD-CSMMA, absorbed and adsorbed water [12] may be the cause of the increase in cohesion. According to Nokhodchi et al. [23], adsorbed water could create liquid bridges between particles (pendular bonds), so that the surfacial tension and the negative capillary pressure in these points would cause an increase in cohesiveness.

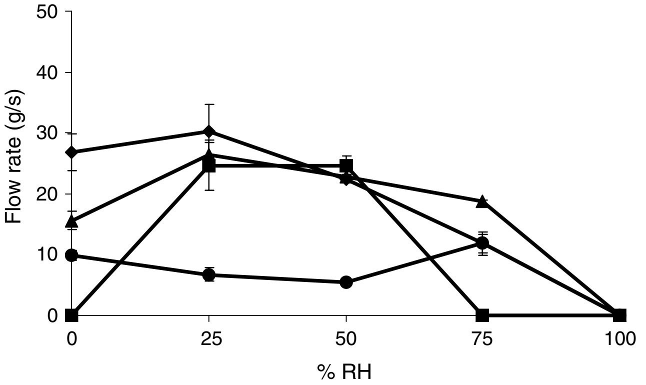

Fig. 2. Flow rate (g/s) vs relative humidity percentage (RH) of OD-HSMMA (■), FD-HSMMA (▲), OD-CSMMA (◆), FD-CSMMA (●) using the glass funnel. Error bars represent the standard deviation.

It is interesting to point out again the more independent behaviour with RH observed for FD-CSMMA samples, as moisture entered the intraparticulate voids and did not influence the interparticulate forces by formation of liquid bridges [6]. The effect of water was only significant at 75% RH ($P < 0.05$), where externally adsorbed water might have a lubricating effect, smoothing out the surface cracks and irregularities [23]. This copolymer offered poor flow characteristics throughout the range of RH, behaviour consistent with the broader particle size distribution and the rough texture observed for this product [10].

The flowability was zero for all copolymers at 100% RH and also for OD-HSMMA at 75% RH (Fig. 2). At these

Table 2
Appparent particle density values (g/cm^3) for the copolymers stored at different RHs

RH (%)	OD-HSMMA	FD-HSMMA	OD-CSMMA	FD-CSMMA
0	1.277 (0.092)	1.240 (0.062)	1.307 (0.034)	1.227 (0.038)
25	1.237 (0.022)	1.209 (0.041)	1.261 (0.020)	1.199 (0.036)
50	1.200 (0.023)	1.179 (0.031)	1.224 (0.046)	1.186 (0.036)
75	1.180 (0.027)	1.157 (0.015)	1.199 (0.020)	1.181 (0.017)
100	1.100 (0.031)	1.080 (0.038)	1.101 (0.062)	1.072 (0.049)

Values in brackets represent the standard deviation ($n = 3$).

conditions, cohesive forces were more important than gravity ones, as was observed by Roe et al. [24] for starch products at RH higher than 80%.

In the best flow conditions (25% RH for OD-HSMMA, FD-HSMMA and OD-CSMMA, 75% RH for FD-CSMMA) there were no great differences related with the drying method in the flow rate of HSMMA products, according to their similar particle size and shape [10]. However, for CSMMA copolymers, the narrower particle size distribution and smoother texture of the OD derivative [10] led to a better flow behaviour compared with its homologous FD.

The flow rate data through the stainless-steel funnel are displayed in Fig. 3. As can be expected, a rise in flow rate was observed with the increase in the funnel diameter. All products were free-flowing (flow rate higher than 10 g/s) for diameter holes $\geqslant$15 mm up to 75% RH for FD-HSMMA, OD-CSMMA and FD-CSMMA and only until 50% RH for OD-HSMMA. The influence of moisture content was more marked when using the 20 mm diameter hole, revealing again a better flow behaviour for OD-CSMMA compared with FD-CSMMA.

