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# Drug release from a new family of graft copolymers of methyl methacrylate. I.

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**Abstract**

Hydrophilic matrices are an interesting option when developing an oral drug release device. In this work we have produced hydrophilic matrices tablets by direct compression. Previously graft copolymers were synthesized as an important component of the tablets: hydroxypropyl starch-methyl methacrylate (HS-MMA), carboxymethyl starch-MMA (CS-MMA) and hydroxypropyl cellulose-MMA (HC-MMA). The polymeric component was mixed with Emcompress®, stearic acid and theophylline. All the products fulfilled the requirements for good flow according to literature. L-formulations show lower values of plasticity than O-formulations. However, L-formulations exhibit higher compactibility values than O-formulations. In general, all the formulations with O-polymers show faster release of the drug at three pHs used. On the other hand, these tablets have the capacity to hydrate quickly forming a gelatinous layer, so it is necessary to achieve controlled drug release from hydrophilic matrices. In relation with the dissolution efficiency over 8 h, formulations with HS-MMAL and NaCMC show very similar results, although the release of theophylline from NaCMC tablets at different pHs was always slightly slower than HS-MMAL tablets.


*Keywords:* Oral delivery; Graft copolymers; Swelling; Methyl methacrylate; Sustained-release tablets

## 1. Introduction

The compaction of a mixture constituted by a drug and a polymer, first proposed by Higuchi (1963), is still one of the most efficient techniques to obtain oral controlled release tablets. In spite of the matrix systems offer a major advantage in the ease of fabrication and manufacture on large scale (Ventouras and Buri, 1976), release kinetics are directly influenced by formulation and

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physico-chemical factors (Flynn, 1974; Salomon et al., 1979; Chilamkurti et al., 1983; Avan and Brossard, 1985; Vázquez et al., 1992). A number of approaches to achieve zero-order release from matrix systems have been proposed. The most notable among them are the swelling controlled delivery systems, pioneered by Hopfemberg and Hsu (Shah et al., 1991).

The formulation of drugs in tablets, using hydrophilic polymers with high swelling capacities as base excipients, is of great interest in the field of controlled release. Alderman (1984) found that the release of a drug by a matrix system was produced by two simultaneous mechanisms: erosion or attrition of the outermost, least consistent gel layer and dissolution of the active principle in the liquid medium and diffusion through the gel barrier when formed. The diffusion of the drug will not only be via water-filled pores, also via the free volume between polymer chains. The incidence of the latter depends on the polymer's physical structure, its crosslinking degree, its degree of crystallinity and also on the possible solute-polymer interactions.

Accordingly, the polymer is the element in the formulation that is most responsible, by hydratation, of the diffusion of the drug and the formation of erosion-resistant gel layer. The use of polymeric mixtures represents a potential way of achieving the required release profiles. However, obtaining technologically acceptable formulations requires, in addition to the drug and the gelling agent, the presence of the other excipients, in particular fillers and lubricants, that can markedly affect release (Alderman, 1984; Vázquez et al., 1992).

The present paper describes a controlled release tablet using new different graft copolymer powders, obtained by graft copolymerization of methyl methacrylate (MMA) on different carbohydrates. In previous papers (Castellano et al., 1996a,b) we studied the reaction parameters and some powder characteristics of the synthesized copolymers. The aim of this work is focussed on knowing the efficiency of control of release and swelling, besides rheological properties and compression behavior, from a new family of graft copolymers of methyl metacrylate in formulations for direct compression matrices with theophylline as model drug.

This drug was chosen because its solubility is relatively little affected by pH in the normal physiological range (Shangraw, 1988).

## 2. Materials and methods

### 2.1. Materials

In this study, we have used some of the graft copolymers synthesized in a previous work (Castellano et al., 1996a), obtained by two different ways: products dried in an oven, called O products, and products dried by lyophilisation, called L products. Graft copolymers used are: 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. Also we have used anhydrous theophylline (batch 1201094), anhydrous dicalcium phosphate dihydrate (Emcompress®, batch 1004X) as filler, and stearic acid (Estearina L2SM®, batch 106) as lubricant.

