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Contribution to the study of new graft copolymer matrices for drug delivery systems. Technological study

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Abstract

Cellulose and starch derivatives have long been used for their ability to sustain the release of drugs. The use of polymer mixtures represents a potential way of achieving the required release properties. It is known that the release of a drug from a matrix system is produced by diffusion through the gel formed. The aim of this work is focused on the study of viscosity, flowability and compactibility values of polymers for drug delivery matrices. Previously synthesized graft copolymers were used: hydroxypropyl starch—methyl methacrylate (HS-MMA), carboxymethyl starch—MMA (CS-MMA) and hydroxypropyl cellulose—MMA (HC-MMA). It is known that polymers with the highest swelling capacity give highest viscosity value. HC-MMA and CS-MMA graft copolymers can be considered pseudogels because through mechanical–dynamical analysis, an intersection point between the storage modulus and the loss modulus can be seen. All the polymers fulfilled in general the requirements for good flow which will predict a good die filling during the tableting. However, L-products have the higher values for the compactibility and lubrication coefficient and the lower values for ejection and maximum upper force. Also, from the study of gel formation done with these products, we can state that L-products will probably lead to more interesting excipients to the obtaining of control release matrices.

Keywords: Graft copolymers; Methyl methacrylate; Viscosity; Flow properties; Direct compression

1. Introduction

The use of drugs incorporated in various polymer matrices to achieve controlled release dosage forms, has been the focus of increasing attention in therapeutics. A matrix is defined as a well-mixed composite of ingredients fixed into a shape by tableting or use of a hard shell-capsule. There have been utilised many products to elaborate

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sustained-release systems, depending on the drug that is going to be used (to avoid incompatibilities between the different components of the formulation) and the effect it is designed for. Cellulose and starch derivatives have long been used for their ability to sustain the release of drugs (Alderman, 1984, Visavarungroj et al., 1990). Synthetic polymers, as methacrylates, have attracted wide attention too in the controlled release of drugs due to their non toxicity and biocompatibility together with their easiness of polymerization (Sanghavi et al., 1994).

Matrix systems have the limitation that the release of the drug from the matrix device follows first-order kinetics. Consequently, a number of approaches have been made to achieve a zero-order release. The most notable among these are the swelling controlled delivery systems pioneered by Hopfenberg and Hsu (1978). The release of a drug physically dispersed in the glassy hydrogel involves the penetration of the surrounding medium into the polymer, accompanied by swelling and the transition of the polymer from a glassy to a rubbery like phase. Besides, due to pH variations throughout the gastrointestinal tract, pH sensitive hydrogels have a potential use as site specific delivery systems since they will have a pH-dependant drug release (Siegel et al., 1988).

Recently much attention has been devoted to the formulation of hydrophillic matrix tablets for drug delivery systems. Direct compression is the preferred method of manufacture to produce tablets intended for immediate or sus-tained drug release, due to the environmental issues that are making other processes less tolerable and more expensive. The election of polymers for tableting depends on the development of highly compressible and free flow powders. From an industrial point of view, new polymers must flow suitably in order to fill the tablet die adequately. By the other side, the influence exerted on drug release by the technological variables involved in the fabrication processes is well known. During the manufacture of tablets by direct compression, air molecules can be entrapped in the pores that can act as barrier to the transport of the drug, hence release would not be governed by diffusion through the pores.

The achievement of technologically acceptable formulations requires a long preformulation study. In some cases, and to improve the effectiveness of the drug release systems, excipients must be added: different types and amounts of lubricants, glidants (to obtain good flow of powders) or diluents or disintegrants (to provide too slow or too high release rate of drugs) whose presence can markedly affect the release (Vazquez et al., 1992).

The use of polymer mixtures represents a potential method to achieve the required release properties. Our recent research work is focused on this way and has dealt with the obtaining of graft copolymers on carbohydrates (Castellano et al., 1996) as a way to obtain suitable materials for matrix drug delivery systems.