When comparing the flow rates for a same material through both funnels at a fixed hole diameter (10 mm), higher values were obtained for the glass funnel. This could be attributed to the different funnel design, which influences the powder discharge characteristics. The higher wall angle and the presence of the stem in the glass funnel would lead to a funnel flow, while the flow through the stainless-steel funnel would approximate mass flow. As the entire material was in motion during discharge in this last flow pattern, the flow rate was slower but the flow profile more uniform and regular than the one through the glass funnel.

3.3. Compression behaviour

Data from Heckel treatment are collected in Table 3. From the tablet-in-die method, relative density values (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 [25]. The higher the mean yield pressure values (K) the smaller the tendency to deform by one or another mechanism.

The densification due to die filling (D_0) seemed to be independent of RH for FD products while a decrease of this parameter was observed for OD-HSMMA at 75% RH and for OD-CSMMA at RH $\geqslant$ 50%. D_0 values were greater than D_b values, indicating that more densification occurred by die filling than by particle rearrangement and fragmentation. In general, CSMMA copolymers showed a higher tendency to densification by particle rearrangement and fragmentation (D_b) than HSMMA products, according to their broader particle size distribution and more irregular surface [10,17,26,27]. Moreover, no definite trend related to the effect of RH on D_b could be identified,

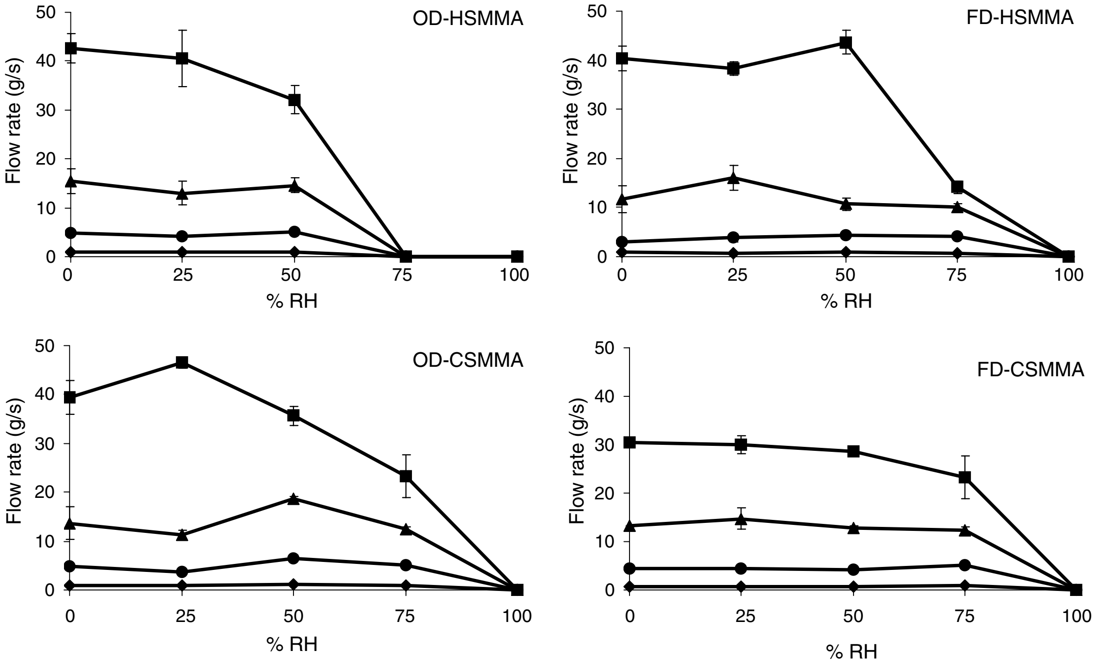

Fig. 3. Flow rate (g/s) vs relative humidity percentage (RH) of the different copolymers using stainless-steel funnels of 20 mm (■), 15 mm (▲), 10 mm (●) and 5 mm (◆) holes. Error bars represent the standard deviation.