### 2.2. Methods

Theophylline (24%) was mixed first with 25% of each polymer under study and 50% of Emcompress® for 15 min in a plastic vessel in an asymetric double-cone mixer (Retsch, Haan, Germany) at 50 rev./min$^{-1}$. After the addition of stearic acid (1%), the mixing procedure was continued for 5 min.

The mixtures were stored under controlled temperature (20°C). All mixtures were passed throughout a 500-$\mu$m size mesh to remove excessive coarse granules.

#### 2.2.1. Flow properties

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

Table 1
Flow rate ($F$) and average of maximum upper force (MUF), ejection force (EF), residual lower punch force (RLPF), lubrication coefficient (R), plasticity (Pl), and compactibility (C) of tablets (25% polymer, 24% theophylline, 50% Emcompress®, and 1% stearic acid) compressed at 4 Kp crushing strength

| Formulations with | F (g/s) | MUF (N) | EF (N) | RLPF (N) | R | Pl (%) | C |
|---|---|---|---|---|---|---|---|
| HS-MMAO | 4.73 | 14 195.02 | 391.90 | 290.42 | 0.854 | 97.18 | 5.17 |
| | (0.26) | (361.35) | (13.89) | (6.32) | (0.002) | (0.85) | (0.16) |
| HS-MMAL | 8.31 | 13 007.09 | 364.04 | 240.06 | 0.831 | 90.55 | 6.03 |
| | (0.35) | (83.07) | (20.51) | (10.32) | (0.006) | (11.06) | (0.86) |
| CS-MMAO | 8.94 | 16 980.68 | 378.90 | 250.85 | 0.839 | 91.75 | 5.50 |
| | (0.42) | (405.96) | (75.72) | (60.37) | (0.003) | (1.22) | (0.21) |
| CS-MMAL | 9.78 | 16 671.28 | 410.21 | 301.86 | 0.832 | 86.77 | 5.16 |
| | (0.60) | (444.58) | (18.20) | (6.98) | (0.011) | (1.04) | (0.18) |
| HC-MMAO | 20.82 | 19 792.38 | 241.46 | 157.46 | 0.843 | 81.86 | 4.33 |
| | (5.01) | (1095.00) | (27.79) | (15.39) | (0.002) | (2.48) | (0.19) |
| HC-MMAL | 17.69 | 7023.67 | 298.55 | 215.25 | 0.846 | 76.20 | 4.46 |
| | (7.27) | (409.56) | (29.04) | (14.15) | (0.010) | (1.43) | (0.22) |
| NaCMC | 6.25 | 9295.28 | 320.97 | 258.85 | 0.850 | 89.62 | 8.60 |
| | (0.03) | (147.80) | (6.61) | (13.43) | (0.009) | (0.43) | (0.16) |
| HS-MMAL (alone) | 28.66 | 9942.39 | 162.50 | 406.19 | 0.713 | 86.07 | 3.99 |
| | (4.53) | (169.19) | (9.07) | (12.95) | (0.006) | (0.62) | (0.10) |
| NaCMC (alone) | 1.82 | 4252.62 | 49.22 | 6.91 | 0.991 | 92.30 | 10.15 |
| | (0.11) | (12.76) | (4.73) | (2.69) | (0.000) | (1.56) | (0.03) |

*2.2.2. 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 compression 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 (C) were studied.

*2.2.3. Standard physical tests of tablets*

To study the variations in the tablet properties, the mixtures were tabletted in a single punch tablet machine (Bonals, Model AMT 300, Spain) running at 30 cycles/min and equipped with a forced feeding system.

Weight of 20 tablets was determined by dusting each tablet off with a camel's hair brush and placing it on an electronic balance (Mettler AE 50, Mettler Instrumentate, Greifensee, Switzerland).

