ELSEVIER

International Journal of Pharmaceutics 136 (1996) 107–115

international journal of pharmaceutics

In vitro evaluation of sustained-release matrix tablets prepared with new modified polymeric carbohydrates

M.V. Velasco[a], A. Muñoz[a], M.R. Jiménez-Castellanos[a,*], I. Castellano[b], I. Goñi[b], M. Gurruchaga[b]

[a]*Departamento de Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, C/ Tramontana s.n., 41012 Sevilla, Spain*
[b]*Departamento de Ciencia y Tecnología de Polímeros, Facultad de Química, Apdo 1072, 20080 San Sebastian, Spain*

Received 21 November 1995; accepted 20 February 1996

Abstract

The study of the rheological and compressional properties of sustained-release matrix tablets prepared with new polymers obtained by graft copolymerization of methyl methacrylate (MMA) on various carbohydrates is the main purpose of this work. All the mixtures had good flow properties, showing cellulose derivatives mixtures the best values. Powders without homopolymers showed a statistically significant lower flow rate than mixtures with homopolymers. All the mixtures with hydroxypropyl starch polymers showed better statistically significant compactibility and plasticity than the hydroxypropyl cellulose derivatives. Practically all the mixtures accomplished with the requirements of direct compression excipients in relation with lubrication coefficient. All the tablets elaborated with mixtures with homopolymers required a total work lower than the mixtures without homopolymers. Tablets from all products passed the test for weight uniformity, except the tablets of carboxymethyl starch (CS-MMA) without homopolymer. Only hydroxypropylcellulose tablets demonstrated an acceptable friability. Only standard tablets and CS-MMA without homopolymers exhibited disintegration times higher than 30 min. A clearly different behaviour between the new polymers and the standards was observed in relation with dissolution test.

Keywords: Sustained-release matrix tablets; Polymeric carbohydrates; Sotalol; Poly(methyl methacrylate); Compression

1. Introduction

In the last years, the need for polymer systems delivery drugs at prolonged but constant rate has become prominent (Davis, 1987; Farina and Llabrés, 1987). Hydrophilic matrices are an interesting option when developing an oral sustained-release formulation. The used polymers can be classified in three groups: (a) non-cellulose natural or semisynthetic polymers, (b) polymers of acrylic acid and (c) cellulose ethers (Vazquez et al., 1992). The importance of choice of matrix material on drug release in formulation of sustained-release tablets is illustrated by many studies (Khanna and Speiser, 1970; Korsmeyer et al., 1983; Carli et al., 1984). Whereas cellulose derivatives have been the

---

* Corresponding author.

PII S0378-5173(96)04501-2

most widely used polymers for this purpose (Buri and Doelker, 1980; Malfroid and Bentejac, 1982), only some investigators mentioned the possibility to use modified starches in this field (Van Aerde and Remon, 1988; Herman and Remon, 1989; Herman and Remon, 1990; Herman et al., 1989; Visavarungroj et al., 1990). On the basis of this knowledge, our research team tried to profit from the experience of previous works in the synthesis of graft copolymers with acrylic and natural polymers (Goñi et al., 1984; Goñi et al., 1992; Castellano et al., 1994). With the aim of obtaining products potentially suitable to be used as sustained-release matrices, the following carbohydrates were utilized: carboxymethyl starch (CS), carboxymethyl cellulose (CC), hydroxypropyl starch (HS) and hydroxypropylcellulose (HC), combined with poly(methyl methacrylate) (PMMA), that is a highly biocompatible polymer widely used in the pharmaceutical industry.

Nowadays, in order to investigate the suitability of a polymer as a matrix forming agent, it is necessary to gather sufficient information about its physical and mechanical properties, since the properties of the matrix will mainly depend on the characteristics of the polymer.

In light of the above, the aim of this work is focussed on knowing the rheological properties and compression behaviour of formulations of direct compression slow-release hydrophilic matrices of sotalol hydrochloride using new modified polymeric carbohydrates.

2. Materials and methods

The preparation of the new polymers was carried out by using methyl metacrilate (MMA) (Merck), ceric ammonium nitratate (Fluka), carboxymethyl-cellulose (Aldrich, Barcelona, Spain, lot no. 19189-2) (CC), hydroxypropyl cellulose (Aldrich, Barcelona, Spain, lot no. 050150F)(HC), carboxymethyl starch (AVEBE, Quicksolan CMS, Holanda, lot no. I123M) (CS) and hydroxypropyl starch (AVEBE, Perfectamy A-5914) (HS). These graft copolymers were synthesized as described previously (Goñi et al., 1992).