Table 3
Typical parameters from Heckel treatment for the copolymers stored at different RHs: tablet-in-die method (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})

Copolymers	% RH	Tablet-in-die method[a]				Ejected-tablet method[b] K_p (MPa)	Both methods K_{et} (MPa)
		D_0	D_b	K_d (MPa)	K_{ef} (MPa)		
OD-HSMMA	0	0.370 (0.027)	0.069 (0.029)	112.23 (3.59)	352.50 (30.86)	146.26	482.36
	25	0.403 (0.043)	0.058 (0.045)	105.99 (3.60)	388.77 (38.88)	147.61	375.90
	50	0.443 (0.015)	0.017 (0.015)	48.69 (0.68)	16.68 (8.29)	112.30	85.96
	75	0.342 (0.040)	0.095 (0.038)	55.08 (2.16)	93.17 (21.77)	138.33	91.52
FD-HSMMA	0	0.366 (0.016)	0.073 (0.026)	116.42 (4.95)	325.16 (38.18)	110.48	[c]
	25	0.384 (0.037)	0.026 (0.035)	62.48 (2.64)	175.80 (17.12)	110.65	143.52
	50	0.355 (0.003)	0.072 (0.011)	79.06 (6.23)	83.84 (4.26)	85.69	1022.65
	75	0.368 (0.001)	0.039 (0.003)	47.63 (1.46)	34.95 (0.64)	141.66	71.77
OD-CSMMA	0	0.403 (0.029)	0.100 (0.029)	77.77 (7.28)	124.77 (10.28)	157.95	153.21
	25	0.405 (0.050)	0.115 (0.056)	82.01 (8.30)	135.22 (18.77)	140.65	196.73
	50	0.319 (0.028)	0.188 (0.044)	91.32 (4.21)	150.89 (6.45)	111.30	508.80
	75	0.296 (0.031)	0.202 (0.038)	62.06 (4.82)	222.90 (38.30)	98.58	167.51
FD-CSMMA	0	0.291 (0.013)	0.149 (0.023)	78.44 (6.28)	175.41 (25.08)	105.05	309.66
	25	0.281 (0.026)	0.176 (0.025)	87.77 (4.85)	388.22 (61.07)	81.88	[c]
	50	0.291 (0.025)	0.148 (0.029)	56.24 (2.09)	157.52 (52.04)	76.12	215.41
	75	0.293 (0.008)	0.157 (0.008)	50.10 (2.51)	244.08 (43.38)	95.70	105.17

Values in brackets represent the standard deviation ($n = 4$).

[a] Correlation coefficients of tablet-in-die method: compression (0.982–0.999) and decompression (0.895–0.996) phases.

[b] Correlation coefficients of ejected-tablet method (0.892–0.999).

[c] The K_d value was higher than the K_p value.

except for OD-CSMMA, which presented a progressive increase of this parameter, especially at RH $\geqslant$ 50%. This presumably was due to interparticulate and die wall lubrication effects which facilitated the slippage and rearrangement of particles during compaction.

For all copolymers, a general decrease in the mean yield pressure of total deformation (K_d) values was observed when increasing RH. This progressive increment of the deformation tendency from 0% to 75% RH was more evident for HSMMA derivatives. In the case of OD-HSMMA, the rise in total deformation might be due, mainly, to an increase of the elastic component (decrease of K_{et} values), especially at RH $\geqslant$ 50%, as great differences in the plastic behaviour (K_p values) were not seen. FD-HSMMA samples showed a parallel behaviour as OD-HSMMA relating plastic deformation (smaller K_p values at 50% RH), however their K_{et} values revealed a different elastic pattern, detecting an actual absence of elastic deformation at 0% and 50% RH and an increase at 25% and 75% RH. Absorbed moisture improved the deformability of the particles with an increased interparticulate bonding area as a consequence [13]. However, during the compaction process, the particle deformation could promote the leak to the surface of part of the water initially absorbed into HSMMA particles, acting as surfacial contaminant which might limit the interparticulate unions [28]. This phenomenon might be the cause of the increase in the elastic deformation at 50% and 75% RH for OD-HSMMA and at 75% RH for FD-HSMMA, and could also justify the resistance to plastic deformation detected at 75% RH for both copolymers. According to compression characteristics, the optimum storage conditions might be: RH < 50% for OD-HSMMA, to prevent the excessive elastic deformation, and RH = 50% for FD-HSMMA, where samples were found to display high plastic and limited elastic deformation.