The individual crown-to-crown for the thickness of 20 individual tablets was determined after dusting off the tablet surface, and then placing it in and parallel to the face of a micrometer (Mitutoyo, sensitivity 0–25 mm). The measurements were recorded and the sample mean and standard deviation were calculated.

Friability (F) was determined by weighting 15 tablets after dusting, placing them in an Erweka TA (Erweka, Heusenstam, Germany) friability tester and rotating the basket vertically at 25 revs./min$^{-1}$ for 4 min. After dusting, the total remaining weight of the tablets was recorded, and the percent friability was calculated.

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

Dissolution rate: dissolution profiles were obtained for six tablets of each formulation with a U.S.P. apparatus (Turugrau automatized dissolution test) and using the basket method at 50

Table 2
Standard physical parameters of tablets: uniformity of weight (mg), uniformity of thickness (mm), friability (F) and disintegration time (DT) (min)

| Formulations with | Weight | Thickness | F (%) | DT |
|---|---|---|---|---|
| HS-MMAO | 495.8 (11.0) CV: 2.23% | 3.24 (0.01) | 2.93 | 0.29 (0.07) |
| HS-MMAL | 507.5 (13.3) CV: 2.64% | 3.28 (0.01) | 1.98 | >30 |
| CS-MMAO | 486.1 (6.0) CV: 1.23% | 3.07 (0.01) | 2.74 | 15.13 (5.20) |
| CS-MMAL | 494.4 (10.3) CV: 2.08% | 3.05 (0.00) | 2.09 | >30 |
| HC-MMAO | 509.4 (6.7) CV: 1.33% | 3.22 (0.01) | 2.94 | 2.44 (0.61) |
| HC-MMAL | 496.6 (14.9) CV: 3.00% | 3.23 (0.01) | 1.94 | 2.49 (0.46) |
| NaCMC | 507.9 (5.4) CV:1.07% | 4.67 (0.01) | 2.66 | >30 |
| HS-MMAL alone | 500.0 (20.0) CV:3.99% | 3.13 (1.69) | 3.80 | >30 |
| NaCMC alone | 489.9 (6.1) CV:1.25% | 3.13 (0.00) | 3.42 | >30 |

revs./min$^{-1}$. The dissolution media were different buffer solutions prepared with HCl for acid medium (1.5) and phosphate heptahydrate, citric acid and potassium chloride (Aldrich) for the 5 and 8 pHs (Elving et al., 1956), but at same ionic strength (0.5 M). The amount of theophylline in solution was monitored continuously by spectrophometry (Diode array spectrophotometer Hewlett Packard) at 270 nm.

Swelling capacity: to study swelling capacity (%SC) of polymers we prepared tablets constituted only by our polymers at fixed crushing strength (4 Kp). Tablets were weighted in the dry form. After, the tablets were swollen in the previously mentioned dissolution buffers (1.5, 5 and 8 pHs) adjusted to a 0.5 M ionic strength. The amount of water absorbed was determined by the relation between water content in hydrated tablets with respect to the weight of dry tablets.

## 3. Results and discussion

In spite of the polymers showing good flow (Castellano et al., 1996b), the high presence of theophylline with bad flow, could explain these results (Table 1). According to this parameter, the best flowability corresponds to HC-MMAO and the worst to HS-MMAO mixtures. Except for both products of HC-MMA O and L mixtures, the mixtures with O-products show lower flowrates than the mixtures with L-products.

The compressional properties of the polymers at 4 Kp are presented in Table 1. The results show