In order to obtain the pure copolymer it is necessary to remove the unreacted carbohydrate and the acrylic polymer formed out of the carbohydrate, called homopolymer (Goñi et al., 1984).

The following materials were also used in this study: sotalol hydrochloride (Bristol Myers-Industrial, U.S.A., lot no. N0C07), dibasic dicalcium phosphate dihydrate (Emcompress®, Julia Parrera, Barcelona, Spain, lot no. 1859), sodium carboxymethyl-cellulose (NaCMC 7MF cellulose gum, Aqualon Co., U.S.A., lot no. 67108), hydroxypropyl cellulose (HXF, Aqualon Co., U.S.A., lot no. 6232) and magnesium stearate (Acofarma, Barcelona, Spain, lot no. 2092).

Powders were stored under controlled temperature (20°C) and humidity (RH = 40%) conditions.

Sotalol HCl (24%), as model drug, was mixed first with 25% of one of the polymers on study and 50% of Emcompress® for 15 minutes in a plastic vessel in an asymmetric double-cone mixer (Retsch, Haan, Germany) at 50 rev.min^{-1}. After the addition of magnesium stearate (1%) as lubricant, the mixing procedure was continued for 5 min.

The flow rate was measured by our data acquisition flowmeter system (Muñoz-Ruiz and Jiménez-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.

The techniques used for determining the static repose angle and compressibility on tamping are described in detail in earlier studies (Borrero et al., 1988). The true density of each powder was determined using a pycnometer (Model SPY-3 stereopycnometer, Quantachrome, Syosset, NY, U.S.A.). The gas used was helium.

The compression characteristics of the 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 (12mm) and flat compacts were prepared at fixed crushing strength (4kp) to study the variations in the compression properties of the powders. Also, to study the tablet 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 following standard physical tests were performed on the tablets produced:

Weight: the weight (mg) of each of twenty individual 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 weight data from the tablets were analyzed for sample mean, standard deviation and coefficient variation (relative Standard Deviation).

Thickness: The individual crown-to-crown for thickness of twenty individual tablets was determined after dusting off the tablet surface, and then placing it in and parallel to the jaw of a micrometer MDC-M293 (Mitutoyo micrometer, Tokyo, Japan). The measurements were recorded and the sample mean and standard deviation were calculated.

Friability: It was determined by weighting fifteen tablets after dusting, placing them in Erweka TA (Erweka, Heusenstamm, Germany) friability tester and rotating the basket vertically at 25 r.p.m. for 4 min (100 drops). After dusting, the total remaining weight of the tablets was recorded, and the percent friability was calculated:

$$\%\,\text{Friability} = \frac{\text{Weight}_{\text{original}} - \text{Weight}_{\text{final}}}{\text{Weight}_{\text{original}}} \times 100$$

Disintegration testing (six tablets) was performed at 37°C in 0.1 N HCl medium using the European Pharmacopoeia apparatus (Erweka ZT3, Erweka, Heusenstamm, Germany).

In vitro dissolution studies: Drug dissolution was carried out on a U.S.P. XXIII apparatus (Turugrau automatized dissolution test) using the basket method at pH 1.2. The drug concentration was monitored continuously using a spectrophotometer (diode array spectrophotometer Hewlett Packard).

3. Results and discussion

From a scientific point of view, the removal of the homopolymer is an experimental step that gives a lot of information about the synthesis reaction. However, from an industrial point of view, this step could be economically non-interesting. This reason led us to study the rheological and compressional properties in both cases: from the crude product and from the product obtained after removing the homopolymer. So, in the results and discussion, we will mention the data obtained from the mixtures 'with homopolymer' and 'without homopolymer'.

