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Influence of poloxamers on the dissolution performance and stability of controlled-release formulations containing Precirol® ATO 5

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Abstract

Lipid excipients are usually used for the development of sustained-release formulations. When used in relatively high quantities, Precirol® ATO 5 imparts sustained-release properties to solid oral dosage forms, by forming a lipid matrix. To control or adjust the drug release kinetics from such lipid matrix however, one must often resort to complementary ingredients or techniques. This study investigates the influence of poloxamers (Lutrol®) included in lipid matrices composed of glyceryl palmitostearate (Precirol® ATO 5) on their dissolution performance and their stability. The addition of these hydrophilic polymers in the lipid matrix increased the amount of theophylline released thanks to the swelling of the hydrophilic polymer and the creation of a porous network into the inert lipid matrix. The grade and the quantity of Lutrol® could modulate the extent of drug release. Theophylline was released mainly by the matrix erosion but also by diffusion through the pores as suggested by the Peppas' model. Moreover, the addition of Lutrol® enhanced the stability during storage. The theophylline release was quite steady after 6 months in different conditions (temperature and humidity). Thus, the mixture of glyceryl palmitostearate and poloxamers is an approach with many advantages for the development of controlled-release formulations by capsule molding.
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Keywords: Capsule molding; Controlled release; Glyceryl palmitostearate; Poloxamer; Precirol®; Swelling

1. Introduction

Lipid excipients are classically used for the preparation of sustained-release formulations due to their lipophilic properties. Among other lipid excipients, Precirol® ATO 5, a glyceryl palmitostearate, has recently been used by various techniques in order to produce sustained-release formulations. Methods of preparation can be spray-chilling (Savolainen et al., 2003), hot-melt coating (Sinchaipanid et al., 2004) or melt granulation (Hamdani et al., 2003). However, the easiest method to produce semi-solid or solid systems with lipids is molding. These formulations can be molded in different shapes: capsules, tablets (Khan and Craig, 2003) or even in ethylcellulose cylinders (Mehuys et al., 2004a,b).

Sustained-release formulations obtained by capsule molding are made at least of the drug substance and the lipid excipient. The drug is released from the matrix system either by diffusion or erosion/digestion, or a combination of both phenomena.

The use of Precirol® ATO 5 by capsule molding can lead sometimes to a drug release too slow due to its high hydrophobicity (hydrophilic–lipophilic balance (HLB) value = 2). Some hydrophilic excipients were already added to Precirol® ATO 5 in order to adjust the drug release from the matrix systems or to solubilize the drug into the matrix system. For example, hydrophilic excipients such as mannitol or hydroxypropylmethylcellulose (Parab et al., 1986) or poloxamers (Savolainen et al., 2003) were already used. These excipients act as wetting agents inducing the creation of new pores in the matrices by penetration of the dissolution medium (Meshali et al., 1995; Miyagawa et al., 1996; Gren and Nyström, 1999; Fonknechten et al., 1999). The swelling of hydrophilic polymers plays also a great part in the creation of such pores (Parab et al., 1986). Poloxamers and Precirol® ATO 5 mixes led to very interesting dissolution patterns when used by spray-chilling. However, neither the addition of such excipient in molded lipid systems nor its stability during storage has been yet evaluated.

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Table 1
Properties of Lutrol® F68 and Lutrol® F127

	Molecular weight (g/mol)	Percentage of polyethylene–glycol polymers	HLB	Melting point (°C)
Lutrol® F68	8436	81.8 ± 1.9	29	52
Lutrol® F127	12330	73.2 ± 1.7	18–23	53–57

The aim of this study is to investigate the influence of two grades of poloxamers upon the dissolution performance of matrix systems obtained with Precirol® ATO 5 by capsule molding. In addition, the stability of the system is studied and the mechanism of drug release is postulated.

2. Materials and methods

2.1. Materials

Anhydrous theophylline (Pfannenschmidt, Germany) is used as a model drug.

Precirol® ATO 5 (glyceryl palmitostearate, Gattefossé, France) is classically used as a lipid vehicle for sustained-release formulations (Savolainen et al., 2003; Sinchaipanid et al., 2004). That excipient is composed of mono-, di- and triglycerides of palmitic acid (C_{16}) and stearic acid (C_{18}), with a hydrophilic–lipophilic balance value of 2 and a drop point ranging from 52 to 55 °C.

Lutrol® F68 and Lutrol® F127 (poloxamer 188 and 407, respectively, BASF, Germany) are hydrophilic block copolymers of ethylene oxide and propylene oxide. Main properties of these Lutrol® are presented in Table 1. Poloxamers were chosen as hydrophilic polymers in this study for two main reasons: first their melting points are ranging from 52 to 57 °C which is suitable for capsule molding and close to the melting point of Precirol® ATO 5; and secondly their HLB are sufficiently high to lower the surface tension between the lipid excipient and the dissolution medium.

2.2. Preparation of sustained-release formulations

Precirol® ATO 5 was melted in a microwave oven and then kept under its liquid form in a stirred-beaker at 70 °C.

Hydrophilic polymer (Lutrol® F68 or Lutrol® F127) was slowly added in the molten excipient under stirring. The grade and percentage of Lutrol® added in each formulation were defined by the factorial design of experiments (Modde, Umetrics, USA). That design of experiments is an orthogonal balanced design with all combinations of the factor levels (Table 2). It is composed of four runs (F1, F2, F4 and F5) as well as a center point performed in triplicate (F3). The confidence level on the model predictions is 95%.