The plasticising effect of absorbed water enhanced the plastic deformation (K_p) of OD-CSMMA samples [2,3,22,29,30], while no important differences were detected related with elastic deformation, except a reduction at 50% RH. As a result, this RH condition (50% RH) might be selected for the storage of this copolymer, as on the whole the plasto-elasticity ratio increased.

Although, once again, FD-CSMMA samples seemed to be least affected by RH in terms of plastic deformation, an increase in the elastic deformation was detected when rising the amount of water in the samples beyond 25% RH. In general, according to this compression parameter, the optimum storage condition for this copolymer might be 25% RH.

In spite of the differences found in K_p values depending on the copolymer type and RH, the dominating compression mechanism appeared to be plastic deformation, in agreement with previous studies [10]. At a given RH, the freeze-drying process also induced an increase in plastic deformation when compared with the oven-drying method.

3.4. Preparation of tablets

The influence of RH on the registered parameters during tablets elaboration was observed mainly at 75% RH (Table 4).

Table 4
Main compression parameters for the copolymers stored at different RHs: 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)

Copolymers	RH (%)	P (MPa)	R	F_e (N)	W_f (J)	W_e (J)	W_{an} (J)	Pl (%)
OD-HSMMA	0	121.79 (0.01)	0.58 (0.00)	825.35 (43.92)	3.82 (0.27)	0.55 (0.07)	11.82 (0.88)	95.58 (0.01)
	25	104.87 (0.01)	0.54 (0.02)	964.35 (147.29)	4.22 (0.67)	0.66 (0.12)	10.71 (1.68)	94.28 (0.00)
	50	105.62 (0.01)	0.55 (0.00)	883.92 (62.30)	3.99 (0.18)	0.41 (0.04)	11.04 (0.60)	96.44 (0.00)
	75	286.51 (0.03)	0.76 (0.01)	1361.64 (76.17)	7.22 (0.57)	2.16 (0.58)	17.52 (1.36)	89.02 (0.02)
FD-HSMMA	0	103.96 (0.00)	0.52 (0.01)	825.94 (50.53)	3.68 (0.13)	0.54 (0.04)	8.20 (0.36)	95.40 (0.00)
	25	79.87 (0.01)	0.57 (0.00)	655.59 (62.98)	3.19 (0.38)	0.26 (0.07)	8.73 (1.12)	97.05 (0.01)
	50	76.50 (0.00)	0.64 (0.00)	674.76 (26.36)	3.44 (0.16)	0.22 (0.04)	8.97 (0.36)	97.60 (0.00)
	75	120.78 (0.01)	0.66 (0.02)	1134.91 (146.70)	4.08 (0.26)	0.34 (0.04)	10.81 (0.63)	96.95 (0.00)
OD-CSMMA	0	123.79 (0.01)	0.62 (0.00)	822.25 (31.68)	2.95 (0.17)	0.61 (0.17)	9.84 (0.49)	94.18 (0.01)
	25	140.71 (0.01)	0.62 (0.01)	855.72 (18.77)	3.31 (0.23)	0.80 (0.07)	11.26 (0.73)	93.35 (0.00)
	50	99.09 (0.01)	0.59 (0.01)	767.67 (64.61)	3.20 (0.30)	0.37 (0.16)	8.39 (1.12)	95.77 (0.01)
	75	263.57 (0.08)	0.80 (0.03)	1693.81 (216.53)	5.13 (1.55)	2.34 (1.22)	12.89 (5.53)	84.66 (0.01)
FD-CSMMA	0	65.62 (0.01)	0.62 (0.03)	529.43 (71.45)	3.04 (0.47)	0.49 (0.41)	7.89 (1.15)	94.20 (0.05)
	25	63.69 (0.01)	0.79 (0.02)	202.13 (22.40)	2.01 (0.21)	1.11 (0.05)	8.10 (1.45)	87.94 (0.03)
	50	50.64 (0.01)	0.63 (0.04)	302.86 (34.16)	2.68 (0.25)	0.15 (0.06)	6.73 (0.79)	97.78 (0.01)
	75	82.72 (0.00)	0.82 (0.02)	139.72 (5.92)	1.69 (0.06)	1.05 (0.02)	6.07 (0.26)	85.29 (0.01)

Values in brackets represent the standard deviation ($n = 4$).