Table 1 gives the results of the flowrate test and the true density of the mixtures under study. According to these results, all the mixtures showed good flow properties (Guyot, 1978; Guyot et al., 1980; Delacourte-Thibaut et al., 1982; Aran and Brossard, 1985). We can observe how mixtures without homopolymers showed a statistically significant lower flowrate (F = 12.016; $\alpha < 0.05$; LSD) than mixtures with homopolymers. Cellulose derivatives mixtures exhibited higher values of flowrate, although no statistically significant difference was found. Only the mixtures of

Table 1
Flowrate and true density of tablets with different polymers. (average of three experiments and standard deviation)

Tablets with	Flowrate (g/s)	True density (g/cm^3)
PMMA	—	1.190
CC	—	1.583
CS	—	1.525
HS	—	1.484
HC	—	1.208
HC-MMA wihtout Hom.	51.15 ± 18.0	1.659 ± 0.013
HC-MMA	63.14 ± 7.37	1.757 ± 0.043
HS-MMA without Hom.	37.39 ± 23.4	1.718 ± 0.012
HS-MMA	61.39 ± 21.5	1.970 ± 0.009
CS-MMA without Hom.	48.11 ± 3.3	1.757 ± 0.031
CS-MMA	58.04 ± 11.3	1.684 ± 0.013
CC-MMA	65.9 ± 6.09	1.686 ± 0.016
NaCMC 7HF	66.05 ± 11.0	1.814 ± 0.012
HPC HXF	61.12 ± 2.82	1.660 ± 0.021

Table 2
Angle of repsoe (σ_{st}), tap volume (V_0), bulk volume (V_{500}), bulk density (d_{500}), compresibility index (% C) and Hausner ratio (H.I.)

Tablet with	σ_{st} (°)	V_0 (mL)	V_{500} (mL)	V_{10}- V_{500} (mL)	d_{500}(g/cm^3)	%C	H.I.
HC-MMA wihtout hom.	37.29 ± 0.43	124 ± 1.6	113 ± 1.9	7 ± 2.0	0.88 ± 0.01	5.8 ± 1.6	1.06 ± 0.01
HC-MMA	37.16 ± 0.64	130 ± 2.8	119 ± 2.0	5 ± 2.0	0.84 ± 0.01	4.0 ± 1.6	1.03 ± 0.01
HS-MMA without hom.	36.87 ± 0.21	138 ± 2.7	124 ± 0.0	8 ± 0.0	0.80 ± 0.00	6.0 ± 0.00	1.06 ± 0.00
HS-MMA	36.06 ± 0.45	117 ± 2.0	100 ± 0.0	8 ± 0.0	1.00 ± 0.00	7.4 ± 0.0	1.08 ± 0.00
CS-MMA without hom.	35.87 ± 0.41	205 ± 3.2	188 ± 0.0	10 ± 2.3	0.53 ± 0.00	5.0 ± 1.1	1.04 ± 0.01
CS-MMA	36.43 ± 0.62	136 ± 2.6	120 ± 0.0	9 ± 2.0	0.83 ± 0.00	6.9 ± 0.0	1.07 ± 0.01
CC-MMA	37.60 ± 0.20	131 ± 2.5	113 ± 2.0	8 ± 3.2	0.88 ± 0.01	6.5 ± 2.5	1.07 ±0.02
NaCMC 7 MF	37.64 ± 0.91	126 ± 2.1	112 ± 0.0	8 ± 0.0	0.89 ± 0.00	6.6 ± 0.0	1.07 ± 0.00
HPC HXF	36.15 ± 1.64	159 ± 2.9	140 ± 0.0	4 ± 0.0	0.71 ± 0.00	2.7 ± 0.0	1.02 ± 0.00

the derivatives without homopolymers showed statistically significant differences ($F = 12.652$; $\alpha < 0.05$; LSD) with the standard mixtures (HPH HXF and NaCMC 7HF).

All the mixtures with homopolymers showed higher values of true density than their correspondent mixtures without homopolymers, except in the case of CS-MMA (without homopolymers: 1.757 and with homopolymers: 1.684) (Table 1). On the other hand, hydroxypropyl derivatives with homopolymers, from cellulose and from starch, had higher values of true density than carboxymethyl derivatives, in opposite to the standard mixtures. In the light of the true density values of the pure products (Table 1), we could deduce that the more PMMA content the lower the density. Thus, in a first approach, the lower true density of the products with homopolymer can be attributed to the presence of the lighter compound that is the PMMA. To understand the different behaviour of the hydroxyderivatives, we must take in account the values of the percent grafting of each graft copolymer (Castellano et al., in press) as well as the percent homopolymer formed. The grafted hydroxy derivatives gave the highest values of the grafted PMMA and not a very large amount of homopolymer; whereas the graft copolymers obtained from CS gave the lowest percent grafting and the highest amount of homopolymer (Castellano et al., in press).

