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Polyoxyethylene-polyoxypropylene block copolymer gels as sustained release vehicles for subcutaneous drug administration

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Summary

Polyoxyethylene-polyoxypropylene surface-active block copolymers (Pluronic®) were evaluated as a vehicle for subcutaneous administration of drugs using a phenolsulfophthalein (PR) as a tracer. The type of Pluronic® copolymer (F108 or F127), and their concentrations, and the effect of solutes (NaOH, NaCl or PR) on gelation properties were studied. Sodium hydroxide and sodium chloride decreased the gel-sol transition temperature, whereas the opposite effect was observed with PR. The 'in vitro' release rates obtained for PR were inversely proportional to the concentration of Pluronic used and a zero-order release rate was observed in all preparations assayed. Pluronic® F127/PR preparations were administered subcutaneously (SC) to Wistar rats and PR plasma levels were compared with those reached after SC or intravenous (i.v.) administration of a PR aqueous solution. The gel formulation produced a sustained plateau level within 15 min that lasted 8–9 h. In vivo data analysis was performed with the JANA and PCNONLIN computer programs. The best fittings for experimental data from Pluronic gels were obtained using a zero-order input and first-order output two-compartment model. The results obtained suggest that PF127 aqueous gels may be of practical use as a vehicle for SC administration of drugs.

Introduction

Pluronic® compounds are surface-active block copolymers of polyoxyethylene-polyoxypropylene with the following chemical structure:

$$HO(CH_2CH_2O)_a(CH(CH_3)CH_2)_b(CH_2CH_2O)_aH$$

A series of Pluronic® copolymers, which vary over a wide range of molecular weights and relative proportions of oxyethylene (OE) and oxypropylene (OP) moieties, are commercially available.

The copolymers with high molecular weights and high percentages of OE form monomolecular micelles in aqueous solution at low concentrations, but once the concentration rises above 20% (w/v), these compounds exhibit reverse thermal gelation (BASF publication no. OS 796).

Pluronic copolymers have been widely used in medical, pharmaceutical and cosmetic systems (Schmolka, 1972; Henry and Schmolka, 1989).

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The toxicity of these copolymers has been extensively studied (Johnston and Miller, 1985) and Pluronic® F108 and F127 have been proven to be the least toxic and skin irritant (Henry and Schmolka, 1989).

In the last few years, Pluronic® gels have been investigated as modern dosage forms for the topical application of cancer (Miyazaki et al., 1984) or burn (Nalbandian et al., 1987) treatments, and for rectal (Miyazaki et al., 1986), ophthalmic (Miller and Donovan, 1982), and nasal administration (Juhasz et al., 1989), as well as subcutaneous use (Morikawa et al., 1987).

The release rate from the gels has also been widely investigated, employing the model compounds of *p*-substituted acetanilides (Collet and Tobin, 1981), lidocaine (Chen-chow and Frank, 1981), 5-fluorouracil and adriamycin (Miyazaki et al., 1984), indomethacin (Miyazaki et al., 1986), diclofenac, hydrocortisone, and ketoprofen (Chi and Jun, 1991).

The Pluronic F108 and F127 aqueous gels appear to be useful in controlled drug delivery systems since they exhibit reverse thermal gelation behavior.

Phenol red (PR) is an organic substance that is used clinically to evaluate renal function, after parenteral administration (Remington Farmacia, 1985). Due to the ease of quantitation, as well as its clinical use, mentioned above, it was chosen as an ideal marker to investigate the in vitro and in vivo release patterns from the gels.

Materials and Methods

Materials

Phenol red was obtained from Hopkin & Williams (U.K.). Pluronics were a gift from BASF Española S.A. and were used as received. All other chemicals were of reagent grade.

Preparation of phenol red solution

The PR solution was prepared according to the USP XV method (Remington Farmacia, 1985). Briefly, a weighed amount of PR was added to ultrapure hot water (Milli-Q system of Millipore Corp.) made isotonic with sodium chloride and rendered soluble with sodium hydroxide.

