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# Progesterone freeze-dried systems in sublingual dosage form

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**Abstract**

Various polymer matrices were tested to enhance progesterone bioavailability as part of an emergency therapy. Among the different polymers used, i.e. poly(*N*-vinylpyrrolidone) (PVP), poly(ethylene oxide) (PEO), Dextran T70 and partially saponified poly(methyl glyoxylate) (PMGz), the latter gives the fastest solubilization rate. The best results were obtained with the lyophilized dosage form instead of a simple mixture of the drug within the polymer matrix. A nearly instantaneous solubilization was observed with PMGz copolymers bearing 10–40% of carboxylic groups and containing up to 20% of the drug. The instantaneous solubilization of the PMGz matrix is due to the hydrophilic moieties, and the presence of hydrophobic zones in PMGz promotes good affinity with the drug and optimal dispersion into the matrix. 

*Keywords:* Lyophilized dispersions; Poly(methyl glyoxylate); Progesterone; Solubilization

## 1. Introduction

Progesterone is involved in all aspects of reproduction. It is generally used for contraception (Progestasert *Therapix*), but when a woman is pregnant, this hormone is essential for the foetus development. Progesterone may therefore be urgently prescribed to prevent spontaneous abortion or premature delivery. In that case, progesterone is usually administered via injection (Tocogestan *Lypha Santé*) which is not comfortable for the patient. Two other methods currently used for progesterone delivery are also peroral and vaginal administrations (Estima *Effik*; Utrogestan *Besisn-Iscovesco*). However, these routes have some disadvantages, such as hepatic first pass metabolism and/or enzymatic degradation within the gastrointestinal tract. High doses of drug are, therefore, necessary for an effective treatment, which lead to side-effects (somnolence, dizziness,…).

Among the various routes of drug delivery, the oral route is regularly preferred by the patient.

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Moreover, the sublingual delivery (which is the delivery of drugs through the mucosal membranes lining the floor of the mouth) is by far the most appropriate administration for drugs with short delivery period requirements and infrequent dosing regimen. Mucosal membranes, which are relatively permeable, promote a rapid absorption and a good bioavailability of many drugs. This route has the advantage of avoiding the first pass effect and the presystemic elimination in the gastrointestinal tract, which is not the case for peroral administration. This route is also generally well accepted (Harris and Robinson, 1992). It is, therefore, of great interest to find a new sublingual galenic form capable of enhancing progesterone bioavailability.

Because of the water-rich environment of the oral cavity, the release system must be a water-soluble biocompatible polymer. In an emergency therapy, the matrix will have to dissolve rapidly in order to release a high drug concentration which will immediately be absorbed across the mucosa in the sublingual region.

As progesterone is slightly soluble in water (12 mg/l at 37 °C), the goal of this work was to choose the best matrix to obtain a very fine and uniform dispersion leading to an instantaneous solubilization of progesterone.

Table 1
Solvent compositions used for the different saponification rates

| Saponification rate $z$ (%) | $H_2O/CH_3CN$ (v/v) |
|---|---|
| 5 | 25/75 |
| 10 | 30/70 |
| 20 | 40/60 |
| 30 | 50/50 |
| 40 | 60/40 |
| 50 | 70/30 |
| 60 | 75/25 |
| 70 | 80/20 |
| 80 | 85/15 |
| 90 | 90/10 |
| 100 | 95/5 |

## 2. Materials and methods

### 2.1. Materials

Acetonitrile and potassium hydroxide were used without further purification. Progesterone (pregnene-4 dione-3,20) was purchased from Aldrich. Poly(*N*-vinylpyrrolidone) (PVP; Kollidon® 30), poly(ethylene oxide) (PEO; Lutrol E 6000) from BASF and Dextran T70 from Pharmacia were used as received. Water was freshly distilled before use.

### 2.2. Experimental methods

#### 2.2.1. Copolymers synthesis

The starting material was poly(methyl glyoxylate) (PMG; $\overline{M_n} = 12\,000$; $I = 2.9$) and its synthesis was described elsewhere (Brachais et al., 1997).

Random copolymers (PMGz) were prepared at room temperature by saponification in dilute conditions (1% w/w) in a mixture of solvents ($CH_3CN/(H_2O + KOH)$) whose composition changed with the saponification rate $z$ (Table 1).

Typically the potassium aqueous solution was added to a solution of PMG in $CH_3CN$ at room temperature and stirred for 6 h. After evaporation and concentration, the aqueous solution was dialyzed and lyophilized.