So, we can expect a small influence of the homopolymer in the true density and a more significative influence of the polymeric chain packing in the graft copolymers on hydroxycarbohydrates, which will give rise to a higher density of the products without homopolymer in opposite to the graft copolymers obtained from the carboxymethyl starch.

Packing characteristics and angles of repose (± S.D.) are represented in Table 2.

Once again (Velasco et al., 1995) it is impossible to distinguish with the angle of repose statistically the different flow properties between mixtures with and without homopolymers and between carboxymethyl and hydroxypropyl derivatives. However, according to the results, all the mixtures showed good flow properties (Delattre et al., 1973), as we concluded with the results of flow rate.

It is remarkable the different behaviour of CS-MMA without homopolymers in the packing characteristics. The apparent volume got a value (V_o = 205 mL) much higher than the other mixtures. With regard to the bulk density (d_{500}), and in opposite to the true density values, we could not obtain conclusions about the different behaviour of the mixtures under study, because whilst a powder can only possess a single true density it can have many different bulk densities,

Table 3
Average of maximum upper force (MUF) (N), ejection force (EF) (N), residual lower punch force (RLPF) (N), lubrication coefficient (R), plasticity (%Pl) and total work (W_t) (J) from tablets of sotalol with different polymers

Tablet	MUF ± S.D.	EF ± S.D.	RLPF ± S.D.	R ± S.D.	%Pl ± S.D	W_t ± S.D.
HC-MMA without hom.	34474.8 ± 1001.0	512.74 ± 18.2	439.6 ± 73.8	0.869 ± 0.00	76.95 ± 1.42	12.95 ± 0.38
HC-MMA	24931.8 ± 980.1	170.91 ± 68.9	109.6 ± 34.0	0.933 ± 0.02	76.87 ± 1.51	9.31 ± 0.59
HS-MMA without hom.	20381.5 ± 270.9	245.2 ± 94.5	198.1 ± 51.6	0.931 ± 0.02	87.89 ± 2.76	10.37 ± 0.46
HS-MMA	17762.7 ± 358.3	408.7 ± 55.6	390.5 ± 79.5	0.901 ± 0.01	78.15 ± 1.20	6.44 ± 0.14
CS-MMA without hom.	4816.9 ± 210.4	81.7 ± 22.4	49.07 ± 14.9	0.928 ± 0.01	94.66 ± 0.86	4.48 ± 0.19
CS-MMA	20349.9 ± 1567.9	364.1 ± 73.5	286.5 ± 53.1	0.887 ± 0.02	84.14 ± 3.04	9.67 ± 0.42
CC-MMA	23505.9 ± 278.1	122.6 ± 18.2	94.83 ± 30.8	0.953 ± 0.00	66.75 ± 0.37	7.78 ± 0.19
Na CMC	17695 ± 306.1	96.6 ± 27.8	74.51 ± 22.2	0.968 ± 0.00	85.46 ± 1.05	8.42 ± 0.19
HPC-HXF	8970.2 ± 1599.7	80.8 ± 8.3	58.21 ± 0.31	0.922 ± 0.00	81.30 ± 1.74	3.94 ± 0.48

depending on the way in which the particles are packed and the bed porosity (Staniforth, 1988). All the mixtures showed good properties to flow according to the difference V_{10}–V_{500}, being the mixtures of CS-MMA without homopolymers in the limits of this property (Guyot, 1978; Delacourte-Thibaut et al., 1982; Aran and Brossard, 1985). Compressibility index and Hausner index showed good properties to flow (Carr, 1965; Hausner, 1972) for all the mixtures under study, however they were not sensitive parameters to assess statistically the different behaviour of the mixtures (Lubner and Ricciardiello, 1977).

To evaluate the compressional properties of the mixtures, the averages of the parameters maximum upper force (MUF), ejection force (EF), residual lower punch force (RLPF), lubrication coefficient (R) and plasticity (Doelker, 1988) in percent (%Pl) were selected and calculated with the values obtained for tablets of 4Kp crushing strength. The parameters are listed in Table 3.