Preparation of Pluronic gels

Pluronic F108 20% and 25% (w/v) and Pluronic F127 20% (w/v) gels were prepared by Schmolka's cold method (Schmolka, 1972). An appropriate amount of the Pluronic copolymer was slowly added to cold distilled water (5–10°C) and constantly agitated with a magnetic stirrer; the dispersion was left overnight in a refrigerator to complete dissolution.

Pluronic/PR gels were formed by the same method adding a weighed amount of the Pluronic to the previously prepared PR solution (5 mg/ml).

Sodium hydroxide (0.1680 g/l) or sodium chloride (9 g/l) were added separately to the Pluronic formulations to study their effect on the gelation temperature, as apart from the PR.

Evaluation of the gel-sol transition temperature

The evaluation of the gel-sol transition temperature was carried out using a modified technique described previously (Vadnere et al., 1984). It consists of a thermostatted glass tube (10 cm long × 0.8 cm i.d.) in which 2 ml of the cold polymer solution were placed. Then, the temperature was raised to 35°C and kept at that temperature for 30 min to achieve complete gel formation. The system was then inverted and the temperature slowly reduced at a rate of about 1°C/15 min (or 0.1°C in the region of the gel-sol transition temperature). The temperature at which the gel started to flow was taken as the gel-sol transition temperature. The sample had completely melted within the 0.2–0.3°C range.

Viscosity measurements

Viscosities of Pluronic® systems were determined using a Brookfield RVTD rotating cylinder synchroelectric viscosimeter.

Samples (200 ml) were left to settle over 30 min at the assay temperature before measurements were taken. The rotation speed of the internal cylinder was 100 rpm for Pluronic F108 20% (spindle no. 4) and 0.5 rpm for Pluronic F108 25% and Pluronic F127 20% (spindle no. 7).

Determination of in vitro release rates from Pluronic gels

Release rates were measured using a thermostatted dialysis cell (37°C).

The volume of each half cell was 5 ml for the donor compartment and 100 ml for the receptor compartment. These half cells were separated by a membrane (Visking 2-18/32 inch, Medicell Int. Ltd) with a surface area of 3.8 cm^2. 5 ml of the Pluronic®/PR formulation was placed in the donor compartment and 100 ml of pH 7.2 phosphate-buffered saline (PBS) in the receptor compartment with slow magnetic stirring. Similar methods have been used by other authors (Collet and Tobin, 1981; Miyazaki et al., 1984, 1986).

Samples (0.5 ml) of receptor medium were periodically removed and replaced with an equal volume of fresh pH 7.2 PBS equilibrated at the experimental temperature; PR concentration was determined spectrophotometrically (Spectronic 2000, Bausch & Lomb) at 558 nm in an alkaline medium.

All experiments were carried out in triplicate and the average values were plotted against the incubation time.

In vivo kinetic studies

Wistar rats (3 months old, weight 250–300 g) were fasted 24 h prior to the experiment but allowed free access to water.

Prior to administration they were anesthetized with intraperitoneal sodium pentobarbital (60 mg/kg), and an 0.2 ml drug-free blood sample was obtained from each rat, via the jugular vein.

Three groups of rats were anesthetized to receive: an intravenous bolus dose of saline PR solution; a subcutaneous dose of saline PR solution; or a subcutaneous dose of PR/Pluronic F127 20% gel.

Administration of all dosage forms was carried out at 20°C at a drug dose of 10 mg/kg.

Serial 0.2 ml blood samples were obtained via the jugular vein at predetermined times following intravenous or subcutaneous administration.

The plasma concentration of PR was determined by a flow injection analysis method using HPLC equipment (Waters 510 HPLC pump). Briefly, blood samples were centrifuged at 5000 rpm for 15 min, and 0.1 ml of plasma was treated with 10% (w/v) trichloroacetic acid to result in protein precipitation. The supernatant was used for PR plasmatic quantitation. 50 μl of the sample was injected into the system (Waters U6K injector) and detected with a tunable absorbance spectrophotometric detector (Waters 484) adjusted at 558 nm. Quantitation was carried out according to the area under the curve in a registrator-integrator (Waters 746 Data module) and transformed to concentration by means of a previously constructed calibration curve for PR in rat plasma.

