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# Poly(methylglyoxylate), a biodegradable polymeric material for new drug delivery systems

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**Abstract**

A biodegradable hydrophobic matrix, poly(methylglyoxylate) and a water-soluble drug, metoprolol, were used to prepare solid dispersions in order to obtain an oral controlled drug delivery system. Preliminary thermal and chemical studies of the polymer revealed sufficient properties to undergo the preparation of solid dispersions as well as satisfactory behaviour in acidic or alkaline medium. Consequently, a first series of co-melts and co-precipitates containing various drug concentrations (75, 50, 35 and 25%, w/w) were prepared with a granulometry varying between 250 and 100 $\mu$m. DSC studies showed a better dispersion of the drug in the matrix for co-precipitates than for co-melts. In vitro dissolution kinetic studies showed an important burst effect during the first 30 min. Then a very slow release of the drug was observed during the last 7.5 h. A second series of co-precipitates with lower drug content (25, 15 and 5%, w/w) and lower granulometry (up to 100 $\mu$m) was tested. Finally, a dissolution profile similar to those of a commercial Seloken 200 LP tablet formulation was obtained, for a 15% (w/w) drug concentration in the polymer matrix and for a solid dispersion prepared by solvent method. 

*Keywords:* Solid dispersions; Poly(methylglyoxylate); Biodegradable matrix; Metoprolol; Dissolution profiles

## 1. Introduction

Biodegradable synthetic polymers have received significant attention in recent years due to their exceptional promise for pharmaceutical and medical applications. In this context, various macromolecular drug carrier systems have been developed in order to control the pharmacokinetic properties of drugs. Among these carrier systems and because of their easier fabrication processes,

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solid dispersions, such as co-precipitates and co-melts, were the selected macromolecular drug carrier systems for this study. In contrast to simple solid powder physical mixtures, solid dispersions are particular systems, in which one or several drugs are dispersed in an inert solid carrier (Chiou, 1971; Duchene, 1986; Block and Speiser, 1987; Ford, 1987). In this work, a hydrophobic polymer matrix, namely poly(methylglyoxylate) (PMG), was chosen owing to its biodegradable properties (Brachais et al., 1998), and the drug dispersed in the matrix was a hydrophilic $\beta$-adrenoceptor blocking agent, namely metoprolol (Benfield et al., 1986).

PMG is a member of a series of potentially biodegradable materials synthesized in our laboratory (Brachais et al., 1997). It is composed of a polyacetal backbone whose sensitivity to acidic medium is well known. Our interest in this polymer lies in its particular degradation (i.e. each main cleavage involves an immediate depolymerisation) and also in the chemical nature of degradation products (Brachais et al., 1998; Brachais et al., in press): one can see that the final step of the PMG in vitro degradation leads to glyoxylic acid which is a metabolite of the Krebs cycle (Brachais et al., 1998; Brachais et al., in press) meaning that this new polymer is a true biodegradable compound. For all these reasons, PMG seems to be a suitable candidate for pharmaceutical applications. Moreover, preliminary toxicity studies of PMG on rats and mice seem to be very hopeful since no toxic effect was detected on animals (Duclos et al., 1995).

The purpose of this work is to present a new application of a biodegradable matrix (PMG) in the field of controlled release. Owing to the highly hydrophobic character of PMG, we proposed that a solid dispersion preparation of a highly hydrophilic drug in this polymer matrix will provide a controlled drug delivery device (Brachais et al., 1994; Duclos et al., 1994). To this aim, solid dispersions containing various concentrations of Metoprolol were prepared, either by fusion or by solvent methods. Chemical and thermal stability studies were performed on solid dispersions using SEC chromatography, differential scanning calorimetry and thermogravimetry analysis. Then, in vitro dissolution kinetics of metoprolol were recorded during 8 h in aqueous solution at pH 7, and compared with the kinetic dissolution of metoprolol from a commercial Seloken 200 LP tablet formulation. The experiment is limited to 8 h since intestinal absorption occurs in this time range and, moreover, previous studies show that there is no degradation of the polymer during this time (Brachais et al., 1998).