According to the results obtained, tablets elaborated with CS-MMA without homopolymers had the highest compactibility because they required much lower applied force to obtain tablets of similar crushing strength to the other mixtures under study. However, we have to express our doubts about these results due to the difficulty to fill the die, a fact that agrees with the high tap volume ($V_o = 205$ mL). In relation to CC-MMA mixtures, we could only elaborate tablets with 2 Kp of crushing strength. It can be related with its low value in plasticity (% Pl = 66.75). Curiously, both products showed the lowest percent of grafted PMMA (Castellano et al., in press). For the above reasons, we make the statistical study only on the hydroxypropyl polymers. All the mixtures with hydroxypropyl starch polymers, showed better statistically significant ($F = 199.43$; $\alpha < 0.05$; LSD) compactibility than the hydroxypropyl cellulose derivatives. Also, always the derivatives with homopolymers required lower forces than the mixtures without homopolymers, although no statistically significant difference was found.

The plasticity values were calculated from the following relationship (Stamm and Mathis, 1976):

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

Where: W_{EXP} is the expansion work
W_{NA} is the apparent net work

Starch hydroxypropyl mixtures showed higher statistically significant ($F = 6.134$; $\alpha < 0.05$; LSD) plasticity values than celluloses hydroxypropyl polymers. Plasticity values are consistent with compactibility values because starch hydroxypropyl derivatives required lower forces to make

Table 4
Weight uniformity, friability, thickness and disintegration time from tablets of 4-kp crushing strength

Tablet	Weight ± S.D. (mg)	Friability ± S.D. (%)	Thickness ± S.D. (mm)	Disintegration ± S.D. (min.)
HC-MMA without hom.	507.5 ± 9.9 C.V. = 1.95%	6.12	3.2 ± 0.07	6.42 ± 0.49
HC-MMA	502.3 ± 3.9 C.V. = 0.77%	1.6	3.1 ± 0.03	7.74 ± 0.82
HS-MMA without hom.	482.8 ± 13.5 C.V. = 2.8	2.23	3.09 ± 0.02	6.29 ± 2.79
HS-MMA	506.2 ± 7.3 C.V. = 1.4%	1.98	2.73 ± 0.02	22.62 ± 1.31
CS-MMA without hom.	533.0 ± 22.8 C.V. = 4.3%	1.30	3.71 ± 0.00	>30
CS-MMA	520.4 ± 4.9 C.V. = 0.9%	2.51	3.3 ± 0.01	6.43 ± 1.75
CC-MMA	520.0 ± 6.05 C.V. = 1.2%	4.59	3.25 ± 0.03	3.87 ± 0.52
Na CMC 7HF	509.1 ± 8.7 C.V. = 1.7%	2.14	3.07 ± 0.02	>30
HPC HXF	482.0 ± 14.6 C.V. = 3.0%	0.64	3.06 ± 0.03	>30

tablets at 4 Kp crushing strength and also exhibited higher plasticity, so they had better compressional properties than celluloses hydroxypropyl polymers.

All the mixtures accomplished with the requirements of direct compression excipients proposed by Bolhuis and Lerk (1973) who established that values of lubrication coefficient (R = maximum lower punch force over maximum upper punch force) must be higher than 0.9. The mixtures with HC-MMA without homopolymer and CS-MMA were the only exceptions because they exhibited the lowest lubrication coefficients (R = 0.867 and 0.887), and HC-MMA showed the highest value. No statistically differences in R values were found between mixtures with hydroxypropyl starch and hydroxypropyl cellulose polymers nor between mixtures using copolymers without homopolymers and with homopolymers.

The results demonstrated that all the mixtures fulfilled the requirements for direct compression excipients proposed by Bolhuis and Lerk (1973) who established that the values of ejection force must be lower than 750 N. The sequence in residual force and ejection force were consistent with the values observed in lubrication coefficient. Values for both parameters followed from maximum to minimum friction the sequence: HC-MMA without homopolymers; HS-MMA, CS-MMA, HA-MMA without homopolymers, HC-MMA; CC-MMA, NaCMC, CS-MMA without homopolymers and HPC-HXF.

All the tablets elaborated with mixtures with homopolymers required a total work lower than the mixtures without homopolymers (HC-MMA without hom. = 12.95; HC-MMA = 9.31; HS-MMA without hom. = 10.37 and HS-MMA = 6.44), with statistically significant difference (F = 17.500; $\alpha < 0.05$; LSD). However, no differences were found between mixtures with hydroxypropyl starchs or hydroxypropyl celluloses.

