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Influence of lecithin on some physical chemical properties of poloxamer gels: rheological, microscopic and in vitro permeation studies

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Abstract

Thermoreversible gels may be used in delivery systems which require a sol-gel transition at body temperature. The influence of the addition of lecithin, a permeation enhancer, on the rheological and in vitro permeation properties of poloxamer 407 gels was investigated. Light microscopy and rheological parameters were used to characterize the microscopic structure of the formulations which showed non Newtonian behaviour, pseudoplastic flow with a yield value. Increased concentrations of lecithin increased the thixotropy, yield value, apparent viscosity, and the gelation temperature of the gels. Light microscopy showed the formation of micellar structures by the addition of lecithin, which may account for changes in rheological properties. In vitro permeation of a model drug, triamcinolone acetonide, was decreased when the lecithin concentration was increased. The presence of lecithin in the poloxamer gel improved the characteristics for topical drug delivery.

Keywords: Poloxamer 407 gels; Rheological study; Lecithin; Penetration enhancer

1. Introduction

Poloxamer 407 is a polyoxypropylene-polyoxyethylene surface-active block polymer composed of approximately 70% ethylene oxide and 30% propylene oxide with average molecular weight of 11 500. Reversible thermal gelation is one of the characteristics of aqueous solutions of this polymer, i.e. a 20–30% solution of poloxamer 407 is fluid at a temperature of approx. (4–5°C), but forms highly viscous gels at room and body temperature (BASF, OS-796).

The reversible sol-gel property of poloxamer 407 allows cool solutions to flow onto the skin or into wounds, permitting intimate surface contact before the formation of a non-occlusive gel on warming. Since the gelation is reversible, removal

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is facilitated by immersion in, or irrigation with cool water (Schmolka, 1972). Many authors have suggested that poloxamer gels have use as potential topical drug delivery systems having advantages over traditional bases in terms of ease of application, and drug release characteristics (Chen-Chow and Frank, 1981).

The flow properties of topical pharmaceutical preparations and their rheological characteristics (Barry, 1974) need to be controlled and understood. Most polymeric systems, like poloxamer gels, exhibit complex flow behaviour, including irreversible shear breakdown, thixotropy, etc. The presence of additives can modify some physical-chemical characteristics of poloxamer gels, such as gel-sol transition temperature (Vadnere et al., 1984), micellar properties (Attwood et al., 1985) and microviscosity (Gilbert et al., 1987). Penetration enhancers may be present in topical and transdermal systems in order to increase the skin permeability to drugs and they can influence the physical-properties of semisolid preparations. (Bentley et al., 1997)

Our previous work showed that the presence of the urea or lecithin as a penetration enhancer influenced the release profile and drug skin retention of a lipophilic model drug in poloxamer 407 gels (Bentley et al., 1995, 1997). In this work we have studied the influence of lecithin on the rheological and in vitro permeation properties of poloxamer 407 gels.

2. Experimental

2.1. Materials and methods

The following compounds were used as received from the suppliers without further purification: poloxamer 407 (BASF, USA), L- α- phosphatidylcholine soy bean (lecithin), triamcinolone acetonide (TA), desonide (Sigma, St Louis, MO) All others chemicals were BDH reagent or HPLC grade.

2.2. Preparation of gels

Twenty five percent w/v poloxamer 407 aqueous solutions were prepared by the cold process. Appropriate amounts of polymer and distilled water were refrigerated to increase the rate of solubilization. A concentrated polymer solution was obtained and lecithin added in the concentration range of 1–8% w/v. Liquid paraffin (5.0% w/v) was necessary to disperse the lecithin. TA (0.1% w/v) was previously dispersed in propylene glycol (5.0% w/v) and then added to the solution. The solutions were then brought to volume with water and throughly agitated while cold. All formulations were allowed to equilibrate for 24 h at room temperature before carrying out the studies.