To select the polymers for particular applications, it is necessary to collect data on the relationship between their structure and properties. Although there is still some debate in the literature, a thorough rheological characterization could provide assistance to predict drug release from hydrophillic matrices. When the system comes in contact with water, partial hydration of the polymer takes place resulting in the formation of an outer gel layer that decreases the drug diffusion. Also, the greater the viscosity of the gel, the more resistant the gel is to dilution and erosion. So, the viscosity of the polymer can be a controlling factor in drug dissolution (Alderman, 1984). With this aim, the polymers viscosity, loss and storage mo-dulus and swelling capacity in DMSO were studied; in order to study the suitability of these products as direct compression excipients, powders flowability and compression characteristics were studied. Besides, as it is known, these parameters will influence the drug release rate.

2. Experimental

2.1. Materials

In this study, we have used some of the graft copolymers synthesized in a previous work (Castellano et al., 1996) obtained by two different

ways: products dried in an oven, called O-product - and products dried by lyophilisation, called L-products. Graft copolymers used were: carboxymethyl starch—methyl methacrylate (CS-MMA) O and L, hydroxypropyl starch—MMA (HS-MMA) O and L and hydroxypropyl cellulose—MMA (HC-MMA) O and L.

Powders were stored under controlled temperature (30°C). All the products were passed through a 500 μm size mesh to remove excessive coarse granules.

2.2. Powders characteristics

In order to provide a better understanding of the relevance of polymer viscosity on drug release from hydrophillic matrices, the polymers were thoroughly characterized by their rheological behaviour as a function of shear rate and related with their swelling ratio in the same medium.

2.2.1. Viscosity

The viscosity of polymers were performed in a CARRI-MED viscosimeter at 37°C in DMSO (4% w/w) and fitted with a 4 cm and 1°58″00 angle stainless-steel cone-plate geometry and a gap setting of 0.5 mm. Rest time in the measuring system before running determinations was of 15 min. Samples were tested using a frequency sweep between 10 and 0.1 Hz. Mean storage modulus (G′) and loss modulus (G″) were calculated.

2.2.2. Swelling ratio

The swelling ratio (SR)(weight of retained solvent/weight of dry polymer) of products was studied in DMSO at 37°C.

2.3. Flow properties of powders

The static angle of repose (α) was measured according to the fixed funnel and free standing cone method (Train, 1958). A funnel with the end of the stem cut perpendicular to its axis of symmetry is secured with its tip 2 cm above a graph paper placed on a flat horizontal surface. Powder is carefully poured through the funnel until the apex of the cone thus formed just reaches the tip of the funnel. The mean diameter of the base of the powder cone is determined and the tangent of the angle of repose is obtained.

Compressibility on tamping (Muñoz et al., 1988), was measured with a sample of 100 g placed in a 250 ml graduated cylinder and the occupied volume (V_0) was determined. After 10 and 500 vibrations, occupied volumes were determined, V_{10} and V_{500} respectively. With these data we obtained the compressibility index (C%):

$$\%C = \frac{d_{500} - d_{10}}{d_{500}} \times 100$$

and Hausner index (HI):

$$HI = \frac{d_{500}}{d_{10}}$$

Flow rate (FR) of powders was measured by our data acquisition flowmeter system (Muñoz and Jimenez-Castellanos, 1993). The vessel used was a glass funnel. A balance with an interface connected to a personal computer (IBM PC compatible) constitute the whole system. A software program for data acquisition, graphics and calculations was used.

2.4. Compression characteristics

The compression characteristics of powders were investigated on an instrumented single punch machine (Bonals AMT 300, Barcelona, Spain) with HBM YL6 strain gauges connected to dynamic amplifiers (NEC Sanei, Tokyo, Japan) and inductive displacement transducers (HBM, Darmstadt, Germany). A quantity of powder (500 mg) was manually filled into the die (12 mm) and flat compacts were prepared at fixed crushing strength (4 Kp). To evaluate the compressional properties of the mixtures, the averages of maximum upper force (MUF), ejection force (EF), residual lower punch force (RLPF), lubrication coefficient (R), plasticity (%Pl) and compactibility (Comp) were studied.