The different tests for tablets are detailed in Table 4.

Tablets from all products passed the test for weight uniformity, except the tablets of CS-MMA without homopolymers (C.V. = 4.3%), because it was difficult to make batches of tablets due to the weight adjustement. As expected from the flow properties, the value of the coefficient of weight variation for HS-MMA without homopolymer was high. The high C.V. in the mixture with HPC-HXF (3%), in spite of its good flowability

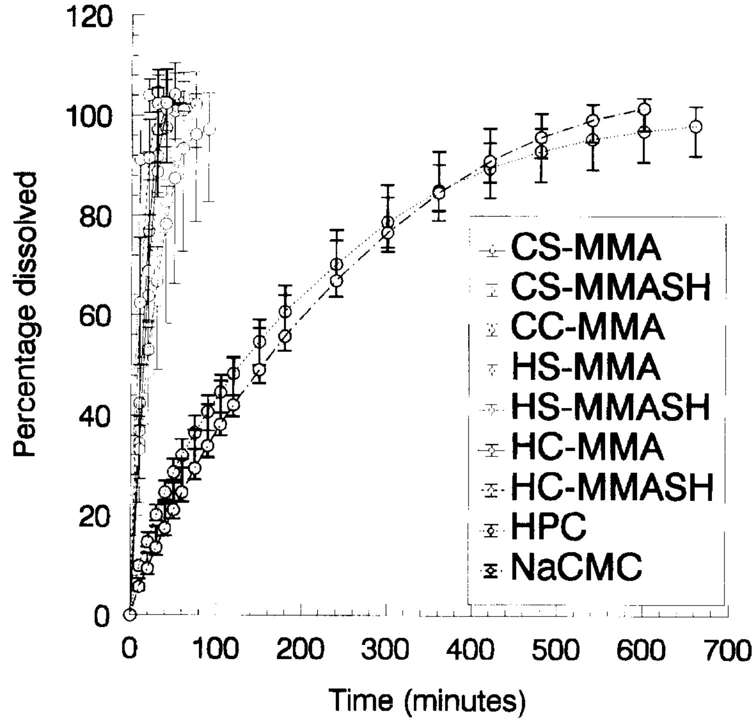

Fig. 1. Profiles of the dissolution test for the different tablets.

(61.31 g/s), may be justified by its capacity to absorbe moisture from the atmosphere (American Pharmaceutical Association and the Pharmaceutical Society of Great Britain, 1986).

Only HPC HXF tablets demostrated an acceptable friability usually considered less than 1% (Mollan and Çelik, 1993). All the tablets with homopolymers exhibited lower friability values than their corresponding without homopolymers, again with the exception of CS-MMA without homopolymers. This fact may be explained due to the moderate binding properties of these materials (Doelker, 1988). On the other hand, hydroxypropyl derivatives without homopolymers tablets showed better friability values than the corresponding carboxy derivatives, in agreement with the easiness in obtaining the tablets.

Only standard tablets and CS-MMA without homopolymers exhibited disintegration times higher than 30 min.

Fig. 1 depicts the profiles of the dissolution test for the different tablets under study. We can clearly observe the different behaviour between the new polymers and the standards. If we study the results of 90–95% dissolved, we can establish the following sequence from slower to faster release: HPC-HXF (540 min) > NaCMC (480 min) ⋙ HS-MMA (75 min) > HA-MMA without homopolymers (60 min) > CS-MMA without homopolymers (40 min) > HC-MMA (35 min) > CS-MMA (30 min) > HC-MMA without homopolymers (20 min) > CC-MMA (10 min). A possible explanation of these results can be found in the effect of the particle size of the polymers. Nakagami and Nada (1988) reported that tablets prepared from finer particles of L-HPC exhibited slow release and Jiménez-Castellanos et al. (1994) found a relation between slow release and the size of two different HPCs. Even for four different batches with fine particle size, Johnson et al (Johnson et al., 1989) showed a slightly faster release profile for the largest particle size of all batches. Our results agree with those of the authors mentioned, because we observe the same sequence for the percent of particules lower than 175 μm (HPC-HXF 89.5%; NaCMC 94.1%; HS-MMA 85%; HC-MMA 62%; CS-MMA 59% and CC-MMA 52%) and the time for 90–95% dissolved, corresponding the lowest time of release to the finer particles.