Then, theophylline was dispersed (14.7%, w/w) in the molten mixture. Finally, formulations were filled into hard gelatin capsules (size 0, Licaps, Capsugel, France) and solidified by cooling at room temperature (at least 24 h). The quantity of theophylline in each capsule is 98.1 ± 0.9 mg.

2.3. Methods of characterization

2.3.1. Differential scanning calorimetry (DSC)

DSC is the most widely used method of thermal analysis to monitor endothermic processes (melting, solid-solid phase transitions and chemical degradation) as well as exothermic processes (crystallization and oxidative decomposition). It can be extremely useful in preformulation studies since it indicates the existence of possible drug-excipient or excipient–excipient interactions in a formulation. In the DSC method, the sample and reference are kept at the same temperature and the heat flow required to maintain the equality in temperature is measured. Five to 10 mg of sample was sealed in aluminum pan and analyzed using a differential scanning calorimeter (Pyris Diamond, Perkin-Elmer, USA) calibrated with benzoic acid (T_m = 122.4 °C) and indium (T_m = 156.6 °C, ΔH_m = 26.6 J g^{-1}). Thermal analysis was carried out between −20 and 120 °C at a heating rate of 3 °C min^{-1}. The range of temperature was focused on the melting temperatures of excipients. As a matter of fact, the analysis of theophylline melting peak is not a reliable indicator of miscibility due to the possible sublimation or degradation of excipients, or even dissolution of the drug into the molten excipients during the analysis (Khan and Craig, 2003).

2.3.2. Hot-stage microscopy (HSM)

Molded formulations as well as bulk materials were examined in a hot-stage microscope (optical microscope, Leitlz Wetzlar, Germany combined with a heating unit FP2HT, Mettler Toledo, France). Samples were heated at 5 °C min^{-1} until the excipient had melted (50–60 °C). Pictures of the sample (Canon Power

Table 2
Compositions of sustained-release formulations

Formulations	Drug	Lipophilic excipient	Hydrophilic excipient	Percentage of Lutrol®
F1	Theophylline	Precirol® ATO 5	Lutrol® F127	25
F2	Theophylline	Precirol® ATO 5	Lutrol® F68	25
F3	Theophylline	Precirol® ATO 5	Lutrol® F68	15
F4	Theophylline	Precirol® ATO 5	Lutrol® F127	5
F5	Theophylline	Precirol® ATO 5	Lutrol® F68	5

Shot S45, Japan) were taken after the excipients had melted in order to see whether any crystals of theophylline could be seen. Since the melting temperature of theophylline is 275 °C and the excipients melt between 50 and 60 °C, crystals of theophylline could be seen by HSM if the drug and the excipients did not form a solid solution.

2.3.3. Rheological properties

Formulations were analyzed directly after preparation with a rheometer (Contraves Rheomat 115, Contraves Rheoanalyser, Switzerland) in order to determine their rheological properties as a function of temperature. Rheological analysis was carried out between 80 °C and solidification of the formulation.

2.3.4. Dissolution studies

In vitro dissolution studies were performed (in triplicate—$n = 3$) using the rotating paddle method (Sotax AT7, Switzerland) according to the "Theophylline extended release capsule" type 2 monograph from the USP 26/NF 21. The dissolution medium (900 mL) was a phosphate buffer solution (pH 4.5) at 37.0 ± 0.5 °C. The paddle rotation speed was 75 rpm.

Capsules were filled with sustained-release formulations (680 ± 10 mg) corresponding to 100 mg of theophylline.

Theophylline was assayed with a UV-spectrophotometer at 271 nm (Hewlett-Packard, 8453, USA) at 5, 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 420 and 480 min. Cumulated released amounts were plotted as a function of time.

Dissolution efficiencies of each formulation were calculated as dissolution specification. Dissolution efficiency is defined as the area beneath the release curve up to 480 min, expressed as a percentage of the area of the rectangle described by 100% release in 480 min (Kahn, 1975).

Experimental data were fitted to Peppas' model (Eq. (1)) in order to analyze the release mechanism (Peppas, 1985).

$$F = kt^n \quad (1)$$

were F is the percentage of theophylline dissolved at time t, k and n are constants.

The dissolution study was also performed on formulations after 1, 3 and 6 months of storage at either 25 °C/60% RH or 40 °C/75% RH.

2.3.5. Water uptake and erosion of matrices

The effects of water uptake and matrices erosion on the theophylline release were analyzed by gravimetric evaluation (Sutananta et al., 1995; Gren and Nyström, 1999; Martin et al., 2002). Formulations, with or without drug, were analyzed (in triplicate—$n = 3$) after preparation, and after 1 or 8 h of dissolution.

The swelling ratio (SR) was calculated according to Eq. (2):

$$\mathrm{SR} = \frac{W_{\mathrm{wet}}}{W_0} \quad (2)$$

were W_0 is the matrix weight before the dissolution study and W_{wet} is the hydrated matrix weight at time t. The sample was kept 10 min at room temperature on paper wipes before weighting.

The water uptake (WU) was calculated according to Eq. (3):

$$\mathrm{WU} = 100 \times \left(\frac{W_{\mathrm{wet}} - W_{\mathrm{dried}}}{W_{\mathrm{dried}}} \right) \quad (3)$$

were W_{dried} is the weight after dissolution and drying at room temperature onto silica gel for at least 80 h up to a constant weight.