2.5. Standard physical test of tablets

To study the variations in the compression properties, the powders were tableted in a single punch tablet machine (Bonals, Model AMT 300,

Spain) running at 30 cycles/min and equipped with a forced feeding system.

The weight of 10 tablets was determined by dusting each tablet off with a camel's hair brush and placing it on an electronic balance (Sartorius AC).

Friability (F) was determined by weighting 15 tablets after dusting, placing them in Erwerka TA (Erwerka, Heusenstam, Germany) friability tester and rotating the basket vertically at 25 rpm for 4 min. After dusting, the total remaining weight of the tablets was recorded, and the percent friability was calculated:

$$\%F = \frac{(\text{original weight} - \text{final weight})}{\text{original weight}}$$

Disintegration Time (DT) was performed at 37°C in 0.1 N HCl medium using the European Pharmacopoeia apparatus (Erwerka ZT3, Erwerka, Heusenstam, Germany).

3. Results and discussion

The choice of the polymeric excipient is of obvious importance to get the desired release profile. To this aim, a good characterization of powders is necessary. Some of the physico-chemical properties of powders: particle size, moisture uptake, density etc. were studied in a previous work (Castellano et al., 1996). So in this one, we are going to study the rheological, compressional and swelling behaviour of polymers, that may provide us with useful information concerning chain entanglements and interactions.

The viscosity measurements can be carried out in different viscosimeters, but to obtain an adequate characterization of a gel, that is to say to determine loss and storage modulus, mechanical–dynamical analysis must be done. We have chosen a Carri-Med viscosimeter because it let us realize dynamic measurements in diverse conditions. To carry out these measurements, the shear stress must be in the linear viscoelastic zone. To determine this zone, we have applied an increasing shear stress at 1 Hz frequency and 37°C. Fig. 1 shows the results obtained from HS-MMAL. It can be observed that the storage modulus (G') and the loss viscosity (η') are independent of the shear stress and the equivalent displacement ($\gamma°$) increases linearly with the shear stress. These results led us to take a fixed value of shear stress for applying to all the samples.

The flow curves of all the polymers are represented in Fig. 2. In order to study these flow curves, they should be fitted to an adequate equation: Carreau, Ostwald, Cheng-Evans etc. In this study, we have fitted our flow curves to Ostwald equation, that is often utilized to describe macromelecular solution behaviours (Opota et al., 1988):

$$\eta = m(\delta)^{n-1}$$

where m and n parameters represent the consistency index and flowability of polymers respectively. Depending on the n parameter values, the behaviour of the solution can be: Newtonian ($n = 1$), pseudoplastic ($n < 1$) or dilatant ($n > 1$) (Opota et al., 1988). In all the cases, an acceptable correlation coefficient of linear fittings, near to 0.9, was obtained. So we can say that the Ostwald model is adequate to describe the rheological behaviour of our polymers. The m and n values obtained for each polymer powders are listed in Table 1. All the polymers presented a pseudoplastic behaviour ($n < 1$). In almost all the cases, the m and n values of each pair of products are similar, being higher for the n value of O-products that leads to a lower consistency of them (less entangled polymer net

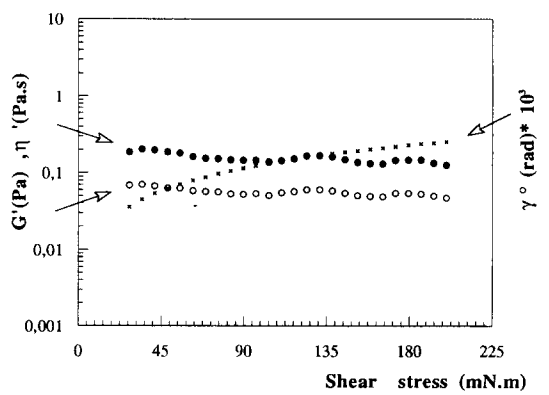

Fig. 1. Determination of the viscoelastic zone of HS-MMAL polymer where (●) is the storage modulus (G'), (○) the loss viscosity (η') and (x) the displacement equivalent ($\gamma°$).