2.3. Determination of gelation temperature

Formulations (0.25g) were enclosed in glass tubes (2 mm inside diameter) and observed over the temperature range 4–5°C. The change from sol to gel (or vice- versa) was determined by inverting the tube. The temperature was changed at a rate of 5°C h^{-1} and the temperature at which the physical state of the formulation was changed was regarded as the gelation temperature. In all cases the gelation temperature was reproducible to within 0.1°C. The gel melted completely within a 0.2–0.3°C range.

2.4. Determination of rheological properties of the gel

Poloxamer 407 gels containing lecithin within the concentration range 1–8% w/v of lecithin were assayed by a continuous shear method using a Rheotest 2.1 viscometer with concentric cylinders, designed for use with preparations with viscosities between 20.000–380.000 centPoise (cP). Samples, 20 ml were subjected to shear rate of 0–164 s^{-1}. The full scale torque was 5.500 dyne cm^{-2}. Samples were cycled through specified shear speeds. All measurements were carried out at specified temperatures.

The shear rate (D) and shear stress (τ) for this apparatus were determined as follows:

$$D = \frac{2\omega R^2}{R^2 - r^2}$$

$$\tau = \frac{M}{2}\pi r^2 L$$

where ω is the angular velocity of the internal cylinder; R the radius of external cylinder (4.0 cm); M the torsion; r the radius of the internal cylinder (3.9 cm); L the effective length of the cylinder (8.0 cm).

The apparent viscosity (η_{ap}) in poise (P) was obtained as:

$$\eta_{ap} = \frac{\tau}{D}$$

The yield value was obtained experimentally by extrapolating the linear portion of the down curve of the rheograms to the shear stress axis.

The reproducibility of the data was assessed by determining the rheograms at 25°C for the poloxamer gel without lecithin ($n = 5$). Viscosities obtained from the individual runs were averaged and the coefficients of variation were calculated, which ranged from 3.2 to 6.8%.

2.5. Light microscopic study

Light microscopy was carried out using a Zeiss Universal microscope with polarized light (rose filter) at 100 × magnification. In order to obtain a thin film suitable for microscopy, the gels were cooled at 4°C before being placed on a slide and covered with a cover glass. The photomicrographs were obtained at 25°C.

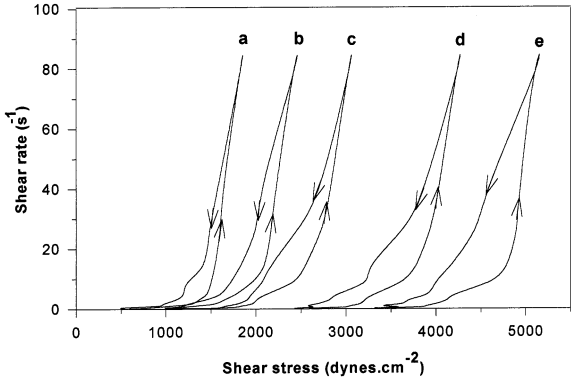

Fig. 1. Rheograms of poloxamer 407 gel (25% w/v) at 25°C as a function of lecithin concentration: (a) 0%; (b) 1%; (c) 2%; (d) 4%; and (e) 8% w/v.

2.6. HPLC analysis

All samples were analysed by HPLC system, Shimadzu model LC 10ADVP; UV detector at 254 nm; C18 reverse- phase colunn 125 mm × 4 mm (5 μm); Hewlett Packard 3390 A integrator; mobile phase methanol:water (60:40) at 1 ml min^{-1} and extraction was carried out using chloroform. Dexamethasone acetate (400 ng ml^{-1}) was used as internal standard. The retention time for TA and internal standard were 3.85 min and 6.10 min, respectively.

2.7. In vitro permeation study

Male hairless mouse HRS/J strain (Jackson Laboratories, Bar Harbor, ME) had their abdominal full-thickness skin excised and mounted in a diffusion cell. 2.0 g of the formulations were placed on the skin and the receptor solution was isotonic phosphate buffer (pH = 7.2) with 0.5% w/v of polyoxyethylene 20 cetyl ether added in order to ensure sink conditions. Samples from the receptor solution were withdrawn at predetermined times over a 12 h period and replaced with the same volume of fresh receptor solution. The amount of TA permeated was analysed by HPLC. After 24 h, the skin was removed, cleaned with cotton soaked in methanol, homogeneized in methanol, filtered, and the amount of TA was analysed by HPLC.