Data analysis

Two nonlinear regression computer programs (JANA and PCNONLIN) (Dunne, 1985; Statistical Consultants Inc., 1986) were used to estimate the pharmacokinetic constants.

The iterative polyexponential curve stripping program JANA was used to obtain initial pharmacokinetic parameter estimates. These were entered in the second program (PCNONLIN), in order to achieve a better adjustment for experimental data, using the Gauss-Newton algorithms.

Results and Discussion

Gel-sol transition temperature

The gel-sol transition temperature was determined for Pluronic F108 at 25% (w/v) and for Pluronic F127 at 20% (w/v). Gel formation was

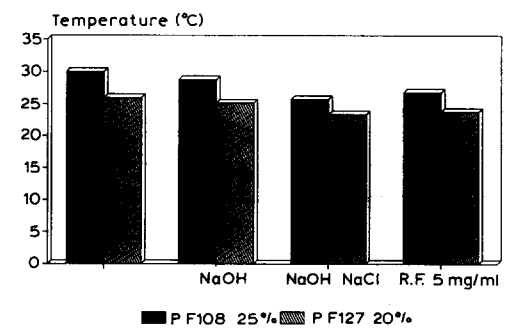

Fig. 1. Gel-sol transition temperature for Pluronic F108 and Pluronic F127. Each value represents the mean of three experiments.

not observed below these polymer concentrations. The results are illustrated in Fig. 1.

The effects of sodium hydroxide, sodium chloride and PR on gelation temperature were also investigated. In all cases, the gel-sol transition temperatures were lower than 37°C. The addition of NaOH and NaCl produced a decrease in this temperature in contrast to the effect observed with PR, which caused a slight increase.

Viscosity measurements

At 37°C, 20% (w/v) Pluronic F108 exhibits an apparent viscosity of 260 cps, whereas at 25% it amounted to 152×10^4 cps which is close to that of Pluronic F127 20% (145.6×10^4 cps). Measurements were carried out at 37°C to simulate physiological conditions and show the great difference between the 20 and 25% (w/v) Pluronic F108 concentrations according to their different physical states (fluid at 20% and gel at 25%).

In vitro release experiments

Fig. 2 shows the cumulative amount of PR release vs time at 37°C, from the formulations studied: Pluronic F108 at 20 and 25% (w/v), and Pluronic F127 at 25% (w/v).

TABLE 1

Amount released in vitro after 6.5 h, release rate and release half-life expressed as time needed for 50% drug release, from 5 mg / ml Pluronic / PR gels

Sample	Amount released (mg)	Release rate (μg/h)	Release half-life (h)
Pluronic F108 20%	6.92	1066	4.7
Pluronic F108 25%	2.35	369	13.5
Pluronic F127 20%	2.86	435	11.5

In all cases a typical zero-order pattern and a sustained release effect were observed.

The apparent release rate was determined by using the least-squares method that measures the slopes of the linear curve obtained from the fitted data. Table 1 lists the results.

The effect of the concentration of the Pluronic used on the release of PR showed an inverse dependence i.e., the higher the Pluronic concentration, the more marked the decrease in release.