#### 2.2.2. Characterization

$^1$H NMR (500 MHz) spectra were recorded on a Brucker AM500 spectrometer using a mixture of deuterated solvents ($D_2O/CD_3CN$) whose ratio is identical to the saponification one.

Gas chromatography (Perkin–Elmer 1020 GC) with a Porapak Q column (*Interchim*) was used to follow the saponification reaction (isothermal at 180 °C). Acetone and acetonitrile were used as internal references.

#### 2.2.3. Dosage form preparation

*2.2.3.1. Lyophilized dispersion.* Thirty milligrams of progesterone hormone was added to 1 l of freshly distilled water. The medium was sonicated for 3 h at 50 °C, cooled and filtered over a 0.22-μm filter (Millipore, GS type). The progesterone content was determined by UV spectroscopy in the 9–12-mg/l range. The polymer

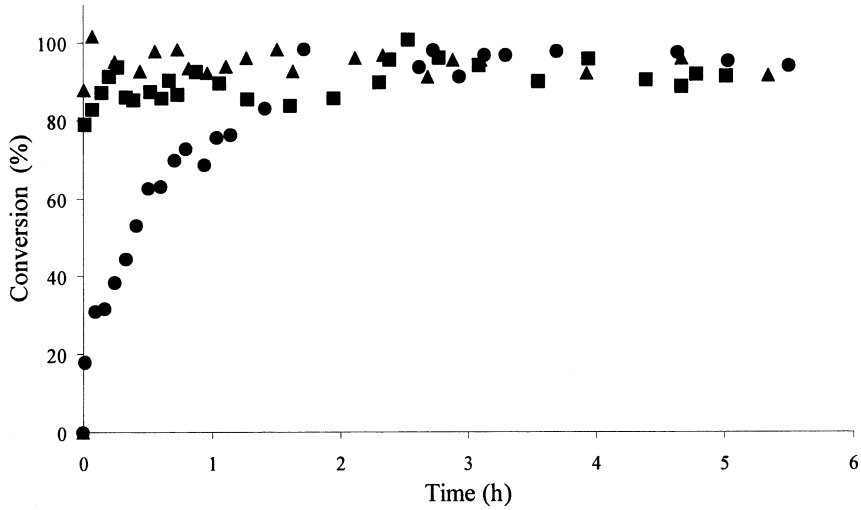



Fig. 1. Conversion versus time of the saponification reaction for three copolymers. $z$%: 32 (▲), 48 (■), 100 (●).

(Dextran, PEO, PVP or PMGz) was then added in order to have the chosen drug concentration (e.g. 10% w/w). After stirring the mixture was lyophilized.

*2.2.3.2. Simple mixture.* Thirty milligrams of progesterone hormone were added to polymer (Dextran, PEO, PVP or PMGz) and mixed in a mortar at the chosen drug concentration.

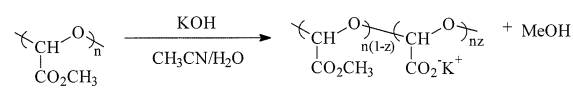
*2.2.4. Dissolution studies*

Dissolution kinetics were carried out with the paddle apparatus of European Pharmacopoeia (Dissolutest Safas, Prolabo) at 37 °C on samples containing 5 mg of progesterone. The dissolution medium was conveyed to a UV spectrophotometer by a peristaltic pump. The absorbance of the solution was monitored at 250 nm. Results were expressed as a percentage of the dissolved drug as a function of time.

## 3. Results and discussion

To obtain an instantaneous solubilization of progesterone, the polymer matrix must first dissolve in water as rapidly as possible. Then, the solubilization rate of the drug will depend upon its dispersion fineness. Therefore, the best results will be obtained when the drug content is low and uniformly dispersed in the matrix.

Among the biocompatible and water-soluble polymers that are currently being used or studied for drug delivery, Dextran, PVP and PEO are potential candidates. Their hydrophilic properties should lead to their fast dissolution in aqueous media. However, the lack of hydrophobic zones could be disadvantageous for the dispersion of a hydrophobic hormone, such as progesterone. These polymers were compared to hydrosoluble amphiphilic copolymers (PMGz), based on PMG, a bioresorbable polyacetal (Brachais et al., 1998). These copolymers have the advantage of bearing hydrophilic groups, which makes them hydrosoluble. Moreover, the presence of hydrophobic zones should lead to good interactions with the hormone. PMGz are obtained by partial saponification of PMG as follows:




PMG PMGz

where $z$ is the ratio of carboxylic groups.