From the permeation profiles the TA flux across the membrane (J) were calculated.

2.8. Statistical analysis

Statistical comparison was made using non parametric Kruskal–Wallis test and Dunn's multiple range test with the help of an SAS program. The level of significance was taken as $p < 0.05$.

3. Results and discussion

Fig. 1 illustrates the shear rate versus shear stress for changes in the rheology of the poloxamers gels (25% w/v) at lecithin concentrations. Initially each formulation behaved like a semisolid,

Table 1
Rheological parameters and gelation temperature of poloxamer 407 gels in the presence of different concentrations of lecithin[a]

Lecithin % (w/v)	η_{ap}[b] (Poise)	Yield value (dyne cm^{-2})	Hysteresis area (cm^2)	Gelation temperature (°C)
0	415.1(±10.3)	1000.8(±21.4)	2.5(±0.11)	12.0(±0.2)
1	455.3(±8.5)	1550.3(±50.4)	3.6(±0.07)	14.0(±0.3)
2	705.9(±17.3)	1580.7(±55.3)	4.1(±0.04)	15.5(±0.2)
4	909.8(±11.5)	2850.3(±61.4)	5.4(±0.02)	16.5(±0.1)
8	1106.9(±27.8)	3750.2(±67.3)	7.8(±0.06)	17.8(±0.2)

[a] Non parametric Kruskal–Wallis statistic $p<0.05$ significant; all the data are summarized as mean ± standard error of mean, $n=10$.
[b] Apparent viscosity.

so that the flow curves are in the form of anticlockwise hysteresis loops, in accordance with the rheological behaviour of poloxamer aqueous solutions at high concentrations (Martin et al., 1964; Tung, 1984). All the rheograms showed a non-Newtonian behaviour of the pseudoplastic flow with, however, yield values. Some materials provide evidence of a yield value, but unlike the rheogram of a Bingham body, their curves are non-linear at greater shear stresses (Barry, 1974). Some thixotropy was observed in the rheograms and the concentration of lecithin had an influence on this parameter. In general, the overall shape of the rheograms remains constant, but the rheogram shifts toward the yield values and the size of the hysteresis loop increased as the concentration of the lecithin increased. The increase of the yield value indicates a gradual strengthening of the three-dimensional network structure of the gels. The yield value is that required to break down the solid structure and to initiate flow and is proper of plastic flow. The unusual rheological behaviour (pseudoplastic flow with yield value) found in the poloxamer gels studied can be the result of the association of liquid paraffin into the polymeric structure of the gel, being that the presence of lecithin interferes even more with the rheological parameter. Miller and Drabik (1983) could not define the flow of different poloxamer gels. The data did not clearly display either pseu-

Table 2
Apparent viscosities of poloxamer gels as a function of temperature and lecithin concentration

Temperature (°C)	0% Lecithin	1% Lecithin	2% Lecithin	4% Lecithin	8% Lecithin
5	28	35	57	73	88
10	29	35	58	72	89
11	33	36	58	73	89
12	95	38	59	81	91
13	190	40	60	81	92
14	220	125	61	83	93
15	260	195	250	87	97
16	280	280	375	450	102
17	300	350	503	600	210
18	330	400	600	720	503
20	399	425	670	820	887
25	415	455	705	909	1106
30	456	477	753	963	1195
35	472	497	783	998	1220
40	485	512	823	1070	1250
45	491	539	829	1080	1280
50	490	540	830	1090	1287

doplastic or simple plastic flow. For topical formulations the yield value must be sufficiently low to permit the removal from the container and facilitate spreading on the skin and yet sufficiently high to prevent the preparation dropping off the skin. The bioadhesive characteristics of polymeric gels have been related to their rheological behavior (Edsman et al., 1996; Jones et al., 1997 Madsen et al., 1998).