## 2. Materials and method

### 2.1. Materials

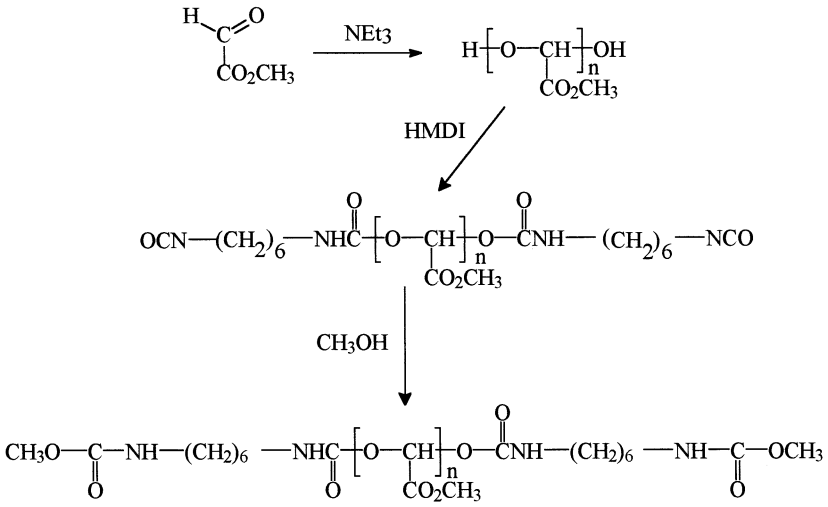
Methyl glyoxylate was kindly supplied by Société Française Hoechst. The commercial products, $CH_2Cl_2$ (SDS), triethyl amine (Fluka), $CH_3OH$ (Carlo-Erba), hexamethylene diisocyanate (Aldrich), chloroform (Prolabo), were used without further purification.

Metoprolol (1-[isopropylamino]-3-[*p*-($\beta$-methoxyethyl)phenoxy]-2-propanolol) tartrate salt (M.P. = 115°C) was purchased from Sigma Chemical Company.

### 2.2. Experimental methods

#### 2.2.1. Summary of the polymer synthesis (Scheme 1)

The first step of PMG synthesis is the purification of methylglyoxylate (MG) by distillation over $P_2O_5$ under 70 mmHg. A pale yellow liquid is obtained and polymerisation is carried out in dichloromethane, under $N_2$, with triethylamine as initiator at $-20$°C ([MG] = 7.6 mol $l^{-1}$ and [Et3N] = $2 \times 10^{-2}$ mol $l^{-1}$). For pharmaceutical applications, end-capping was performed using hexamethylene diisocyanate (HMDI) as terminating agent. A large excess of HMDI (twice with respect to chain extremities measured by SEC analysis) was used in the presence of a small amount of dibutyl tin dilaurate as catalyst, at room temperature for 24 h and at 40°C for 12 h. By pouring the polymer in methanol, the second isocyanate function reacts with the solvent and the PMG chains become chemically inert. The PMG synthesis is particularly delicate and a com-




Scheme 1. Synthesis of poly(methylglyoxylate).

plete procedure is described elsewhere (Muller, 1992; Vairon et al., 1994a,b).

### 2.2.2. Preparation of solid dispersions by the fusion method

Five g of physical mixtures of metoprolol/PMG at various drug concentrations (25, 35, 50 and 75%, w/w) were prepared and melted with continuous stirring in a silicone oil bath at 115°C. When the melt was homogeneous, the sample was removed from the oil bath and kept at room temperature until solidification. Then, the co-melts were desiccated during 48 h, pulverized and sieved to particle sizes between 250 and 100 $\mu$m for the first series (75, 50, 35 and 25%, w/w).

### 2.2.3. Preparation of solid dispersions by the solvent method

Five g of the above-mentioned physical mixtures were dissolved in chloroform, placed in the round-bottomed flask of a rotative evaporator, and maintained at 55°C in a thermostat-controlled water bath. The solvent was then removed under vacuum and the co-precipitates were desiccated, pulverized and sieved to particle sizes between 250 and 100 $\mu$m for the first series of samples (75, 50, 35 and 25%, w/w). The second series of samples (25, 15 and 5%, w/w) was prepared in the same way but was finally sieved to particle sizes less than 100 $\mu$m.