The maximum applied upper punch pressure (P) necessary to obtain tablets with a crushing force of 70–80 N showed a similar behaviour for all the copolymers, with a decrease at intermediate RH conditions (25–50%) and an increment, more important for OD products, at 75% RH. This behaviour would be consistent with the improvement in interparticulate unions formation found in presence of small amounts of water [1,6,13]. Moreover, Heckel analysis results (Table 3) showed an increase in plastic deformation, mainly at 50% RH, improving the compaction behaviour of dried starch products [31]. At high RH (75%), water weakened the interparticle bonding because of its surfacial contaminant behaviour [28,32]. At these conditions, an excessive adhesion over punch surfaces was detected, obtaining tablets with insufficient mechanical integrity, especially for CSMMA samples, which stored higher amount of water (Table 1). At 100% RH the presence of moisture made impossible the copolymers compaction, probably due to the hydrodynamic resistance of water in the solid, joined to the surfacial contaminant effect of adsorbed water [6,28]. As it was pointed out in the flow studies, the negative effect of an excess of adsorbed water onto the particles was noticed also in compression.

At each RH, the FD products needed less pressure requirements to achieve the specified crushing force values. These results agree with the findings of Ferrero and Jiménez-Castellanos [10] at room conditions and were explained because of the higher plastic deformation of FD copolymers.

The lubrication ratio (R), i.e., the ratio of the lower punch force to the upper punch force at maximum pressure, remained relatively constant with the RH. Only a slight improvement was detected at 75% RH, but in no case reached the value of 0.9, considered as indicative of adequate lubrication for direct compression excipients [33].

The maximum ejection force (F_e) revealed, for OD-HSMMA, FD-HSMMA and OD-CSMMA samples, a considerable increase at 75% RH, where values obtained for this parameter were clearly higher than 750 N, established as maximum limit for direct compression excipients [33]. This behaviour would show the increase in frictions between the tablet once formed and the die walls, due to the adhesion forces created in presence of an excess of moisture. FD-CSMMA samples showed a completely different behaviour, with F_e values lower than 750 N and a slightly worse value for dried samples (0% RH) because water not accumulated in the intraparticulate voids acts as a lubricant by forming a film on the surface of the particles.

The Juslin's friction work (W_f) remained almost constant in the range 0–50% RH for all the copolymers. For RH > 50% a difference between FD-CSMMA and the other three copolymers was revealed. Similarly to F_e values, the W_f parameter increased for OD-HSMMA, FD-HSMMA and OD-CSMMA at 75% RH, while FD-CSMMA showed a little decrease at this RH level, as a result of the lubricant effect of adsorbed water over the particle surface irregularities [6,34], also detected when studying the copolymer flow behaviour.

Although a clear increase of the expansion work (W_e) at 75% RH was seen for the OD products, the FD derivatives did not show a clear trend. These data could not be correlated with K_{ef} values obtained from Heckel compression cycles. This could be attributed to the different measuring conditions: K_{ef} values are obtained from a linear phase of Heckel compression cycles while W_e takes into account the whole process of elastic expansion during decompression.

The Juslin's apparent net work (W_{an}) increased at 75% RH for HSMMA copolymers, showing that the increment in W_f and/or W_e did not counteract the important work made by the upper punch to obtain tablets at the desired crushing force. CSMMA products did not show a clear tendency with RH. OD copolymers were characterised by higher W_{an} values than FD ones.