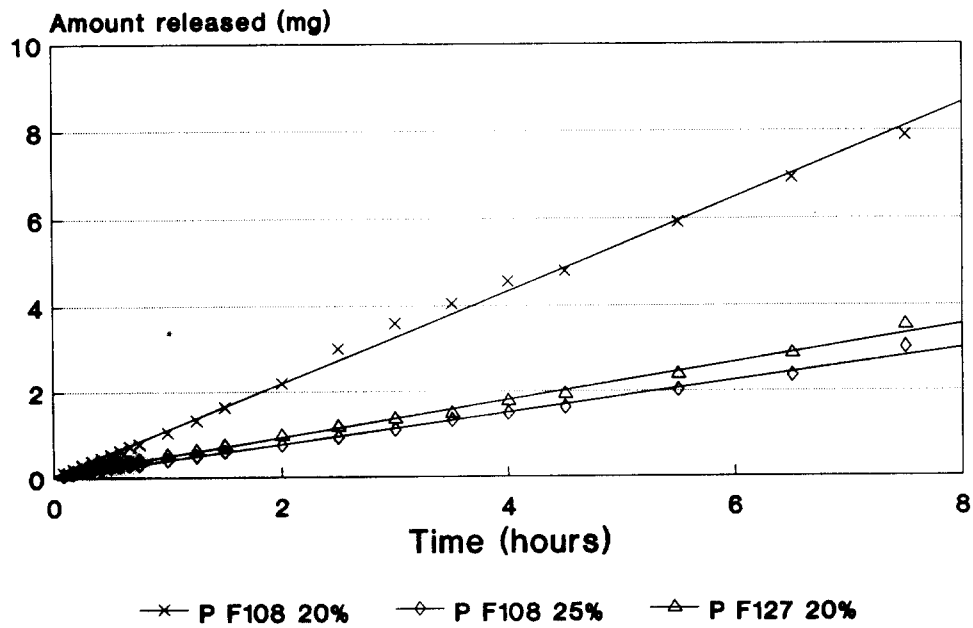

Fig. 2. Release of PR from 20 and 25% (w/v) Pluronic F108 and 20% (w/v) Pluronic F127 gels at 37°C. The concentration of PR was 5 mg/ml. Each value represents the mean of three experiments.

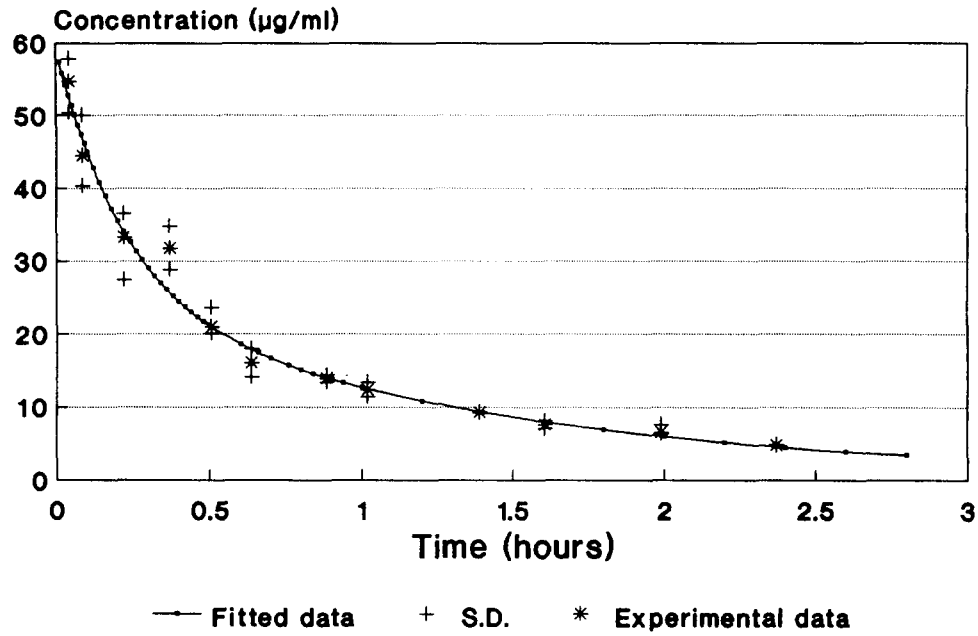

Fig. 3. PR plasma levels after i.v. administration of PR solution.

For 25% (w/v) Pluronic F108 and 20% (w/v) Pluronic F127 the amounts released at the end of the assay were of the same order of magnitude.