### 2.2.4. Size exclusion chromatography (SEC)

The average molecular weight was computed from chromatograms obtained by using a Waters 410 Gel Permeation Chromatograph with polystyrene standards. The SEC system consisted of two columns, PL-Gel 5 $\mu$ mixed-C, serially connected and working in methylene chloride. The detection was done using a Waters refractometric detector. All the samples ($C = 20$ mg/ml) were eluted at a flow rate of 1 ml/min.

### 2.2.5. Differential scanning calorimetry (DSC) analysis

DSC was used to determine the glass transition temperature ($T_g$) of the polymer and the crystallization behaviour of pure metoprolol and solid dispersions using a Perkin-Elmer DSC-7. The reported $T_g$ was taken at the onset of the curve. The heating rate was 10°C $min^{-1}$ and the sample weight was about 10 mg. The calibration was achieved with indium as reference material.

### 2.2.6. Thermogravimetric analysis (TGA)

The polymer thermal stability was followed by thermogravimetric analysis (TGA-7, Perkin-Elmer). Experiments were carried out on samples of about 10 mg at a heating rate of 20°C $min^{-1}$ from room temperature to 350°C. Isothermal measurements at different temperatures versus time were performed on the same apparatus.

*2.2.7. Dissolution studies*

Dissolution kinetics were carried out with the paddle apparatus of European Pharmacopeae (Dissolutest Safas, Prolabo) at 37°C on samples containing 200 mg of metoprolol. The dissolution medium (distilled water) was conveyed to a UV spectrophotometer by a peristaltic pump. The absorbance of the solution was monitored at 283 nm. Results were expressed as percentage of dissolved drug as a function of time and were the mean of six determinations.

## 3. Results and discussion

### *3.1. Physical properties of PMG*

From the SEC chromatograms, the average molecular weights of the polymer are $\overline{M_n} = 12500$ and $\overline{M_w} = 19500$ (Fig. 1, curve a) as determined from polystyrene standards.

By DSC analysis, PMG exhibits a glass transition temperature at 32°C, close to room temperature (Fig. 2, curve a). Thermogravimetric analysis does not reveal any degradation up to 150°C by heating the polymer at 20°C $min^{-1}$. Isothermal stability measurements at different temperatures pointed out a starting loss weight of 0.5% due to residual water content, and only 1% more at 115°C for 1 h against 10% at 150°C. From these results, PMG is considered to be sufficiently stable at 115°C to undergo the preparation of solid dipersions by the fusion method.

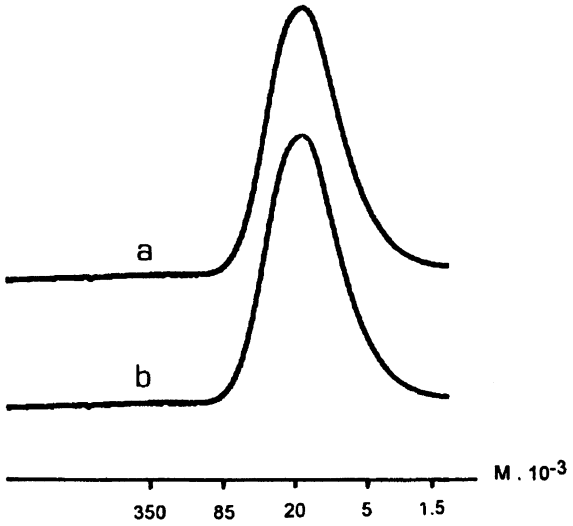



Fig. 1. SEC chromatograms: (a) initial PMG; (b) after 8 h in aqueous solutions at pH 1.3, 7.4 and 8.