Table 5
Tablet test results for the different copolymers at each RH condition: average weight and relative standard deviation (R.S.D.), thickness and friability (*F*)

Copolymers	RH (%)	Average weight (mg)	Thickness (mm)	*F* (%)
OD-HSMMA	0	495 (5) R.S.D. = 1.0	4.654 (0.011)	2.95
	25	500 (3) R.S.D. = 0.6	4.561 (0.028)	3.04
	50	502 (9) R.S.D. = 1.9	4.583 (0.016)	2.19
	75	501 (23) R.S.D. = 4.6	4.449 (0.101)	1.14
FD-HSMMA	0	494 (11) R.S.D. = 2.1	4.966 (0.036)	2.75
	25	500 (8) R.S.D. = 1.6	4.902 (0.007)	3.25
	50	503 (9) R.S.D. = 1.8	4.787 (0.105)	1.71
	75	500 (13) R.S.D. = 2.6	4.352 (0.032)	1.17
OD-CSMMA	0	495 (8) R.S.D. = 1.5	4.441 (0.025)	1.69
	25	498 (8) R.S.D. = 1.6	4.397 (0.312)	1.14
	50	493 (6) R.S.D. = 1.1	4.155 (0.008)	0.79
	75	486 (33) R.S.D. = 6.7	3.695 (0.091)	0.80
FD-CSMMA	0	497 (9) R.S.D. = 1.8	5.048 (0.025)	2.03
	25	500 (8) R.S.D. = 1.6	5.031 (0.024)	2.52
	50	497 (9) R.S.D. = 1.7	4.647 (0.010)	1.02
	75	490 (23) R.S.D. = 4.6	3.967 (0.030)	0.40

Values in brackets represent the standard deviation.

Plasticity percentages obtained were, in general, in agreement with K_p data from the Heckel study, showing maximum values at 50% RH.

3.5. Standard physical test of tablets

Results from the physical testing of tablets obtained from the different copolymers are presented in Table 5.

The tablet average weight and the relative standard deviation for the different copolymers were in agreement with their better flow properties observed at 25–50% RH [35]. The worse flow characteristics, generally observed at 75% RH, were the cause that none of the batches fulfilled the guidelines specified in European Pharmacopeia [18].

A decrease in tablet thickness was observed with the increased moisture content due to the water plasticising effect [2,6]. FD products were characterised by higher values than OD ones, which was attributed to a more porous structure in those tablets [10]. In the same sense, a reduction in the friability percentage of tablets at RH $\geqslant$ 50% [36] was detected. The results of these two tests revealed the cohesive effect of water, which made that only OD-CSMMA at 50% and 75% RH and FD-CSMMA at 75% RH batches had friability percentages lower than 1%, as it is recommended by the European Pharmacopeia [18]. The resistance to crushing test confirmed the values of 70–80 N for all batches. Related with the disintegration study, all batches showed disintegration times larger than 30 min, remaining the tablets nearly intact after the test.

4. Conclusions

This paper has shown the relationship between the moisture content of methyl methacrylate–starch copolymers and their mechanical properties, such as flow and compression. For all copolymers, the best storage and manipulation conditions appeared to be 25–50% RH. At these conditions, an improvement in flow behaviour was observed for OD-HSMMA, FD-HSMMA and OD-CSMMA because of the lubricant effect of water. Concerning the consolidation behaviour, intermediate moisture contents were also preferable, as the plasticising effect of water promoted an improvement in the plastic consolidation mechanism combined with a nonexcessive elastic deformation component. In the case of FD-CSMMA copolymer, although no positive effect on flow or plastic deformation was achieved, the absence of elastic deformation at 25% RH made this condition also the optimum for its storage. The effect of moisture on the mechanical properties of the copolymers under study has demonstrated to be a balance between the amounts of monolayer adsorbed, internally absorbed or externally adsorbed moisture. At 25–50% RH, the absorbed water behaved as a plasticising agent and the monolayer adsorbed water as lubricant, improving the binding formation between particles during compression and decreasing the adhesion of the tablets to the die wall. Conversely, at 75% RH, the surfacial contaminant effect of multilayer adsorbed water difficult the unions formation, avoiding the tablet elaboration at 100% RH.

In summary, the technological properties of the test materials are maximised at the usual conditions of storage and manipulation, another point that guarantees the use of these products as direct compression excipients.

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