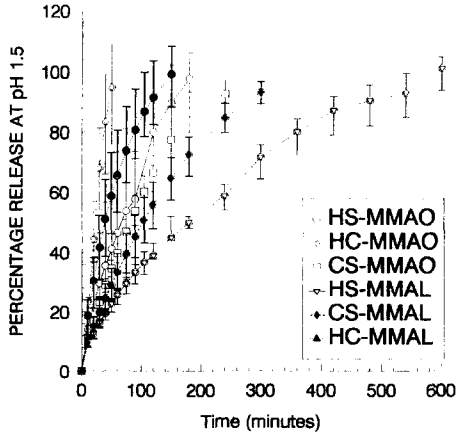


Fig. 1. The dissolution tests (mean and S.D.) for each formulations at pH 1.5

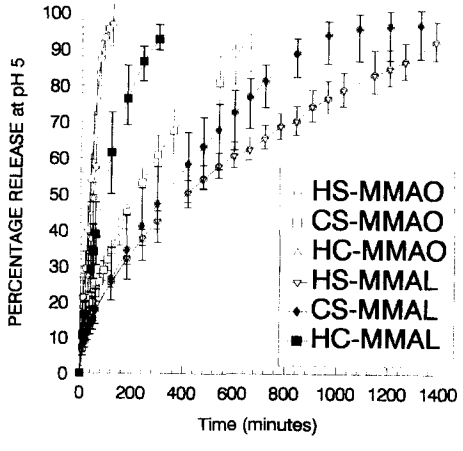


Fig. 2. The dissolution tests (mean and S.D.) for each formulations at pH 5

that, although all formulations have values for the ejection force higher than 200 Newtons, all of them fulfilled the requirements for direct compression formulations (Bolhuis and Lerk, 1973). Again, HC-MMA formulations show the lowest values. Different behavior is observed between O and L polymers in HS-MMA formulations and the others, because in the latter L mixtures have higher values of EF and residual lower punch force.

As we suggested in the polymer tablet study (Castellano et al., 1996b), the addition of a lubricant (stearic acid) improve the lubrication coefficient (Doelker, 1978), with values close to the requirements proposed by Bolhuis and Lerk (1973) (0.9).

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

$$\%Pl = \frac{W_{NA}}{W_{NA} + W_{exp}} \times 100$$

where $W_{exp}$ is the expansion work and $W_{NA}$ is the apparent net work. L formulations show lower values of plasticity than O formulations. As in rheological properties, again HC-MMA mixtures have a different behavior, with the lowest values for this parameter.

L-formulations exhibit again similar compactibility values to O-products. In general, all the formulations improve this characteristic in relation to polymer tablets (Castellano et al., 1996b) due to the addition of Emcompress® and theophylline.

Tablets from all mixtures passed the test for weight uniformity (Table 2). Unlike polymers alone (Castellano et al., 1996b), no relation can be found between flow properties and the coefficient of weight variation (Cole et al., 1974).

Even though the tablet formulations do not show acceptable friability (less than 1%) (Mollan and Celik, 1993), the addition of a 50% of a filler for direct compression (Emcompress®) diminished the values for this parameter enormously in relation with polymer tablets (Castellano et al., 1996b). In relation with disintegration time, only HS-MMAL and CS-MMAL show values higher than 30 min. The high concentration of anhydrous Emcompress® and the fixed crushing strength (4 Kp) support the results of rapid disintegration in comparison with polymer tablets (Castellano et al., 1996b), due to the effect of the hydrogen bonds formed within the polymeric granules, when they are compressed without the filler.

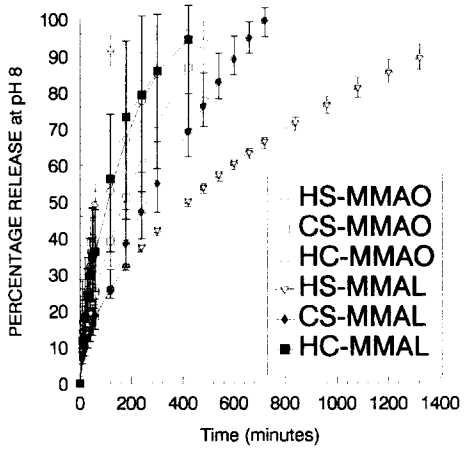


Fig. 3. The dissolution tests (mean and S.D.) for each formulations at pH 8

The dissolution tests (mean and S.D.) for each formulation at different pHs, are shown in Figs. 1–3. The curves were characterized using a model-independent parameter, the dissolution efficiency over 8 h (Khan and Rhodes, 1972) (Table 3). If we take into account that Emcompress® is an insoluble direct compression excipient that does not swell (Lemos et al., 1982) and that the solubility of theophylline is relatively littl affected by pH in the normal physiological range (Shangraw, 1988; Uko-Nne et al., 1989), the different release rates at different pHs of formulations could be attributed only to the molecular structure and nature of different polymers (Branon-Peppas and Peppas, 1989). Therefore, in a particular formulation, pH could be a critical factor in the release rates to affect also the filler (Lin and Kao, 1990).