A marked reduction in the release rate was observed when the Pluronic F108 concentration was changed from 20 to 25% (w/v). This de-

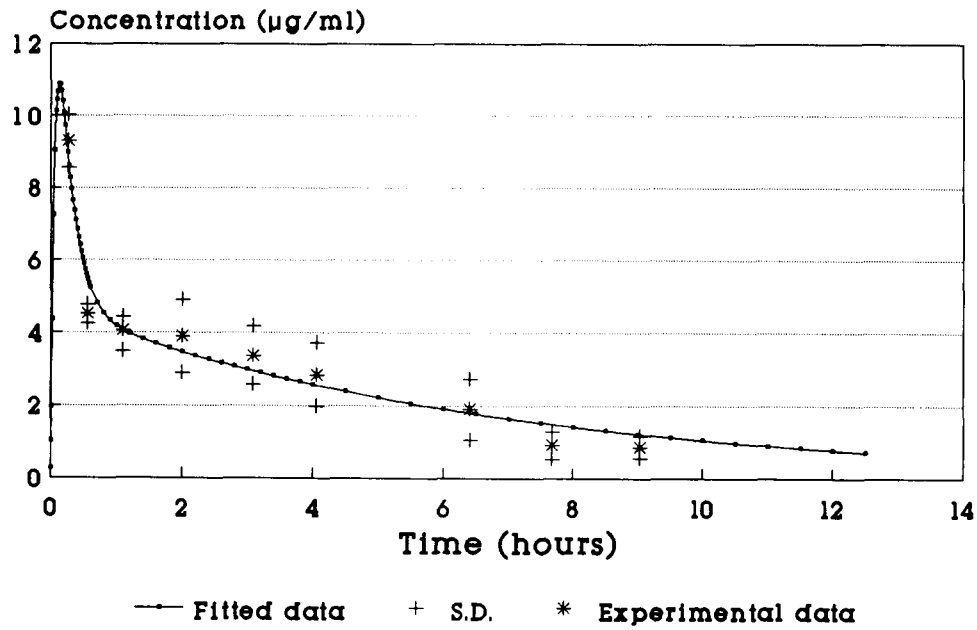

Fig. 4. PR plasma levels after SC administration of PR solution.

crease may be correlated with an increase in the viscosity of the vehicle.

Pharmacokinetic studies

The viscosity and gelation temperature results indicate that Pluronic F108 at 25% (w/v) and Pluronic F127 at 20% (w/v) were gels at the temperature of the in vitro release assays.

Release at 37°C was slightly faster from Pluronic F127 20% (w/v) than from Pluronic F108 25% (w/v), although of the same order of magnitude (release rate 369 and 435 μg/h, respectively).

On the basis of these small differences, Pluronic F127 was chosen for the in vivo experiments due to its very low toxicity, and because a lower amount of polymer would be administered.

The administration of PR was carried out under the three experimental conditions previously mentioned.

Intravenous administration of PR solution was performed in order to calculate the pharmacokinetic parameters of the drug.

The plasma PR concentration/time profiles have been plotted in Fig. 3. The data are presented as means $\pm$ standard deviation ($X \pm$ SD) with the nonlinear curve fitted data obtained from the PCNONLIN program with a bolus input, first-order output two-compartment model.

The correlation coefficient between the calculated and experimental data was 0.985.

Experimental data obtained in SC administration of PR solution were treated in the same way. First, a coarse data fitting was obtained with the JANA program ($A_0 = 23.71$ μg/ml, $B_0 = 5.63$ μg/ml, $K_{01} = 7.26$ h^{-1}, $\alpha = 7.21$ h^{-1} and $\beta = 0.25$ h^{-1}, $r = 0.889$). Thereafter, the data were fitted in a first-order input, first-order output, two-compartment model. The plot of the data is shown in Fig. 4.

Sustained plasma PR levels were observed after SC administration of Pluronic F127/PR gel.