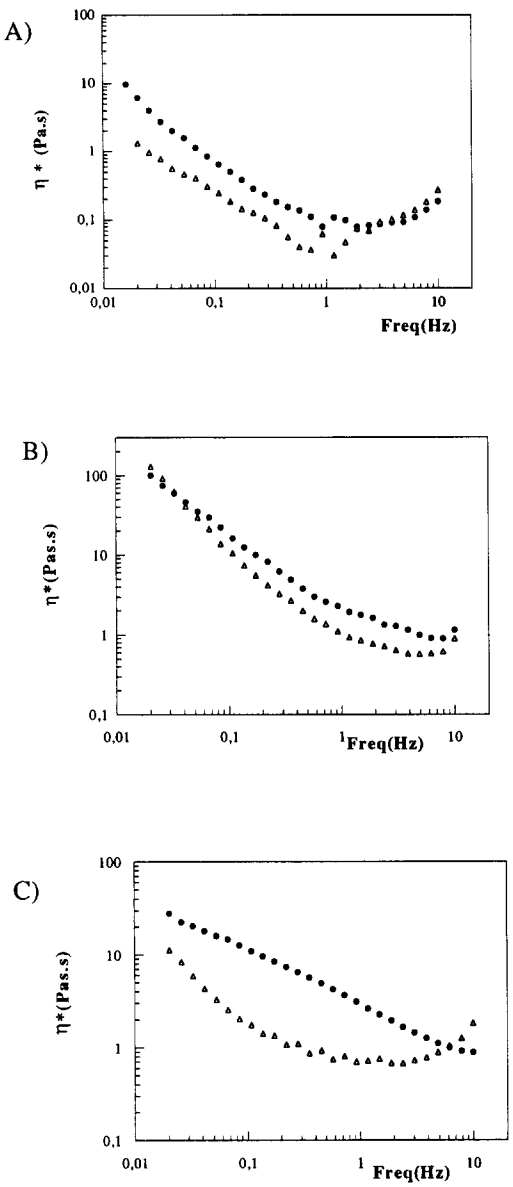

Fig. 2. Flow curves of different graft copolymers (A) HS-MMA; (B) CS-MMA; and (C) HC-MMA where (●) represents L products and (△) O products.

works (Rossi et al., 1994) with respect to L-products). This higher consistency of L gels will be reflected in a higher viscosity of gels, that is one of the requirements of polymers for drug delivery matrices (Alderman, 1984).

Table 1
Ostwald equation parameters

	m	*n*	*r*
HS-MMAO	0.049	0.141	0.994
HS-MMAL	0.085	0.128	0.982
CS-MMAO	1.163	0.074	0.992
CS-MMAL	2.066	0.032	0.996
HC-MMAO	0.563	0.446	0.967
HC-MMAL	2.909	0.417	0.999

For a better correlation between the viscosity values, we have also determined the swelling ratio of powders in DMSO, (Fig. 3). The higher values of the swelling ratio are given by L-products, as it could be predicted from the viscosity values. This fact can be explained taking into account the particle size of powders. In a previous work it was found that O products have a less wrinkled topography and lower average particle size than their corresponding L-products. So, smaller scarfaced particles can retain a less amount of solvent molecules than larger particles, so they will give lower swelling ratio values. Higher amounts of retained solvent molecules would produce higher links or interactions inside the polymer, that would lead to a higher consistency of the polymer and consequently to a higher viscosity of it.