In general, all the formulations with O-polymers show faster release of the drug at the three pHs used, although we only find remarkable differences between the HS-MMA products. Also, in general, starch derivatives release the drug slower

Table 3
Values of dissolution efficiency over 8 h and swelling capacity at 8 h of matrix tablets at different pHs but at same ionic strength (0.5 M)

| Formulation with | $DE_{8h}$ (pH) 1.5 | $DE_{8h}$ (pH 5) | $DE_{8h}$ (pH 8) | SC (pH 1.5) | SC (pH 5) | SC (pH 8) |
|---|---|---|---|---|---|---|
| HS-MMAO | 0.824 | 0.915 | 0.708 | 0.442 | 0.470 | 0.610 |
| HS-MMAL | 0.577 | 0.264 | 0.352 | 0.281 | 0.282 | 0.386 |
| CS-MMAO | 0.798 | 0.442 | 0.580 | 0.479 | 0.737 | 0.701 |
| CS-MMAL | 0.740 | 0.292 | 0.445 | 0.663 | 0.934 | 0.898 |
| HC-MMAO | 0.953 | 0.806 | 0.865 | 0.628 | 0.69 | 0.788 |
| HC-MMAL | 0.899 | 0.685 | 0.781 | 0.825 | 1.204 | 1.104 |
| NaCMC | 0.392 | 0.148 | 0.247 | — | — | — |

than cellulosic derivatives (HS-MMAO < HC-MMAO, HS-MMAL < HC-MMAL). This can be explained due to the higher capacity of the starch to absorbed water (Castellano et al., 1996a) and to give gel layers, in relation with cellulosic derivatives (Castellano et al., 1996b).

The swelling capacity of polymer tablets formulated with different polymers are depicted in Figs. 4–6. HC-MMA products have the highest swelling capacity being the lowest HS-MMA products. In relation with this parameter, tablets formulated with HS-MMA polymers have a different behavior than the other two types of tablets. So, for this polymer, the product with higher swelling capacity (O) releases the drug faster than the polymer with lower swelling capacity (L) (Table 3). An inadequate compression pressure to prevent the disintegration of HS-MMAO matrix tablets could explain this different behavior (Ventouras and Buri, 1976; Huber and Christenson, 1968; Bams and Walker, 1971), if we observe the different disintegration times for both formulations (0.29 min and > 30 min for HS-MMA O and L, respectively).

In relation to CS-MMA and HC-MMA, L polymers, that absorb higher amounts of water (Castellano et al., 1996a), give lower drug release rate than their corresponding oven dry polymers (CS-MMAO and HC-MMAO). This agrees with the swelling capacity of CS-MMA and HC-MMA products that arise the equilibrium swelling value before 5 min. On the other hand, HS-MMAL tablets have a lower swelling degree than expected from its hydrophilicity, that could be due to the

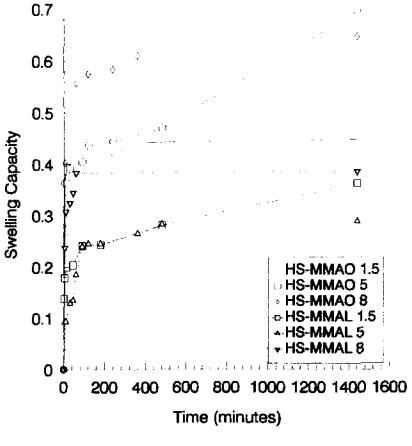


Fig. 4. Swelling capacity of polymer tablets formulated with HS-MMA, O and L products, at different pHs.