Experimental data were entered in PCNONLIN and fitted in the two-compartment model with first-order input and output obtaining a correlation coefficient for the calculated and observed concentrations of 0.776.

Data were also fitted with a two-compartment model with zero-order input and first-order output, which generated a better adjustment (corre-

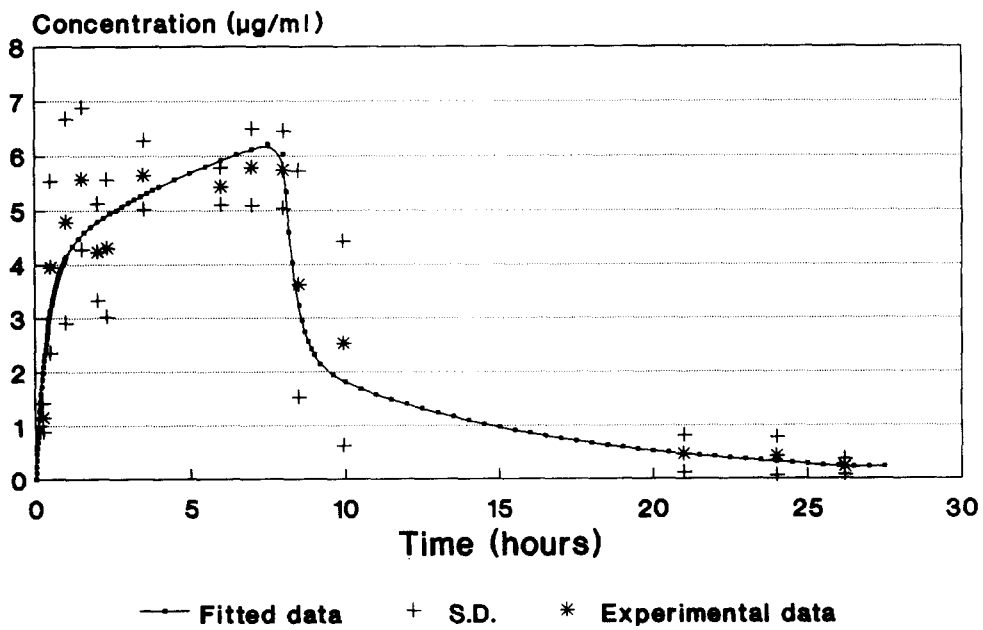

Fig. 5. PR plasma levels after SC administration of PR/Pluronic F127 gel.

lation coefficient of 0.961). Fig. 5 shows plasma PR levels and the fitting obtained vs time.

Discussion

F108 and F127 Pluronic copolymers have an OE content above 70% and respective molecular weights of 14 600 and 12 600.

These copolymers present reverse thermal gelation behavior at concentrations above 25% (w/v) for F108 and 20% (w/v) for F127 at 37°C. Previous studies have indicated that the minimum concentration needed for gel formation is 20% for Pluronic F108 at 37°C (Miyazaki et al., 1986). Our results do not agree with this assertion. After 0.5 h at 37°C, Pluronic F108 at 20% (w/v) shows low viscosity (260 cps), whereas at 25% (w/v), the viscosity was 152×10^4 cps. Nevertheless, a gradual increase in consistency was observed with time, but it was not homogeneous. This could be due either to air/gel interface surface gel formation from a low degree of water evaporation or to differences between batches in polymer synthesis, as has been suggested previously by others.

The thermal gelation mechanism can be explained by micellar desolvation and swelling to form a pseudo-cross-linkage among the polymer micelles. This swelling has been associated with conformational changes in the methyl groups of the polyoxypropylene chain. The network between the polymer molecules produces a progressive increase of the viscosity and the consistency of the vehicle upon heating.

Differential scanning calorimetry studies for Pluronic F127 solutions (Lenaerts et al., 1987) show that the cross-links between the polymeric chains are generated by relatively weak interactions, probably hydrogen bonds and/or Van der Waals forces (Vadnere et al., 1984). The hydroxyl groups are accessible by desolvation and can develop hydrogen and polar bonds. Likewise, gelation temperature decreases with increasing Pluronic concentration, since raising the concentration reduces the intermicellar distances and the degree of micellar swelling necessary for polymers to contact one another.