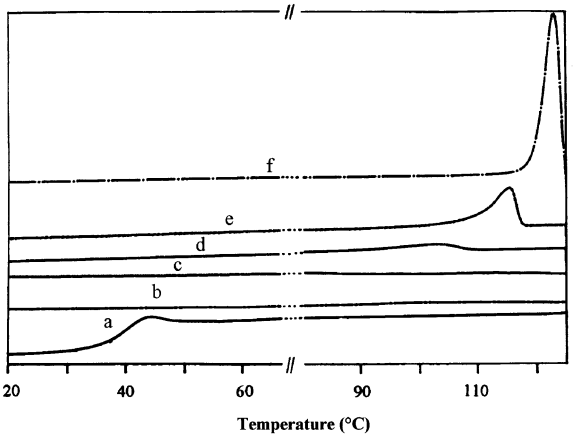



Fig. 2. DSC analysis of solid dispersions by fusion method: (a) initial PMG; (b), (c), (d), (e) and (f), respectively, with 25, 35, 50, 75 and 100% (w/w) metoprolol.

For pharmaceutical applications, the chemical stability of PMG, which is a hydrophobic polyacetal bearing methyl esters groups, has to be accurately determined. So, a degradation study, on a short time scale (8 h) corresponding to human transit, was carried out in various buffered aqueous solutions at pH 1.3, 7.4 and 8 (pH of stomach, blood and intestine, respectively). Then, the PMG was recovered from the three media and dried in order to perform a new SEC study. In each case, SEC analysis show that the chromatograms are similar to initial PMG chromatogram. This observation clearly proves that no degradation occurs in this time range for these three pH (Fig. 1, curve b). Indeed, in a previous study, degradation was found to occur after 9 days in neutral water (Brachais et al., 1998).

### *3.2. Metoprolol–PMG solid dispersions*

The ability of PMG matrix to release, in a controlled way, a definite amount of drug being totally unknown, the first step of this work was to test its performance with various amounts of incorporated metoprolol. To this aim, four samples

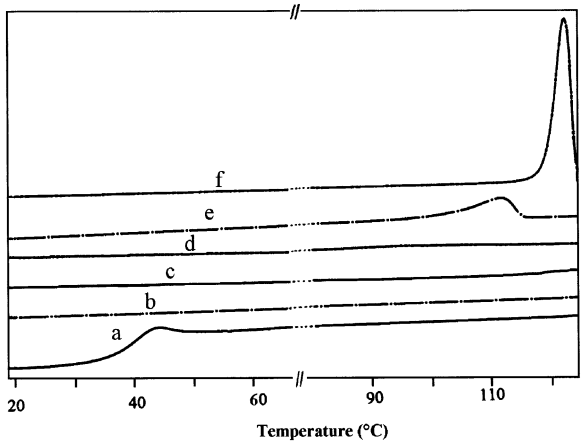



Fig. 3. DSC analysis of solid dispersions by solvent method: (a) initial PMG; (b), (c), (d), (e) and (f), respectively, with 25, 35, 50, 75 and 100% (w/w) metoprolol.

containing respectively, 25, 35, 50 and 75% (w/w) of drug were initially prepared by fusion or by solvent methods.

The pulverisation phase, which follows the preparation of the solid dispersions, proceeds in a mixer. If the temperature inside the mixer exceeds the glass transition temperature of the PMG ($T_g = 32$°C), the powder sticks to the apparatus and becomes rubbery. This phenomenon was observed in all cases, and thus reduction of the pulverisation time is indicated. The direct consequence is the limitation of the particle size, which varies between 250 and 100 $\mu$m. Thermal properties (Figs. 2 and 3) as well as SEC analysis were performed on these batches.

Firstly, it is noteworthy that metoprolol acts as a plasticising agent for PMG and decreases the glass transition temperature below 20°C. Secondly, for both co-melts (Fig. 2) and co-precipitates (Fig. 3), DSC curves exhibit a decrease of endothermic peak area and a lower melting temperature of the metoprolol phase when the concentration of active substance decreases. Moreover, no endothermic peak was detected for co-melts containing up to 35% of drug against 50% for co-precipitates. This result indicates that the sample preparation by the solvent method leads to a better drug dispersion in the PMG matrix. Finally, all the SEC chromatograms of co-melt and co-precipitate solutions in $CH_2Cl_2$ exhibit a polymer peak similar to initial PMG, as in Fig. 1, and another peak at the total permeation volume which corresponds to free metoprolol. These results show that polymer matrices were not degraded by the presence of metoprolol, and that there are no covalent bonds between polymer and drug as one could expect.