The percentage of matrix erosion (weight loss, WL) was calculated according to Eq. (4):

$$\mathrm{WL} = 100 \times \left(\frac{W_0 - W_{\mathrm{dried}}}{W_0} \right) \quad (4)$$

Before and after dissolution, sample appearance was analyzed with a stereomicroscope (MZ12, Leica, Germany), the diameter and the length were measured with an electronic digital micrometer (Codiam Scientific, France) and the pycnometric density was measured with an helium pycnometer (Accupyc 1330, Micromeritics, USA) with a 3.5 mL insert.

3. Results and discussion

3.1. Differential scanning calorimetry

Samples of excipients and theophylline, binary mixtures and formulations were melted and then analyzed by DSC in order to check possible interactions between these components (Fig. 1 and Table 3). The ratio between components corresponded to the formulation F1 or F2.

Binary mixtures of Precirol® ATO 5 and either Lutrol® F127 or Lutrol® F68 showed onset melting temperatures of 46.62 and 45.99 °C, respectively, showing a slight decrease when compared to the onset melting temperatures of these excipients analyzed alone.

Ternary mixtures corresponding to formulation F1 and F2 presented onset melting temperatures of 45.98 and 44.26 °C, respectively, close to the placebo temperature (i.e. binary mixture). The main interaction in these formulae seemed to be between Precirol® ATO 5 and poloxamers.

3.2. Hot-stage microscopy

Samples of excipients, binary mixtures and formulations were analyzed by HSM with a magnification of 10.

Precirol® ATO 5 presents a crystalline structure with a crux shape (Fig. 2A). The sample melting was achieved at 56 °C.

Table 3
Onset temperature and maximum temperature of excipients, theophylline and their mixtures during the first fusion by DSC

Excipient or mixtures	T_{onset} (°C)	T_{max} (°C)
Precirol® ATO 5	51.93	55.44
Lutrol® F127	53.81	56.87
Precirol® ATO 5 + Lutrol® F127	46.62	49.83
Precirol® ATO 5 + Lutrol® F127 + theophylline	46.01	50.97
Lutrol® F68	52.06	54.92
Precirol® ATO 5 + Lutrol® F68	46.05	51.53
Precirol® ATO 5 + Lutrol® F68 + theophylline	44.29	50.11

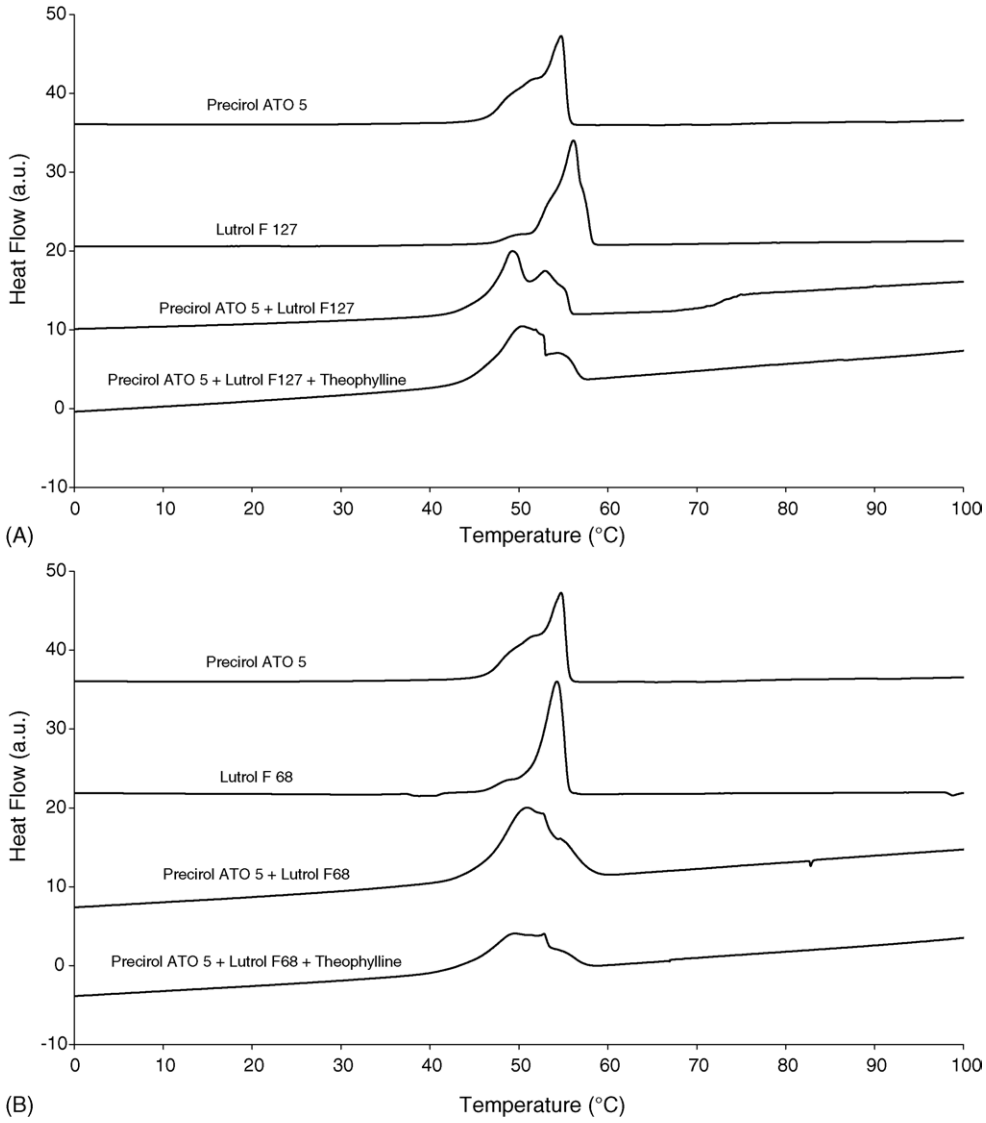

Fig. 1. DSC analysis of bulk materials, binary and ternary mixtures with Lutrol® F127 (A) or Lutrol® F68 (B).