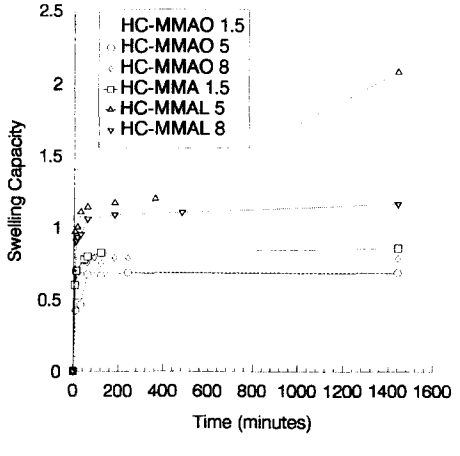


Fig. 5. Swelling capacity of polymer tablets formulated with HC-MMA, O and L products, at different pHs.

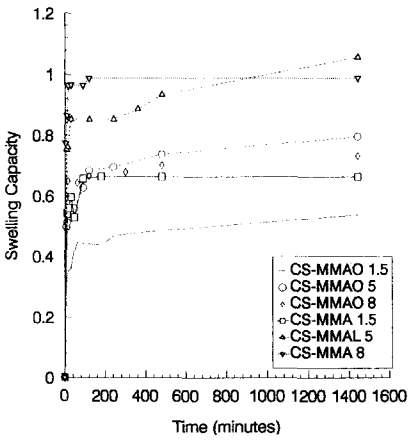


Fig. 6. Swelling capacity of polymer tablets formulated with CS-MMA. O and L products, at different pHs.

strong intramolecular hydrogen ability (Lenaerts et al., 1991).

All the tablets, irrespective of the polymer backbone structure, give higher swelling and, in consequence, lower release rate at high pHs.

Another consideration is the viscosity of the formed gel. It seems that comparing O and L products, the ones that have lower particle size (O polymers) (Castellano et al., 1996b) give lower viscosity and also, together with the lower swelling capacity and disintegration time, release the drug faster than its corresponding L polymer tablets.

Although, in general, our new polymers are showing as good candidates to controlled release of drugs, specially HS-MMAL continued by CS-MMAL with lower dissolution efficiency at all pHs, it is necessary to make matrix tablets at higher pressure to obtain better disintegration properties, specially with HS-MMAO and HC-MMA polymers.

To demonstrate the quality of our polymer (HS-MMAL), we compared its rheological, compressional and specially drug release properties of tablets first compressed alone and afterwards in the formulation containing theophylline in relation with NaCMC (7MF, Aqualon Company, US). While HS-MMAL powders show high flowability (Table 1), NaCMC powders did not fulfil the requirements proposed by different authors (Guyot, 1978; Guyot et al., 1980; Delacourte-Thibaut et al., 1982; Avan and Brossard, 1985). Also, the results show that, although lower friction and ejection properties were obtained with NaCMC tablets, HS-MMAL tablets fulfilled the requirements of ejection force proposed by Bolhuis and Lerk (1973). However, NaCMC tablets exhibit higher compactibility values than HS-MMAL. On another hand, similar results were obtained for HS-MMAL and NaCMC tablets in relation with friability and disintegration time (Table 2).

In spite of the addition of theophylline and excipients to HS-MMAL diminished the flow rate in comparison with polymer alone, the value was slightly higher than NaCMC formulation. Similar results were obtained for both formulations in relation with compressional properties and disintegration time; however, HS-MMAL tablets showed better friability than NaCMC.

According to the dissolution efficiency over 8 h, both formulations show very similar results, although always the release of theophylline from NaCMC tablets at different pHs was slightly slower than HS-MMAL (Table 3). Finally, it must be pointed out that starch is one of the main available carbohydrates for humans, due to the presence of specific enzymes that allow its biodegradation. This implies an advantage in relation with cellulose and its derivatives, that can not be digested by humans and other mammalians.

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