### 3.3. In vitro controlled release of metoprolol

The dissolution profiles of co-melts and co-precipitates for the first series (granulometry up to 250 $\mu$m) are presented in Figs. 4 and 5. The shape of the curves clearly shows two different parts, before and after 30 min.

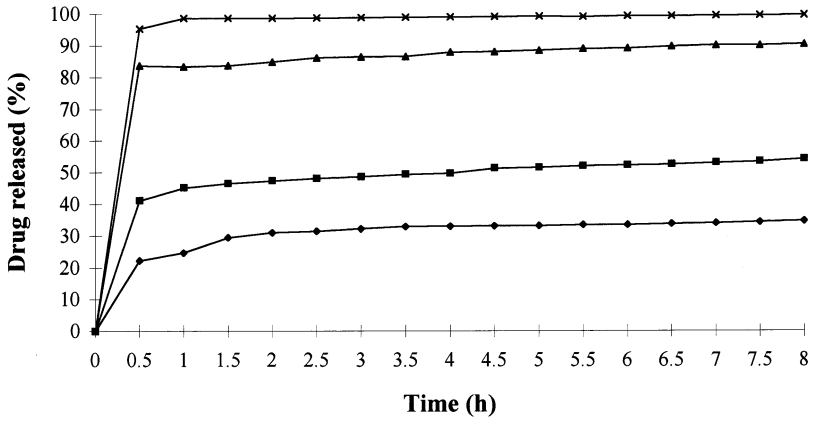



Fig. 4. Percent (w/w) of released drug from co-melts versus time (granulometry between 250 and 100 $\mu$m): (◆) 25, (■) 35, (▲) 50, (×) 75.

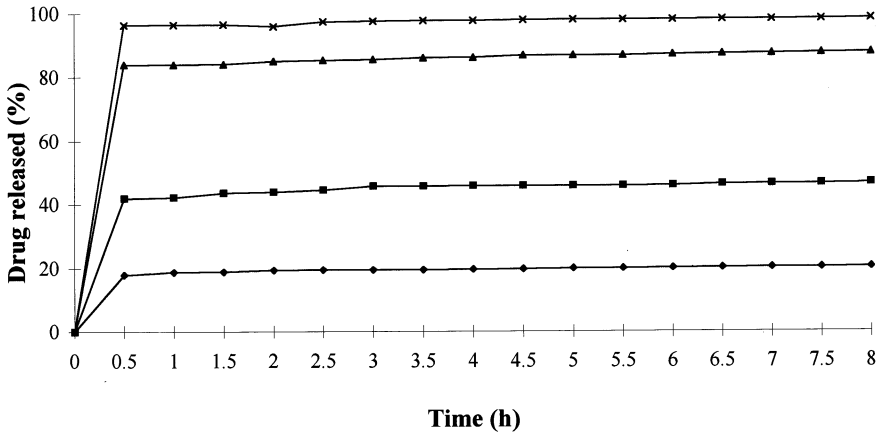



Fig. 5. Percent (w/w) of released drug from co-precipitates versus time (granulometry between 250 and 100 $\mu$m): (◆) 25, (■) 35, (▲) 50, (×) 75.

In the first part, for all solid dispersions, a fast release of metoprolol can be observed. The amount of released drug before 30 mn, is all the more important as the initial metoprolol concentration is high. This result can be explained by a non-homogeneous dispersion of the drug in the polymer. So, the initial burst effect is attributed to the excess of unincorporated metoprolol around the matrix which immediately dissolves in the medium. The low solubility of the drug in the polymer matrix involves an increase of drug aggregation, within and around the matrix, which finally leads to drug crystallisation. This behaviour is in good agreement with DSC studies which showed an increased amount of metoprolol crystalline phase when its concentration increases in the matrix.