Lutrol® F68 and Lutrol® F127 present also crystalline structures (Fig. 2 B and C, respectively) composed of multi-color sea-urchin like patterns. Their structures were close from one another, but clearly different from the one observed with the Precirol® ATO 5 sample. However, Lutrol® F127 crystals were rounder than those of Lutrol® F68. The complete melting temperature of Lutrol® F68 and Lutrol® F127 were, respectively, 53.5 and 56.2 °C.

Binary mixtures of Precirol® ATO 5 and poloxamers in various proportions showed crystalline structures close to the one developed by Precirol® ATO 5 but with smaller crux-shaped crystals. Fig. 3 presents the micrograph of the binary mixture of Precirol® ATO 5 and Lutrol® F 127 (29.3%, w/w) at 25 °C. After the complete melting of the mixture one homogeneous liquid phase was observed, both excipients seemed to be miscible in the ratio used in this study.

Ternary mixtures with theophylline present also crystalline structures close to the one observed on the Precirol® ATO 5 sample but with large crystals of theophylline (Fig. 4A). Previously binary mixtures of theophylline with either Precirol® ATO 5 or a poloxamer had shown that the drug is practically insoluble in both of these excipients. After the complete melting of Precirol® ATO 5 and poloxamers, crystals of theophylline were still observed by HSM (Fig. 4B). The mixture of these excipients did not solubilize the active substance and form a solid dispersion (Craig, 2004).

3.3. Rheological properties

The mixture viscosity rose with percentage of poloxamer in the formulation. For preparations containing 25% of poloxamer, the apparent viscosity was greater with Lutrol® F127 than with Lutrol® F68 (Table 4). That difference was due to the physicochemical properties of these excipients. As a matter of fact, Lutrol® F127 has a greater molecular weight than Lutrol® F68 and can be used to prepare more viscous solutions. On the other hand, apparent viscosity of the formulations containing 5% of poloxamer was the same whatever the grade of Lutrol®. The

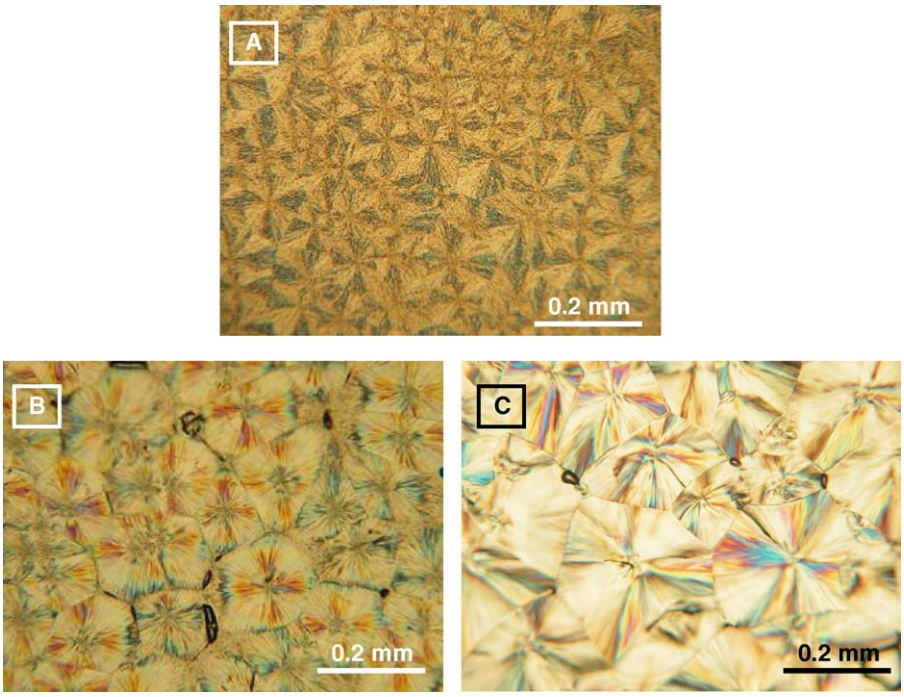

Fig. 2. Hot-stage micrographs of Precirol® ATO 5 (A), Lutrol® F127 (B) and Lutrol® F68 (C) at 25 °C.

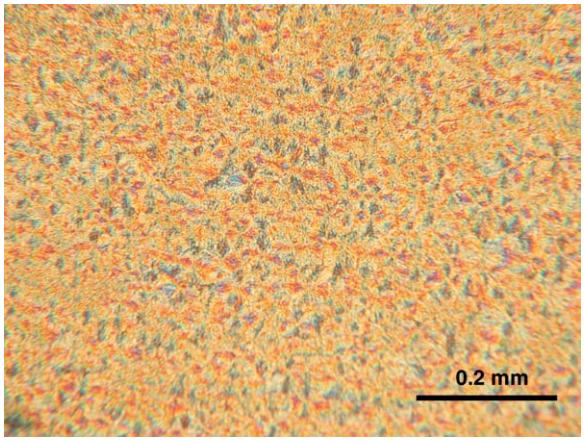

Fig. 3. Hot-stage micrographs of the binary mix of Precirol® ATO 5 and Lutrol® F127 (29.3%, w/w) at 25 °C.