Finally, in hydroxypropyl derivatives, we can also find a relation between the best compactibility and plasticity with lower release.

As a conclusion, we can asses that the best values of both, the rheological and compressional properties, are obtained from sustained-release matrix tablets prepared with the compounds with homopolymer. An exception of this behaviour is showed by the CS-MMA, which is the graft copolymer that gives the lower yield in the synthesis reaction.

So, from an industrial point of view, the homopolymer extraction will be an uneconomical step.

Acknowledgements

The authors would like to thank the Diputacion Foral de Guipúzcoa for funding this work through project 'Soportes poliméricos para fármacos bioadhesivos'.

References

American Pharmaceutical Association and the Pharmaceutical Society of Great Britain. *Handbook of Pharmaceutical Excipients*. The Pharmaceutical Press, London, 1986.

Aran, J.L. and Brossard, C., Mise au point et développement tecnologiques de matrices hydrophiles par compression directe sur machine rotative. *Sci. Techn. Pharm.*, 1 (1985) 516–522.

Bolhuis, G.K. and Lerk, C.F., Comparative evaluation of excipients for direct compression. *Pharm. Weekbland*, 108 (1973) 469–481.

Borrero, J.M., Jiménez-Castellanos, M.R. and Faulí, C., Estudio comparativo de cinco excipientes para compresión directa. *Il Farmaco*, 3 (1988) 101–109.

Buri, P. and Doelker, E., Formulation des comprimés à libèration prolongée. II. matrices hydrophiles. *Pharm. Acta Helv.*, 55 (1980) 189–197.

Carli, F., Capone, G., Colombo, I., Magarotto, L. and Motto, A., Surface and transport properties of acrylic polymers influencing drug release from porous matrices. *Int. J. Pharm.*, 21 (1984) 317–329.

Carr, R.L., Evaluating flow properties of solids. *Chem. Eng.*, 72 (1965) 163–168.

Castellano, I., Gurruchaga, M., Goñi, I., Muñoz, A. and Jiménez-Castellanos, M.R., New graft copolymers on carbohydrates for drug delivery systems. *Polymer* (in press).

Castellano, I., Pascual, B., Vazquez, B., Goñi, I. and Gurruchaga, M., Graft copolymerization of different mixtures of acrylic monomers on amylopectin. Swelling behaviour. *J. App. Pol. Sci.*, 54 (1994) 577–584.

Davis, S.S., The design and evaluation of controlled dosage forms for oral delivery. *S.T.P. Pharma*, 3 (1987) 412–417.

Delacourte-Thibaut, A., Guyot, J.C. and Traisnel, M., Formulation technologiques des comprimés. Etablissement de fiches techniques. *Sci. Tech. Pharm.*, 11 (1982) 131–140.

Delattre, L., Gillard, J., Roland, M. and Jaminet, F., Relation entre la vitesse d'ecoulement et les propriétes angulaires ou le comportement au tassement des diluants pour la compression directe. *J. Pharm. Belg.*, 28 (1973) 575–590.

Doelker, E., Recents advances in tableting science. *Boll. Chim. Farm.*, 127 (1988) 37–41.

Farina, J.F. and Llabrés, M., Sustained-release pharmaceutical oral dosage forms. Review of patented manufacturing processes registered in the US Patent Office (1970–1985). *S.T.P. Pharma*, 3 (1987) 505–509.

Goñi, I., Gurruchaga, M., Valero, M. and Guzman, G.M., Graft polymerization of acrylic monomers onto starch fractios. III. Effect of carbohydrate structure. *J. Pol. Sci. Pol. Chem. Ed.*, 22 (1984) 1327–1333.

Goñi, I., Gurruchaga, M., Valero, M. and Guzman, G.M., Synthesis of graft copolymers of acrylic monomers onto amylose. II. Study of the ceric ion behavior. *J. Appl. Pol. Sci.*, 45 (1992) 981–986.

Guyot, J.C., Critères technologiques de choix des excipients de compression directe. *Sci. Techn. Pharm.*, 7 (1978) 551–559.

Guyot, J.C., Delacourte-Thibaut, A. and Traisnel, M., Comment devrait-on aborder la mise au point des comprimés?. *Sci. Techn. Pharm.*, 9 (1980) 459–468.