Polymeric gels can be classified into different groups depending on the process from which the

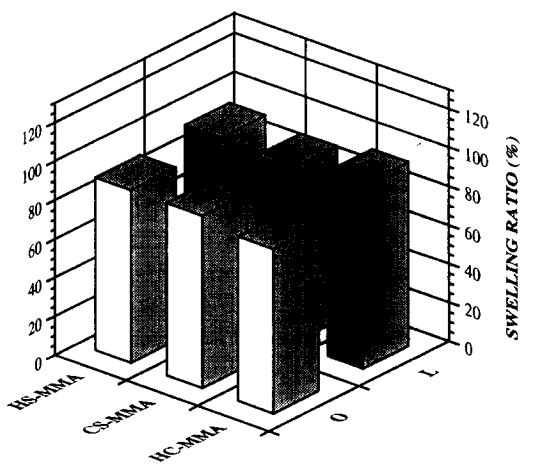

Fig. 3. Swelling ratio of different graft copolymers in DMSO at 37°C.

gel has been constituted: chemical gels (formed by covalent links), physical gels (formed by weak interactions between chains) and pseudogels (formed by pseudonetwork or entangled networks). The rheological differentiation between these networks can be carried out by mechanical–dynamical analysis. The typical behaviour of the chemical gels shows that both modulus (G′ and G″) are insensitive to the frequency increase. If G′ is higher than G″ (in HS-MMAL copolymer for example) we have a physical gel formed by physically crosslinked chains. Pseudogels are characterized by an intersection point between the storage modulus (G′) and the loss modulus (G″) at an intermediate frequency. This behaviour is observed for HC-MMA and CS-MMA products (Fig. 4), so they can be considered as pseudogels. In all graft copolymers, L-products have a higher G′ and G″ values than O-products, as could be predicted by the flow curves. A higher G′ (a measure of the resistance to elastic deformation (Mortazavi et al., 1992) will involve the formation of a stronger gel network from L products with respect to their corresponding O-products (HS-MMAO and HC-MMAO).

The aforementioned allow us to state that, all products fulfilled two of the conditions necessary for a good control of the drug release. By one side, the polymer swells quickly enough to form a gel layer and besides the viscosity of them is highly enough to decrease the release rate of the drug (Alderman, 1984). Furthermore, the greater the viscosity of the gel, the more resistant the gel is to dilution and erosion (Bonferoni et al., 1992).

Pharmaceutical industry needs to characterize flow properties of the powders that make it possible to estimate their suitability for direct compression excipients. In this work we will use some of these tests: compressibility on tamping, static angle of repose and flow rate. In the development laboratory, these tests could be used to characterize routinely bulk solids before compression. So, better optimization of flow properties can be achieved in experimental formulations.

Typical parameters of flow properties: angle of repose (α), compressibility (%C), Hausner index (HI) and flow rate (FR), are included in Table 2.

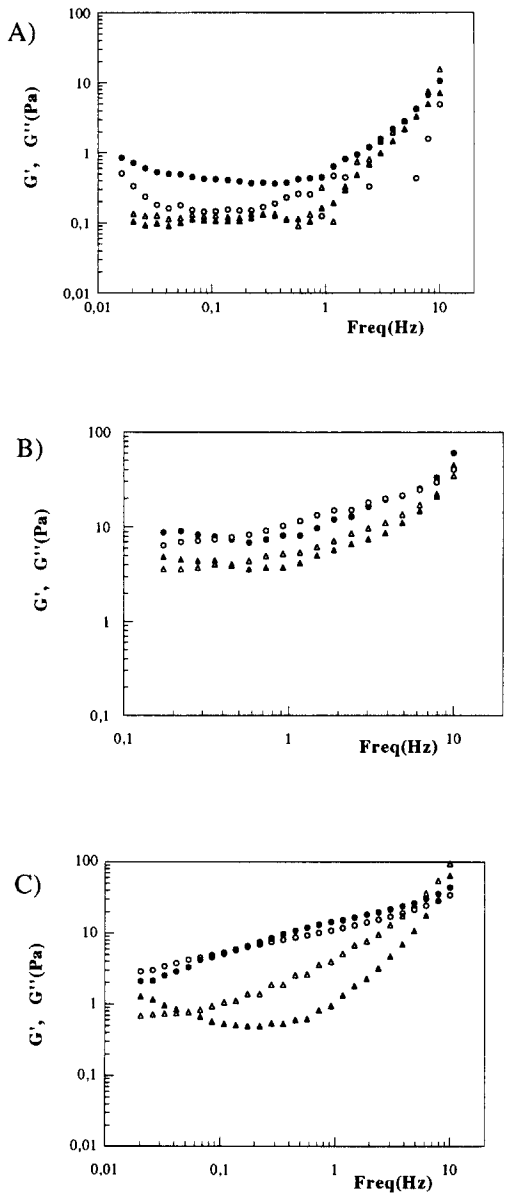

Fig. 4. The storage modulus (G′) ((●) representing L products and (▲) O products) and the loss modulus (G″) ((○) representing L products and (△) O products) of different graft copolymers (A) HS-MMA; (B) CS-MMA; and (C) HC-MMA.