The saponification rate can be followed thanks to gas chromatography, by monitoring the delivered methanol. At room temperature, the reaction may be considered as instantaneous (Fig. 1) and no degradation of the backbone occurs (Vauge-

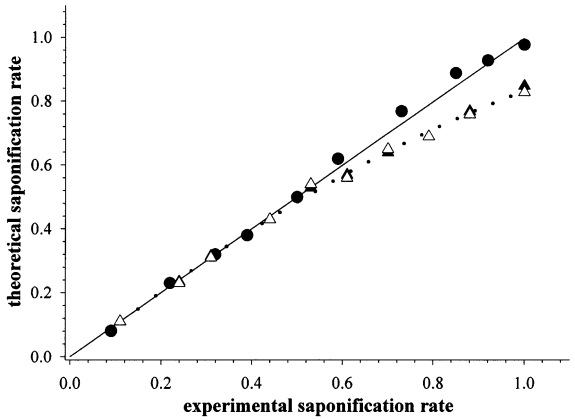



Fig. 2. Theoretical saponification rate versus experimental rate. $^1$H NMR (●); thermogravimetry (▲); flame photometry (△).

lade et al., 2000). A different pattern is observed in the case of the polysalt ($z = 100\%$). In fact, at the beginning of the reaction, PMG is not soluble in the media ($H_2O/CH_3CN$: 95/5 v/v). In this case, PMGz is solubilized as the saponification reaction increases, i.e. as $z$ increases.

Depending on the value of $z$, copolymers with variable hydrophilic/hydrophobic properties can be obtained. Therefore, by choosing the appropriate balance, one can control the release rate (Lescure et al., 1994).

### 3.1. Copolymer characterization

The difficulty was to know exactly the value of $z$ with respect to the amount of KOH used for the saponification. Indeed, methods, such as flame photometry and thermogravimetry analysis, leading to the $K^+$ content, are based on weighing. Thus, the presence of linked and free $H_2O$, which increases with the proportion of carboxylic groups, alters the measurements (Vaugelade et al., 2000). The experimental values of $z$ were therefore determined by $^1$H NMR. These values were found to be very close to the theoretical ratios of saponification when the analyses were carried out in a mixture of solvents ($D_2O/CD_3CN$) which was identical to the volume ratio used for the synthesis, whatever the value of $z$ (Fig. 2).

### 3.2. Progesterone dispersions

Lyophilized and mixed progesterone dispersions were prepared at various drug contents (10

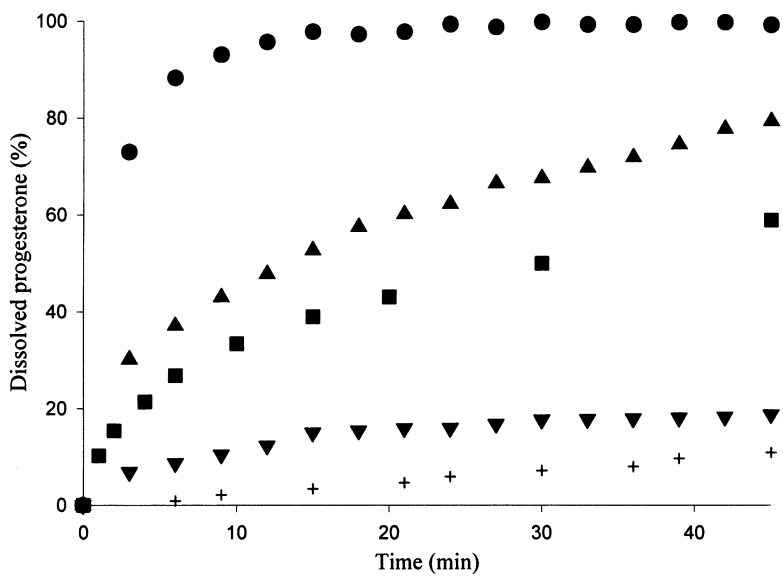



Fig. 3. Progesterone dissolution versus time for lyophilized dosage forms. PMG10 (●), PEO (▲), Dextran (■), PVP (▼), pure progesterone (+). Drug content: 10% w/w.