Furthermore, if the ionic strength of the solution is increased, part of the water will be engaged in ion solvation, so the number of accessible hydroxyl groups and the degree of micellar swelling will be increased, consequently reducing the gel transition temperature. The effect observed in Pluronic preparations with sodium chloride and sodium hydroxide (Fig. 1) can be explained with the above statement. These sodium compounds were necessary for the adequate preparation of phenolsulphophthalein injection USP, sodium hydroxide as a solubilizing agent and sodium chloride as an isotonicity-adjusting agent. In contrast, the effect observed with PR is the opposite. PR is slightly soluble in water, but is freely soluble in an alkali hydroxide solution by means of sodium salt formation. Since part of the sodium ions are engaged in this process, the gel-sol transition temperature rises slightly.

The size of the pores created between cross-links limits the release rate of the drugs (Lenaerts et al., 1987) which diffuse through the water channels in the gel matrix. As the concentration of Pluronic in the vehicle increased and the yield strength or rigidity of the gels rose, the release rate decreased (Table 1). Our results agree with the findings of earlier workers.

The increase in vehicle viscosity retards in vitro PR release, with zero-order kinetics being observed for all cases, in the order of least to greatest of Pluronic F108 25% < Pluronic F127 20% < Pluronic F108 20% (Fig. 2).

The PR plasma levels after i.v. administration allowed us to calculate the pharmacokinetic parameters of the drug and to evaluate the bioavailability of the SC preparations. In SC administration of the PR solution, higher PR plasma concentrations were quickly reached. Rapid absorption of PR was produced and maximum plasma concentration (C_{max} 10.89 μg/ml) was reached at 0.15 h (T_{max}), with an absorption rate constant of 16.19 h^{-1}. The observed sharp peak in the plasma concentration may be responsible for the standard deviation associated with this parameter.

The use of a Pluronic dispersion as an injectable preparation is based on the fact that when cold these formulations are solutions, and after injection they are warmed and form a gel that would constitute a depot within the muscle

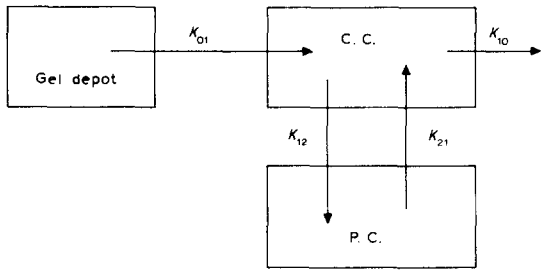

Fig. 6. Scheme of the zero-order input and first-order output two-compartment model, together with its general equation. K_{01}, input constant; K_{10}, output constant; K_{12} and K_{21} are distribution constants between the central and peripheral compartments.

$$C(t) = A[\exp(-\alpha t) - \exp[-\alpha(t - t_i)]] + B[\exp(-\beta t) - \exp[-\beta(t - t_i)]]$$

where t_i = length of release; $A = [(D/t_i)(K_{21} - \alpha)V^{-1}]/[(\alpha - \beta)\alpha^{-1}]$; $B = [-(D/t_i)(K_{21} - \beta)V^{-1}]/[(\alpha - \beta)\beta^{-1}]$; D = dose; V = volume of distribution.

or subcutaneous site. The SC administration of the Pluronic F127 gel preparation, in contrast to the administration of the PR solution, resulted in a sustained plateau plasma level of the drug within 10 min that lasted for 8 h (Fig. 5).

To fit the data to a pharmacokinetic model, it was assumed that an SC depot was formed at the injection site.

The high value obtained for K_{01} for the SC administration of PR solution (absorption half-life: 0.042 h) together with the zero-order kinetics of Pluronic F127/PR in in vitro release experiments suggest that the PR absorption process could be controlled by the release of PR from the gel subcutaneous depot.