Hausner, H., The role of interparticle friction in powder technology. In Goeldberg, A.S. (Ed.), *Proc. 1st Int. Conf. on the Compaction and Consolidation of Particulate Matter*. Brighton, 1972, pp. 7–12.

Herman, J. and Remon, J.P., Modified starches as hydrophilic matrices for controlled oral delivery. II. In vitro drug release evaluation of thermally modified starches. *Int. J. Pharm.*, 56 (1989) 65–70.

Herman, J. and Remon, J.P., Modified starches as hydrophilic matrices for controlled oral delivery. III. Evaluation of sustained-release theophilline formulations based on thermal modified strach matrices in dogs. *Int. J. Pharm.*, 63 (1990) 201–205.

Herman, J., Remon, J.P. and Vilder, J., Modified starches as hydrophilic matrices for controlled oral delivery. I. Production and characterization of physically modified starches. *Int. J. Pharm.*, 55 (1989) 614–617.

Jiménez-Castellanos, M.R., Zia H. and Rhodes, Ch.T., Effect of addition mode of the polymer on the release and adhesion of sotalol tablets, *S.T.P. Pharma*, 4 (1994) 101–106.

Johnson, J.L., Skinner, G.W. and Holinej, J., Effect of particle size of hydroxypropylcellulose on tablet compressibility and drug release from sustained matrix tablets. *16th Proc. Intern. Symp. Control. Rel. Mater.*, Chicago, 1989, pp. 376–377.

Khanna, S.C. and Speiser, P., In vitro release of chloramphenicol from polymer beads of alpha-methacrylic acid and methylmetacrylate. *J. Pharm. Sci.*, 59 (1970) 1398–1401.

Korsmeyer, R.W., Gurny, R., Doelker, E., Buri, P. and Peppas, N.A., Mechanisms of potassium chloride release from compressed, hydrophilic, polymeric matrices: Effect of entrapped air. *J. Pharm. Sci.*, 72 (1983) 1189–1191.

Lubner, G.C. and Ricciardiello, G., Influence of flow promoting agents on the properties of mixtures of powders and on the physical properties of the resulting tablets. *Boll. Chim. Farm.*, 116 (1977) 50–53.

Malfroid, F. and Bentejac, R., Formulation de comprimés à liberation prolongée de type matrice hydrophile. Etude de dérives cellulosiques. *Labo-Pharam, Probl. Tech.*, 30 (1982) 727–734.

Mollan, M.J. and Çelik, M., Characterization of directly compressible maltodextrins manufactured by three different processes. *Drug Dev. Ind. Pharm.*, *19* (1993) 2335–2358.

Muñoz-Ruiz, A. and Jiménez-Castellanos, M.R., Integrated system of data acquisition for measure of flow rate. *Pharmaceut. Technol. Internat. Biopharm.*, 8 (1993) 21–29.

Nakagami, H. and Nada, M., Application of micronized insoluble cellulose to sustained-release tablets. *15th Proc. Inter. Symp. Control. Rel. Mater.*, Basel, 1988, pp. 11–12.

Stamm, A. and Mathis, C., Etude de la comprimabilité de différents excipients pour compression directe. *Sci. Techn. Pharm.*, 5 (1976) 245–253.

Staniforth, J.N., Powder flow. In Aulton, M.E. (Ed.), *Pharmaceutics: The Science of Dosage Form Design*, Churchill Livingstone, Edinburgh, 1988, pp. 616–628.

Van Aerde, P. and Remon, J.P., In vitro evaluation of modified starches as matrices for sustained-release dosage forms. *Int. J. Pharm.*, 45 (1988) 145–152.

Vazquez, M.J., Pérez-Marcos, B., Gomez-Amoza, J.L., Martinez-Pacheco, R., Souto, C. and Concheiro, A., Influence of technological variables on release of drugs from hydrophilic matrices. *Drug Dev. Ind. Pharm.*, 18 (1992) 1355–1375.

Velasco, M.V., Muñoz-Ruiz, A., Monedero, M.C. and Jiménez-Castellanos, M.R., Flow studies on maltodextrin as directly compressible vehicles. *Drug Dev. Ind. Pharm.*, 21 (1995) 1235–1243.

Visavarungroj, N., Herman, J. and Remon, J.P., Crosslinked starch as sustained-release agent. *Drug Dev. Ind. Pharm.*, 16 (1990) 1091–1108.