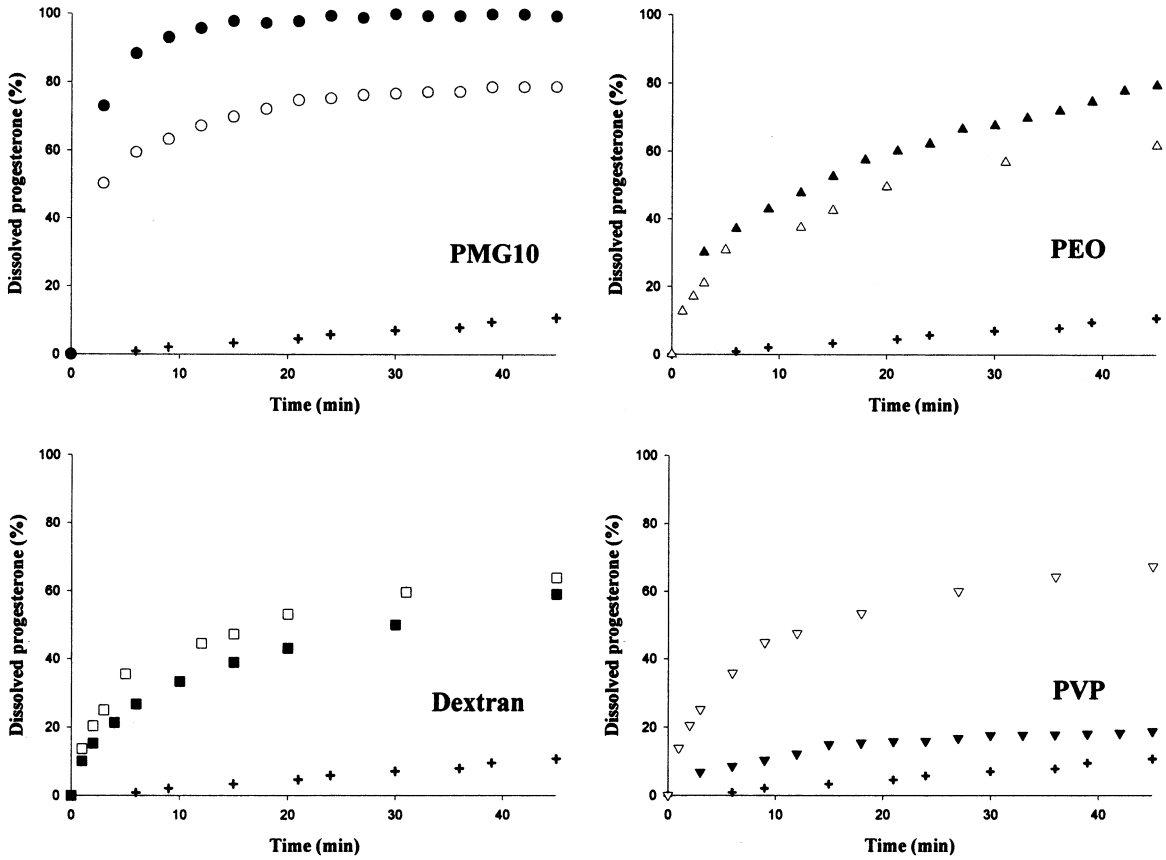



Fig. 4. Progesterone dissolution versus time for lyophilized (solid symbol) and mixed (open symbol) dosage forms. PMG10 (●, ○), PEO (▲, △), Dextran (■, □), PVP (▼, ▽), pure progesterone (+). Drug content: 10% w/w.

and 20% w/w) with Dextran, PEO, PVP, and PMGz. The resulting products were analysed by DSC in order to estimate the quality of the dispersion of progesterone in the different matrices. Progesterone exhibits a melting peak at 136 °C. Thus the presence of this endothermic peak reveals a poor dispersion of the drug in the matrix. It is the case of PVP, even for low drug content (5%). No peak was observed for Dextran, PEO and PMGz. Nevertheless, concerning PEO, this semi-crystalline polymer melts at about 60 °C and the influence of this transition on progesterone dispersion is difficult to evaluate.

### 3.3. Influence of the preparation of polymer matrix

Solubilization kinetics, at a constant drug content (10%), were achieved with a dissolution test coupled to a UV spectrophotometer, and in comparison to the dissolution of pure progesterone in water. In this study, the solubility of the matrices was assumed to be instantaneous whatever the type of preparation, i.e. simple mixture or lyophilized form. Thus, the observed experimental solubilization rates were only due to the physical morphology of progesterone, i.e. crystallized (small or large crystals), aggregated or free. First, one can notice in Fig. 3 that the lyophilized PMG10 matrix greatly improves progesterone solubilization with regards to PEO, Dextran and especially PVP matrices. Secondly, by comparing simply mixed and lyophilized products (Fig. 4), freeze-dried products lead to a quicker bioavailability of the hormone in the case of

PMG10 and PEO. This phenomenon was also observed by Hong et al. (1998) in the release rate of the 17β-oestradiol. In the case of PVP, and to a lesser extent of Dextran, slower solubilization kinetics are observed. For PVP, this abnormal result comes from the high hygroscopy of the lyophilized form which leads to an agglomeration of the preparation. In these conditions, it is the slow solubilization of the bulky matrix which controls the solubilization rate. Nevertheless, the worst result obtained for the PVP matrix was foreseeable following the DSC analysis; the presence of the melting transition of progesterone indicated a poor dispersion within the matrix.