Table 4
HLB value, dissolution efficiency and apparent viscosity at 60 °C of the five formulations

Formula	HLB	Dissolution efficiency (%)	Apparent viscosity at 60 °C (mPa s)
F1	7.9	22	506
F2	9.9	10	315
F3	6.7	5	180
F4	3.2	3	111
F5	3.6	3	113

impact of apparent viscosity on dissolution performance will be studied later in this paper.

3.4. Dissolution studies

Fig. 5 presents the dissolution profiles of the five formulations containing Precirol® ATO 5 and either Lutrol® F68 or Lutrol® F127.

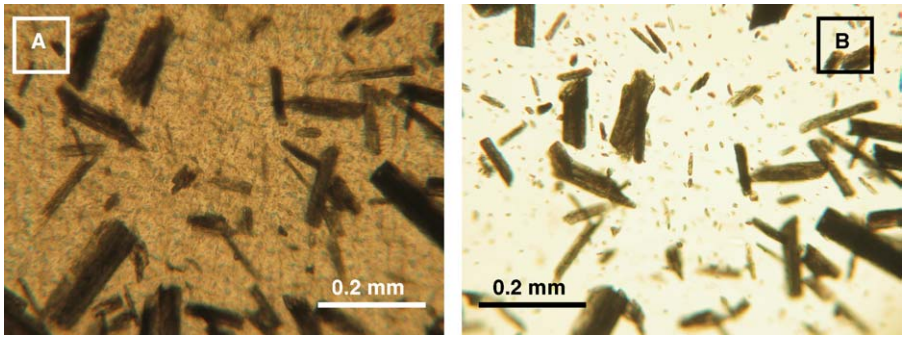

Fig. 4. Hot-stage micrographs of the formula F1 composed of theophylline, Precirol® ATO 5 and Lutrol® F127 at 25 °C (A) and 56.3 °C (B).

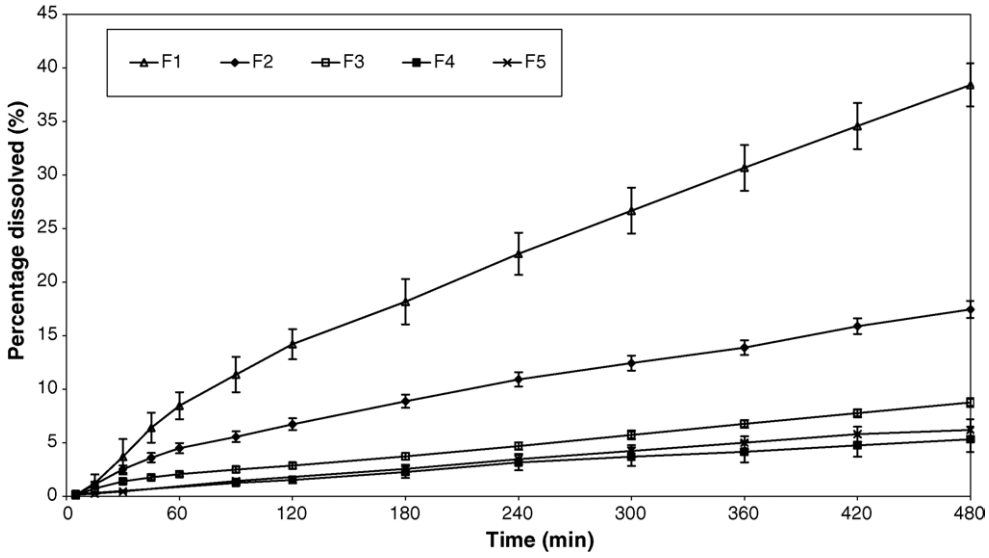

Fig. 5. Dissolution profiles of theophylline within formulations composed of Precirol® ATO 5 and Lutrol® mixes.

The best result in term of drug release was obtained with the formula F1 composed of 60.3% (w/w) of Precirol® ATO 5 and 25% (w/w) of Lutrol® F127. As a matter of fact that formula reached about 40% of theophylline released in 8 h, twice as much drug than the formula F2 containing 25% (w/w) of Lutrol® F68 or even 40 times more theophylline than the matrix without the hydrophilic polymer addition (Fig. 6).

These dissolution profiles show that the drug release and the dissolution efficiency (Table 4) increase when the quantity of poloxamers in the formula increases and when the grade of Lutrol® used is F127.

3.4.1. *Influence of the HLB*

The HLB value for each formulation was correlated to the drug release in term of percentage and grade of hydrophilic polymer. However, these effects were opposed. The addition of Lutrol® (whatever the grade used) into the lipid-matrix increased the HLB value and its drug release thanks to the less hydrophobic nature of the formula. On the other hand, for high quantity of Lutrol® (25%), the use of Lutrol® F68 instead of L utrol® F127 increased the HLB value but decreased the drug release. That behavior could be explained by the physico-chemical properties of these both Lutrol® (Table 1).