A zero-order input and first-order output two-compartment model was used to test this hypothesis and resulted in a close fit of the experimental data ($r = 0.961$).

Fig. 6 shows a scheme for such a pharmacokinetic model.

No significant differences were observed in either the area under the PR plasma level-time curve (AUC) amongst the three groups ($P < 0.05$) [i.v. administration (42.49 ± 5.19), SC solution (33.58 ± 7.98) and SC gel (50.89 ± 10.9)] or in the pharmacokinetic constants ($P < 0.01$) K_{10} and K_{12} (Table 2). In contrast, the K_{21} distribution

TABLE 2

PR pharmacokinetic parameters after an i.v. bolus dose of saline PR solution, SC dose of saline PR solution and SC dose of PR / Pluronic F127 20% gel ($X \pm S.D.$)

Parameter (units)	PR solution (i.v.)	PR solution (SC)	Pluronic F127 gel (SC)
C_{max} (μg/ml)	59.15 ± 2.79	10.89 ± 0.22	6.25 ± 0.32
α (h^{-1})	4.59 ± 1.76	4.70 ± 1.88	2.62 ± 1.07
β (h^{-1})	0.72 ± 0.26	0.15 ± 0.01	0.12 ± 0.09
K_{01} (h^{-1})		16.19 ± 10.01	364 (μg/h) [a]
K_{10} (h^{-1})	1.39 ± 0.20	1.48 ± 1.01	1.43 ± 0.51
K_{12} (h^{-1})	1.53 ± 0.53	1.45 ± 1.63	1.09 ± 0.63
K_{21} (h^{-1})	2.39 ± 1.40	1.91 ± 1.04	0.22 ± 0.15
A (μg/ml)	33.61 ± 8.01	16.18 ± 47.17	83.79 ± 26.01
B (μg/ml)	25.54 ± 9.03	4.69 ± 0.22	83.79 ± 26.01
AUC (μg ml^{-1} h^{-1})	42.49 ± 5.19	33.58 ± 7.98	50.89 ± 10.90
$K_{01} \cdot T_{1/2}$ (h)		0.04 ± 0.26	3.85 [a]
$K_{10} \cdot T_{1/2}$ (h)	0.49 ± 0.07	0.43 ± 0.80	0.48 ± 0.17
$\alpha \cdot T_{1/2}$ (h)	0.15 ± 0.06	0.15 ± 0.21	0.26 ± 0.11
$\beta \cdot T_{1/2}$ (h)	0.95 ± 0.34	4.64 ± 1.47	5.62 ± 4.03
Volume ($1/K$)	0.16 ± 0.011	0.62 ± 0.25	0.12 ± 0.03
Correlation coefficient	0.985	0.965	0.961

[a] Values calculated from the equation:

$C_{ss} = K_{01}/V_c \cdot K_{10}$.

constant was significantly decreased in the gel preparation (0.22 ± 0.15 h^{-1}).

The absorption constant (K_{01}) for SC administration of the PR/Pluronic preparation was calculated from the steady-state concentration (C_{ss}) using the equation:

$$C_{ss} = K_{01}/V_c \cdot K_{10}$$

where V_c is the distribution volume and K_{10} the elimination constant.

Under these conditions, the time needed for 50% drug depot absorption (K_{01} $T_{1/2}$) was 3.85 h, when K_{01} was 364 μg h^{-1}. This value is relatively close to the release rate observed for Pluronic F127 20% (w/v) in the in vitro release assays (Table 1). On the other hand, the absorption rate for SC administration was higher for the PR solution than for the gel preparation, which supports the above hypothesis.

These results suggest that Pluronic F127 gels possess several properties (gelation and low toxicity) which appear to be particularly suitable for the preparation of controlled drug delivery systems for subcutaneous administration. Furthermore, their considerable solubilization characteristics for different drugs makes them useful in solubilizing water-insoluble drugs into these gels.

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