The flow rate is a direct measurement of powder flowability and the most representative parameter of flowability. All polymers exhibit good flowrates because they are higher than 10 g/s (Guyot, 1978; Guyot et al., 1980; Delacourte-

Table 2
Flow properties of graft copolymer powders

	α(°)	%C	IH	FR (g/s)
HS-MMAO	38.08 ± 1.03	6.27 ± 0.53	1.06 ± 0.00	22.99 ± 6.87
HS-MMAL	39.87 ± 1.11	4.21 ± 0.60	1.04 ± 0.00	28.66 ± 4.53
CS-MMAO	38.76 ± 1.66	4.31 ± 0.55	1.04 ± 0.00	32.91 ± 3.68
CS-MMAL	41.27 ± 0.54	3.64 ± 0.02	1.04 ± 0.00	21.88 ± 1.22
HC-MMAO	34.61 ± 0.88	5.77 ± 1.12	1.06 ± 0.01	21.50 ± 20.19
HC-MMAL	39.72 ± 0.72	7.41 ± 0.00	1.08 ± 0.00	18.95 ± 0.64

Thibaut et al., 1982; Aran and Brossard, 1985). Except for HS-MMA products, L-products show lower flowrates than O-products. According to this parameter, the best flowability corresponds to CS-MMAO and the worst to HC-MMAL.

The angle of repose is considered an indirect measurement of powder flowability (Staniforth, 1988). According to the Delattre classification all the polymers except CS-MMAL are classified as free-flowing powders because the angles of repose are lower than 40°. These results are consistent with flowrate values. However, L series results do not agree with size characteristics because powders with small particles have worst flow properties and L-products have larger particles (Lerk et al., 1974). This behaviour can be explained taking into account the different morphology of the L and O particles of each graft copolymer. In a previous work (Castellano et al., 1996) it was found that L particles have a more wrinkled topography than their corresponding O particles. This is due to the crushing applied process that it is necessary to apply to the O particles in order to obtain particles of less than 500 μm; this process gives cut smooth faces that will improve the flowability even being smaller particles.

Hausner and compressibility index show the characteristic values of the packing properties. The Hausner index (Hausner, 1972), indicative of inter-particle friction, does not permit discrimination between the polymers studied. According to the classification proposed by Carr in relation to %C, indicative of aptitude of a material to diminish in volume (Carr, 1965), all polymers have excellent flow but, again, do not discriminate. However, we agree with Lubner and Ricciardiello (Lubner and Ricciardiello, 1977) who indicated that these parameters were not able to distinguish between similar materials.

To study the compressional properties of the polymers at 4 Kp the average of the next parameters are calculated: maximum upper force, ejection force, residual force at the lower punch, lubrication coefficient, plasticity and the ratio between crushing strength and net apparent work (Table 3).

To evaluate the frictional properties of the polymers, the average of the lubrication coefficient (R, maximum lower punch force over maximum upper punch force) was calculated (Doelker, 1978). Results demonstrated that none of the polymers accomplished with the requirements of direct compression excipients proposed by Bohuis and Lerk (Bohuis and Lerk, 1973) that establish that values of R must be higher than 0.9. For the above reason, all the polymers will need the addition of lubricants when formulated. In general, the highest values are found in L-products.

The maximum ejection force (maximum force exerted on the lower punch during ejection of the tablet) probably is the parameter most widely used to measure tablet friction (Sadjady et al., 1993). For our materials this parameter is in all cases higher than 200 N, with the exception of HS-MMAL that shows the best ejection properties. However, the results show that all O-products carry out the requirements proposed by Bohuis and Lerk (Bohuis and Lerk, 1973) with values lower than 750 N. Besides, L-products show lower values than O-products, in agreement with the results of the lubrication coefficient.