The percentage of released metoprolol and the corresponding residual drug in the matrix (expressed in mg) at the end of the first step ($t = 0.5$ h) are reported in Table 1.

For the same initial drug concentration in the sample, and whatever the method of preparation used, no significant difference in the residual drug content can be noticed. However, the less the initial concentration is, the more the residual content. This result is due to a better dispersion of the drug in the matrix.

Concerning the dissolution profiles beyond 30 min, one can assume that release rates are in any cases very low and similar for both co-melts and co-precipitates containing the same metoprolol percentage, taking into account the accuracy of the measures (Table 1). Thus, the required times to release all the drug from the solid dispersions are far too long. The hydrophobia of the matrix and ionic interactions or hydrogen bonds between the drug and the polymer may explain this low release.

These preliminary results emphasize that lowering the concentration of the drug in the matrix improves the dispersion of the metoprolol in the polymer, reduces the initial burst effect and increases the remaining drug available for further release. However, a too slow release is observed whatever the initial drug content. In order to enhance this release, we have chosen to reduce the drug diffusion time through the matrix with lower granulometric delivery systems. Thus, a new series of co-precipitates containing 25, 15 and 5% (w/w) of metoprolol with a granulometry up to 100 $\mu$m were prepared by the use of a 'cryomixer' which allows mixing at $-18$°C. This low temperature avoids any aggregation of the powder during the mixing step.

Fig. 6 shows the dissolution profiles obtained for these co-precipitates during 8 h. Effectively, one can notice a significant improvement of the release. For the co-precipitate containing 25% (w/w) of metoprolol an important burst effect of about 50% is still observed during the first 15 min. This burst effect is greater than the one of the

Table 1
Percent of released drug, corresponding residual drug during the first step of the dissolution kinetic (0.5 h) and % of released drug at $t = 8$ h

| Drug content (%) in the solid dispersion at $t = 0$ h | Percent of released drug in the medium at $t = 0.5$ h | | Residual drug (mg) in the matrix at $t = 0.5$ h | | Percent of released drug in the medium at $t = 8$ h | |
|---|---|---|---|---|---|---|
| | Co-melts | Co-precipitates | Co-melts | Co-precipitates | Co-melts | Co-precipitates |
| 75 | 95.4 | 96.4 | 9.2 | 7.2 | 99.8 | 98.6 |
| 50 | 83.8 | 84.0 | 32.4 | 32 | 90.6 | 87.8 |
| 35 | 41.1 | 41.9 | 117.8 | 116.2 | 54.2 | 46.7 |
| 25 | 22.3 | 17.9 | 155.4 | 164.2 | 34.1 | 20.4 |

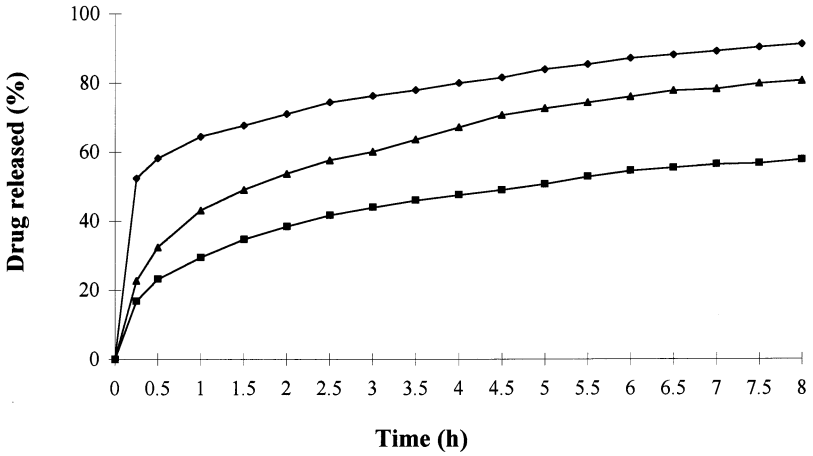



Fig. 6. Percent (w/w) of released drug from co-precipitates versus time (granulometry up to 100 $\mu$m): (■) 5, (▲) 15, (◆) 25.

corresponding co-precipitate with higher granulometry (about 20% in Fig. 5), probably on account of an increase of the overall particle area. However, 35% of drug is released for 7.5 h against 2.5% in the previous system. On the other hand, no burst effect is really detected before 15 min for the 15 and 5% (w/w) co-precipitates, and the shape of the curve is much more similar to those usually observed for controlled release systems. The 15% (w/w) metoprolol/PMG co-precipitate releases, in a controlled way, 80% of the drug after 8 h. This formulation seems to have suitable properties for a potential use in the field of controlled release.