PEO and Dextran-based lyophilized preparations had roughly the same behaviour and about 30 and 25% of drug, respectively, were solubilized after 5 min. The best result was obtained with PMG10 with about 85% of drug solubilized after 5 min. Therefore, in a general way, only hydrophilic matrices exhibited slower solubilization profiles. For these systems, the poor affinity between the polymer and the drug probably led to the presence of segregated zones of crystallized or aggregated progesterone, which explains why slower solubilization kinetics were observed.

### 3.4. Influence of saponification rate

The influence of copolymer composition was then studied on lyophilized PMGz matrices. The solubilization kinetics of progesterone for various values of $z$ ($z = 10$, 40, 100%), at constant drug content (10%), were achieved (Fig. 5).

As expected, PMG100, which is highly hydrophilic, had the slowest solubilization profile. An incomplete dissolution of the hormone is observed after 1 h, whereas 15 min were enough for a complete progesterone solubilization with PMG10 and PMG40. Due to their hydrophobic zones, PMGz copolymers with low values of $z$ have a good affinity with the drug. This leads to an optimal dispersion within the matrix and thereby to easy and similar solubilization in the aqueous medium.

### 3.5. Influence of drug content

PMG10 and PMG100 matrices were loaded with 10 and 20% (w/w) of progesterone. In agree-

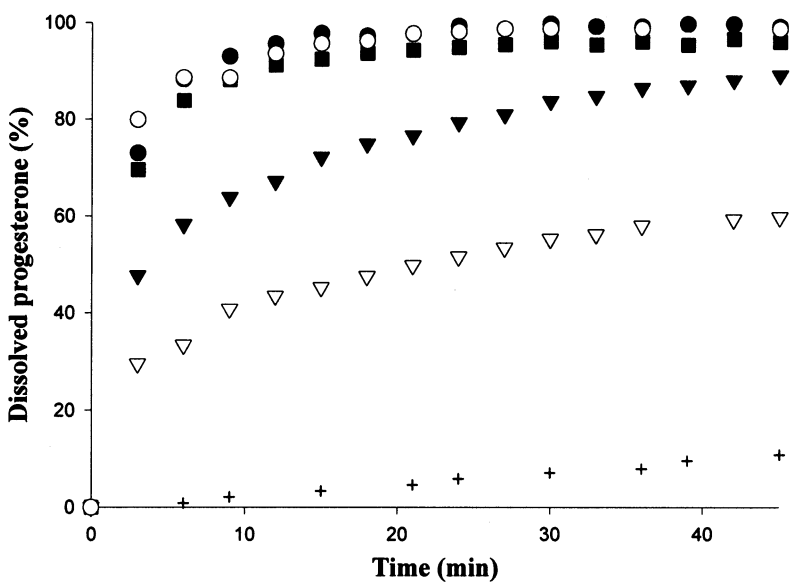



Fig. 5. Progesterone dissolution versus time at various drug contents: 10% w/w: PMG10 (●), PMG40 (■), PMG100 (▼) and 20% w/w: PMG10 (○), PMG100 (▽). Pure progesterone (+).

ment with the former explanation, a drop of the solubilization rate is observed for PMG100 as drug content increases (Fig. 5). In return, solubilization profiles are similar for PMG10, which reveals a clearly good interaction between the drug and the matrix.

## 4. Conclusion

Our goal was to design a sublingual delivery form giving a rapid absorption of the hydrophobic hormone. The suitable matrix should be hydrosoluble, in a lyophilized dosage form, with an optimal hydrophilic/hydrophobic balance.

PMGz copolymers are, therefore, of great interest since it is possible to modulate their hydrophilic/hydrophobic balance and to select the best suitable one. In the case of progesterone, fast solubilization was obtained with copolymers bearing 10–40% of carboxylic groups, containing up to 20% of drug. These results are very decisive, and new experiments with other highly hydrophobic drugs will be carried out to extend the use of these copolymers.

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