Lutrol® F68 is composed of more hydrophilic polyethylene glycol polymers than Lutrol® F127. That composition leads to a higher HLB value and a greater tendency to solubilize into the water. On the other hand, Lutrol® F127 is less water-soluble and swells more into water than Lutrol® F68.

The swelling of hydrophilic polymers is known to create porous matrix systems allowing the drug release (Miyagawa et al., 1996; Martin et al., 2002). Then the greater swelling of Lutrol® F127 could explain the higher drug release of formula F1 in comparison to F2.

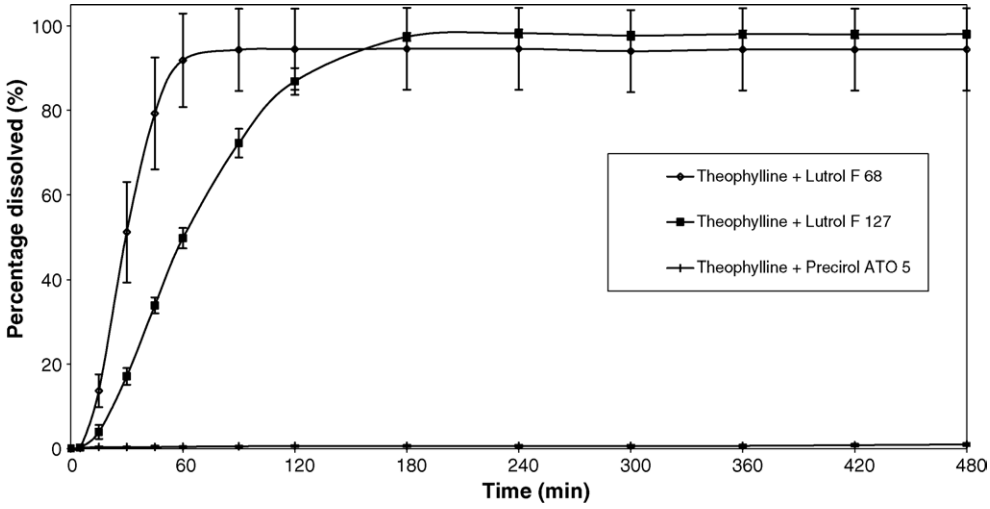

Fig. 6. Dissolution profiles of theophylline within formulations composed either of Precirol® ATO 5 or Lutrol®.

Table 5
Non-linear regression of the dissolution profiles with Eq. (1)

Formula	k	n	R^2
F1	0.3499	0.7609	0.9971
F2	0.2496	0.6869	0.9975
F3	0.0826	0.7499	0.9919
F4	0.0287	0.8475	0.9968
F5	0.0259	0.8918	0.9985

3.4.2. Influence of the apparent viscosity

The apparent viscosity of these formulations could also be linked to the drug release. Higher viscous formulations (F1 and F2) induced a greater percentage of theophylline dissolved. That kind of correlation was already described for lipid matrices. However, for these lipid formulations the drug release percentage increased when the apparent viscosity decreased (Duclos et al., 1999; Ratsimbazafy et al., 1999).

The addition of hydrophilic polymers, which increased the mixture viscosity (Table 4), reversed that relation because the drug release mechanism was different from the one of lipid matrices. As a matter of fact, if the mixture viscosity increased, the polymer needed more time to be dissolved in the dissolution medium and hence tended to swell. The swelling of hydrophilic polymers is well known to control the drug release.

Theophylline release from the five formulations was correlated to their apparent viscosities at a given temperature. For example at 60 °C, the relation followed Eq. (5).

$$\mathrm{DE} = 1.4743 + 0.0074\eta + 0.0001\eta^2; \quad R^2 = 0.9998 \qquad (5)$$

were η was the apparent viscosity at 60 °C (mPa s) and DE was the dissolution efficiency (%).

Finally formulations composed of Precirol® ATO 5 and Lutrol® increasing the percentage of theophylline dissolved into the dissolution medium could be screened by a rheological measurement.

3.4.3. Release mechanism

In addition, these dissolution profiles were fitted with the Peppas' release model (Table 5) with exponent n ranging from 0.75 to 0.89, indicating that all these formulations presented a dissolution behavior controlled by two concomitant mechanisms: diffusion (when n tends toward 0.5) and erosion (when n tends toward 1). Exponent n decreased with the quantity of Lutrol® in the matrix, so the diffusion mechanism gained more and more influence in the drug release. An equilibrium between the two phenomena was even reached with 25% of Lutrol® F127 (Formula F1) because the exponent n was equal to 0.75.

It should be noted that the Peppas' model fits perfectly the data after the first 11 min of dissolution. This "lag-time" could be explained by the time needed by the hydrophilic polymer to swell.

All these formulations were very hydrophobic because they contained more than 60% of Precirol® ATO 5. The drug was mainly released by the erosion of the matrices surface. However, matrices of Precirol® ATO 5 were solid and erosion-proof which explained the low dissolution rate. The addition of Lutrol® seems to help (i) the swelling of the matrix, (ii) the penetration of the dissolution medium inside the porous matrix due to their surfactant properties and (iii) the diffusion of the dissolved theophylline. These assumptions will be evaluated later in that paper.

3.4.4. Dissolution performance of Lutrol® matrices

Matrix formulations containing only the hydrophilic polymer and the active substance were also evaluated in term of dissolution. These formulations exhibited a fast drug release (Fig. 6). The formula containing Lutrol® F127 had a lower dissolution rate than the other formula. As a matter of fact, some studies showed already that the high molecular weight and viscosity of hydrophilic polymers decrease the dissolution rate (Salsa et al., 1997).