The residual lower punch is the force remaining in the lower punch after compression and prior ejection (Sadjady et al., 1993). In the hydroxy

Table 3
Average of maximum upper force (MUF), ejection force (EF), residual lower punch force (RLPF), lubrication coefficient (R), plasticity (PI), compactibility (Comp) of tablets compressed at 4 Kp crushing strength

	MUF (N)	EF (N)	RLPF (N)	R	PI (%)	Comp
HS-MMAO	12 839.51 ± 751.23	426.69 ± 10.06	340.06 ± 38.11	0.688 ± 0.010	95.33 ± 0.74	2.95 ± 0.16
HS-MMAL	9942.39 ± 169.19	162.50 ± 9.07	406.19 ± 12.95	0.713 ± 0.006	86.07 ± 0.62	3.99 ± 0.10
CS-MMAO	11 079.28 ± 1373.57	422.55 ± 72.45	436.97 ± 82.87	0.705 ± 0.009	90.40 ± 2.69	4.64 ± 0.81
CS-MMAL	6617.82 ± 99.40	359.40 ± 29.04	234.77 ± 9.22	0.715 ± 0.013	89.77 ± 0.57	5.50 ± 0.10
HC-MMAO	12 760.32 ± 1121.80	510.25 ± 40.46	388.23 ± 39.12	0.656 ± 0.005	92.84 ± 3.45	4.64 ± 0.38
HC-MMAL	5984.40 ± 60.61	397.14 ± 4.37	272.08 ± 11.57	0.634 ± 0.015	92.47 ± 0.47	6.13 ± 0.24

polymers, the L-products seem to have higher values or RLPF, whereas in the carboxy polymers, the L-products have lower values than O-products.

The plasticity values, calculated from the following relation (Doelker, 1978):

$$\%P1 = \frac{W_{NA}}{(W_{NA} + W_{exp})} \times 100$$

where W_{exp} is the expansion work and W_{NA} is the apparent net work, showed small discrimination, having in general the L-products with lower values of plasticity.

The compactibility, defined as the ratio between crushing strength and net apparent work, is indicative of the easiness of the elaboration tablet. Again, the higher values for this parameter are observed in L-products. These results are consistent with higher lubrication coefficient, lower ejection and lower maximum upper force.

Tablets from all polymers passed the test for weight uniformity (not more than two of the tablets differ from the average weight by more than the 5% and no tablet differs by more than 10%) (Table 4). As expected from the flow properties, the values of the coefficient of weight variation for O-products were lower than for L-products.

Tablets of polymers do not demonstrate acceptable friability (< 1%) (Mollan and Celik, 1993). For this reason, it will be necessary to elaborate them at higher crushing strength than the fixed at this work (4 Kp).

In relation to the disintegration time, all the polymers exhibited high values. These results sustain their use as control release excipients.

In conclusion, if we have to choose between L and O-products, according to viscosity, compression and friction results, L-products are better than O-products. In relation to flow properties, O-products are better. However, all the polymers fulfilled the requirements of good flowability, so it is not a critical property.

Moreover, from the study of gel formation done with these products, we can also assess that L-products will probably give rise to more interesting excipients to the obtaining of control release matrices.

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Table 4
Tablet properties

	W (mg)	CV (%)	F (%)	DT (min)
HS-MMAO	499 ± 8	1.70	3.95	> 30
HS-MMAL	500 ± 20	3.99	3.80	> 30
CS-MMAO	505 ± 6	1.22	5.53	> 30
CS-MMAL	485 ± 15	3.12	3.21	> 30
HC-MMAO	474 ± 15	0.97	2.73	22.7 ± 6.4
HC-MMAL	492 ± 5	0.99	3.30	> 30

Uniformity of weight (W), coefficient of weight variation (CV), friability (F), disintegration time (DT).

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