So, we tested, under the same conditions, a tablet of Seloken 200 LP (Astra, France) also containing 200 mg of metoprolol. The dissolution curve of the tablet is reported in Fig. 7, and the metoprolol release rate, recorded during 8 h, is similar to the one obtained for the 15% (w/w) metoprolol/PMG co-precipitate. Nevertheless, even if the release rates of these two systems are similar, their difference lies in their respective concentration. The Seloken tablet (weight = 341 mg) contains 60% of drug compared to a maximum of 15% for the metoprolol/PMG co-precipitate (weight = 1.33 g). So, for the same dose (200 mg) of drug, the total amount of co-precipitate powder is four times higher than the one of the Seloken tablet.

## 4. Conclusion

From these results, we show that we are able to prepare a sustained release device containing a highly hydrophilic drug dispersed in a highly hydrophobic polymeric matrix. However, for high drug contents (75, 50, 35 and 25%, w/w) an important burst effect is observed in all cases, followed by a slow liberation of the drug in the medium. One explanation for these slow dissolution kinetics is the high hydrophobia of the PMG which limits the water diffusion inside the matrix. Such findings where observed on hydrophobic poly(methylmethacrylate) (PMMA) implants containing gentamicin and tobramycin (Robinson and Sampath, 1989; Weston et al., 1991), which also showed incomplete and poorly controlled release. In our study, lowering both the drug concentration in the solid dispersion and the granulometry of the powder seems to be a good way to prevent aggregation and avoid important initial burst effect. Moreover, the 15% (w/w) metoprolol/PMG co-precipitate releases about 80% of drug during 8 h and thus seems to be a suitable candidate for the preparation of an oral drug delivery system. However, the total amount of excipient used in the solid dispersion formulation is to high compared to the Seloken tablet one. So, we now plan to increase the percentage of incorporated drug in the formulation by increasing progressively the hydrophilic character of the ma-

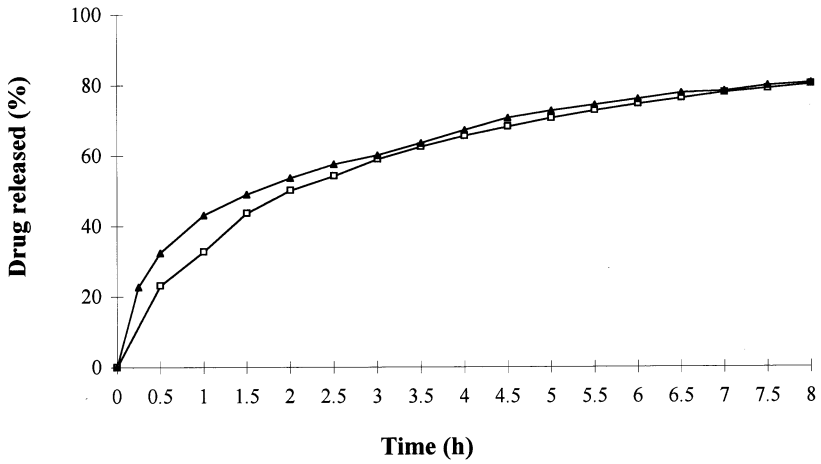



Fig. 7. Percent of released drug from a Seloken tablet (□) and from the 15% (w/w) (▲) co-precipitate (granulometry up to 100 $\mu$m) versus time.

trix. This can be done by modification of the hydrophilic/hydrophobic balance of the PMG matrix by partial hydrolysis of the methyl ester groups to hydrophilic carboxylic functions.

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