The Precirol® ATO 5 use in these hydrophilic matrices could control the drug release by limiting the hydration of the polymer. It favored also the process feasibility by decreasing the apparent viscosity of the mixture.

3.5. Water uptake and erosion of matrices

3.5.1. Stereomicroscopic observation of matrices

Fig. 7 presents the matrices after 8 h of dissolution. The swelling of these matrices increased with the quantity of hydrophilic polymer and the length of the dissolution testing.

Formulation F1 containing 25% (w/w) of Lutrol® F127 after 8 h of dissolution shows a dramatic increase of its size and the creation of many cracks more or less profound (Fig. 7A). The apparent volume of that formulation increased by 40% after the dissolution test.

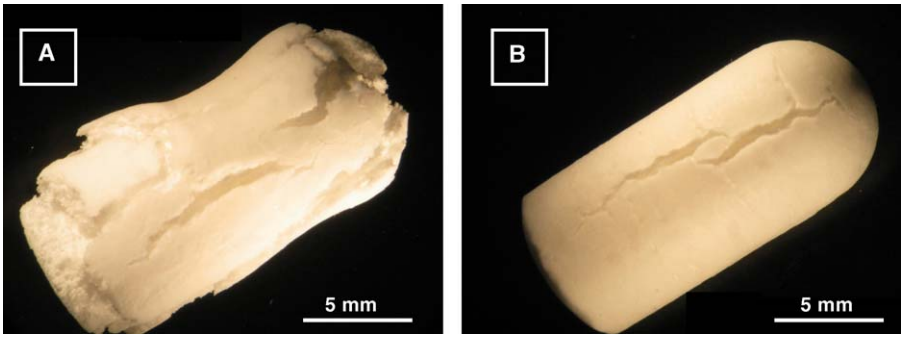

Fig. 7. Formulations F1 (A) and F2 (B) after 8 h of dissolution and drying onto silica gel at room temperature.

Formulation F2 containing 25% (w/w) of Lutrol® F68 after 8 h of dissolution shows a slight increase of its size and the creation of some cracks (Fig. 7B). The apparent volume of that formulation rose by 8% after the dissolution test.

Finally formulations with 5 or 15% of poloxamers showed a very limited increase of their sizes and nearly no crack. The increase of apparent volume for formulations F3, F4 and F5 were, respectively, of 4, 3 and 1% after 8 h of dissolution.

The apparent volume variation was correlated to the drug release and was more influenced by the grade than the percentage of Lutrol®.

It should be noted that placebo of these formulations presented higher increase of their apparent volumes after 8 h of dissolution. For example placebo of formulations F1 and F2 exhibited an increase of 75 and 32%, respectively. The addition of theophylline into these formulations limited their swelling. It could be due to the relatively low solubility of theophylline in the dissolution medium.

3.5.2. Gravimetric estimation of water uptake and erosion of matrices

Table 6 describes the swelling ratio, water uptake and weight loss of the five formulations after 1 and 8 h of dissolution.

The swelling ratio increased with the quantity of Lutrol® in the formulation and was more pronounced with Lutrol® F127. Again the placebo swelling ratio was dramatically superior confirming the observations made with the stereomicroscope.

The penetration of water into matrices was significantly lower for formulations with a low quantity of poloxamers. As a matter of fact, water can either be adsorbed by the hydrophilic polymer or entrapped into the cracks of the matrix. The surfactant properties of Lutrol® can explain the high penetration of water into the matrix inducing the swelling of the polymer. Lutrol® F127 is less water-soluble than Lutrol® F68, swells more and presents also a higher water uptake. Water seemed to be entrapped in the cracks of the matrices. On the other hand, the penetration of water was rather quick as about a third of that phenomenon happened during the first hour of dissolution.

The erosion increased with the quantity of Lutrol® in the formulation. Precirol® ATO 5 is hydrophobic and confers to the matrix system a resistance to erosion by avoiding the surface disintegration. That resistance gave matrices less sensitive to agitation rates in comparison to hydrophilic matrices and could lead to reproducible drug release in the complex hydrodynamic environment of gastro-intestinal tract.

These parameters were correlated to the drug release and could explain the release mechanism. During the first hour of dissolution, the hydrophilic polymer hydrated itself and the high amount of water uptake solubilized the theophylline. Then the hydrophilic polymers formed a gel and swell leading to a steady increase of the apparent volume and the creation of cracks by which the dissolved theophylline will diffuse out.

Table 6
Swelling ratio (Eq. (2)), water uptake (Eq. (3)) and weight loss (Eq. (4)) of the five formulations after 1 and 8 h of dissolution

Formula	SR	WU (%)	WL (%)
F1—1 h	1.21 ± 0.02	26.3 ± 0.9	4.5 ± 0.6
F1—8 h	1.54 ± 0.01	87.8 ± 4.3	17.7 ± 1.6
F2—1 h	1.09 ± 0.00	14.0 ± 0.6	4.0 ± 0.3
F2—8 h	1.21 ± 0.02	36.0 ± 2.3	11.4 ± 0.4
F3—1 h	1.04 ± 0.00	4.8 ± 0.3	1.2 ± 0.1
F3—8 h	1.10 ± 0.01	15.4 ± 0.5	4.7 ± 0.1
F4—1 h	1.02 ± 0.01	2.6 ± 0.6	0.5 ± 0.1
F4—8 h	1.06 ± 0.01	8.0 ± 1.1	1.9 ± 0.3
F5—1 h	1.01 ± 0.03	1.9 ± 0.4	0.5 ± 3.5
F5—8 h	1.04 ± 0.00	5.8 ± 0.3	1.6 ± 0.0

3.5.3. Pycnometric density of matrices

For formulations containing 15 or 25% (w/w) of Lutrol®, the pycnometric density increased after dissolution with the quantity of poloxamers and the length of dissolution. For example, formulations with 25% of Lutrol® F127 or Lutrol® F68 presented an increase of pycnometric density of 9% and the formulation with 15% of Lutrol® F68 of only 3%.

That pycnometric volume decrease and the concomitant increase of apparent volume of these formulations were due to the creation of cracks in the matrix system during the dissolution study.

3.6. Dissolution study of formula F1 after storage

After 1 month of storage at either 25 °C/60% RH or 40 °C/75% RH, the quantity of theophylline dissolved increased slightly (Fig. 8) as well as the exponent *n* from the Peppas' model (from 0.75 to 0.86). The dissolution profiles obtained after 3 or 6 months in the same conditions gave the same results (Table 7). The matrix system exhibited a dissolution mechanism with a more pronounced erosion behavior than after production.

The matrix system was quickly stabilized even after 1 month at 25 °C, then a suitable thermal treatment of that formula should be able to fasten that evolution.

In addition, during the first 2 h of dissolution, the profile was identical whatever the temperature or length of storage.

These results were quite satisfying because lipid systems obtained with the capsule molding process can exhibit dramatic changes of dissolution profile after storage. In addition, Precirol® ATO 5, like many other lipid excipients, presents a complex behavior in term of crystallization leading sometimes to a variation of drug release over time (Evrard et al., 1999; Hamdani et al., 2003). The addition of Lutrol® F 127 into Precirol® ATO 5 lipid matrix improved its stability over time even at 40 °C.

Table 7
Dissolution efficiencies of formulation F1 stored at 25 °C/60% RH and 40 °C/75% RH up to 6 months

Length of storage	Dissolution efficiency (%)	
	25 °C/60% RH	40 °C/75% RH
Initial	22	
1 month	23	26
3 months	25	27
6 months	24	27

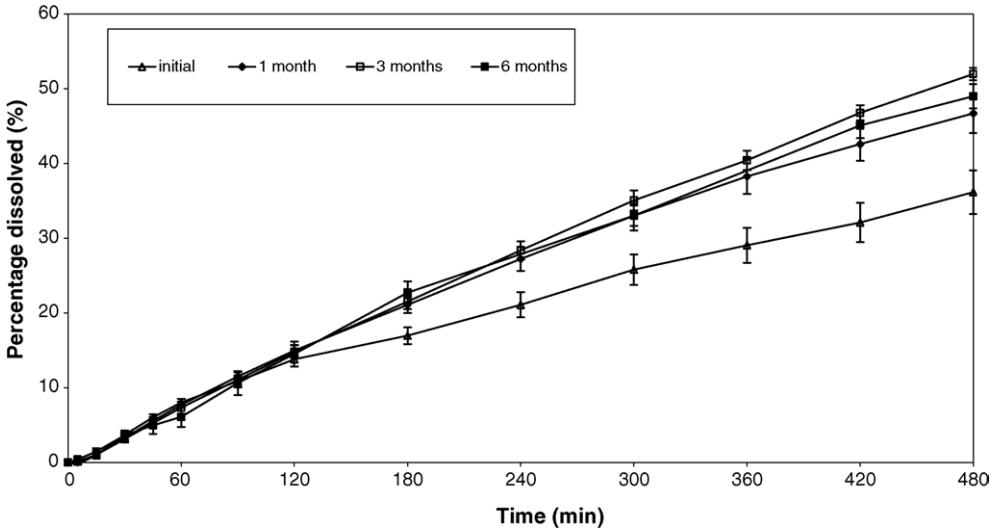

Fig. 8. Dissolution profiles of formulation F1 stored at 40 °C and 75% RH up to 6 months.

4. Conclusions

The addition of hydrophilic polymers such as Lutrol® in a solid matrix of Precirol® ATO 5 increased the quantity of theophylline released thanks to the swelling of the matrices with a growth of their sizes and the formation of pores. The increase of the poloxamer percentage in the formula helped to increase the drug release and the dissolution efficiency. These matrices underwent a gradual swelling that increased with the quantity of hydrophilic polymer. The grade of Lutrol® influenced also the dissolution, Lutrol® F127 giving a higher drug release (that polymer is less water-soluble). Furthermore the apparent viscosity of the formula increased with the Lutrol® addition. The drug release was correlated to the formula viscosity.

The swelling of these formulations created some pores into the matrix system inducing the theophylline release. Formulations with Lutrol® F127 presented a swelling ratio greater than the formulation with Lutrol® F68 and led to a more porous system hence a greater drug release. Theophylline was released mainly by the matrix erosion but also by diffusion through the pores, both phenomena increasing with the percentage of hydrophilic polymer.

The dissolution profiles over time were promising because the theophylline release was quite steady after 1, 3 or 6 months at either 25 °C/60% RH or 40 °C/75% RH.

The development of a theophylline controlled-release formulation with a mixture of Precirol® ATO 5 and a hydrophilic polymer such as Lutrol® F127 showed many advantages such as an increase in the drug release and a stabilization of the dissolution profile over time.

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