The rheological parameters and gelation temperature of the gel formulations studied are shown in Table 1. It can be seen that as concentration of lecithin increased there was an increase in the apparent viscosity (η_{ap}) of the gels. Such behaviour could be as a result of a decrease in the amount of the water in the formulation, resulting from the addition of lecithin. The increase of the concentration of lecithin increases the hysteresis area, indicating that it improves the thixotropic properties of the poloxamers gels. This behaviour may be attributed to the presence of liquid paraffin and phospholipid. The system promoted emulsion formulation, where micelles are formed, thus increasing the degree of strengthening of gel structure. This observation can be linked to the increase of the gelation temperature of the gels. Vadnere et al. (1984) found similar result when sodium dodecylsulfate was added to poloxamer gels, i.e. the transition temperature increased. The authors attributed this behaviour to the micellar solubilization provoked by the presence of the surfactant.

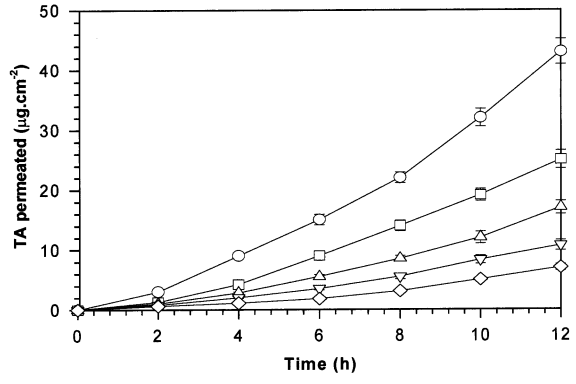

Fig. 2. In vitro permeation profiles of TA through hairless mouse skin from poloxamer 407 gels at different concentrations of lecithin: (○) 0%; (±) 1%; (△) 2%; (▽) 4%; and (◇) 8% w/v. Vertical bars indicate are mean ± standard error of mean, $n = 3$.

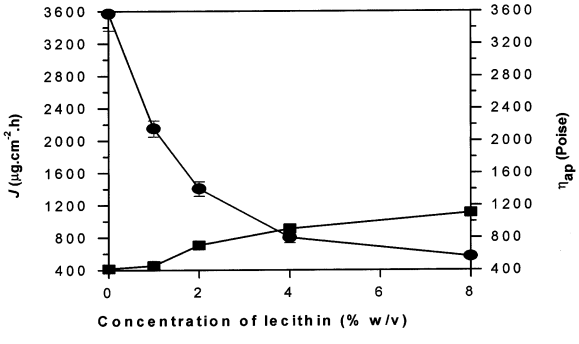

Fig. 3. Relationship between: (●) flux (J) of TA through hairless mouse skin and (■) apparent viscosiy (η_{ap}) as a function of concentration of lecithin. Vertical bars indicate as mean ± standard error of mean, $n = 3$.

The rheological parameters and gelation temperature were significantly different ($p < 0.05$) for gels containing 2, 4 and 8% w/w lecithin in comparision to that of the control (0% w/w lecithin).

Table 2 indicates the apparent viscosities (η_{ap}) of poloxamer gels at specified temperatures. It can be seen that at particular temperatures the η_{ap} shows a marked increase. These increases represent the sol-gel transition and occur at similar temperatures to those where a sol-gel transition was determined by the visual method.

The Fig. 2 shows the permeation profile of TA from poloxamer gels through hairless mouse skin. A linear relationship was obtained when the log total amount of TA in the receptor solution was plotted against time, indicating that the hairless mouse skin is permeable to the model drug and the permeation profile may be described by first order kinetic. As can be seen an increase of the concentration of lecithin led to a decrease in the amount of TA permeation. The flux (J) of the model drug and the apparent viscosity (η_{ap}) decreased and increased, respectively, as a function of the increase of lecithin concentration (Fig. 3). It may well be that the increase in the viscosity of the gel could be retarding the migration of the drug through the vehicle. Another explanation is that the lecithin could be interacting with TA molecules providing in this way a good solubilization medium for this lipophilic drug. Since polox-

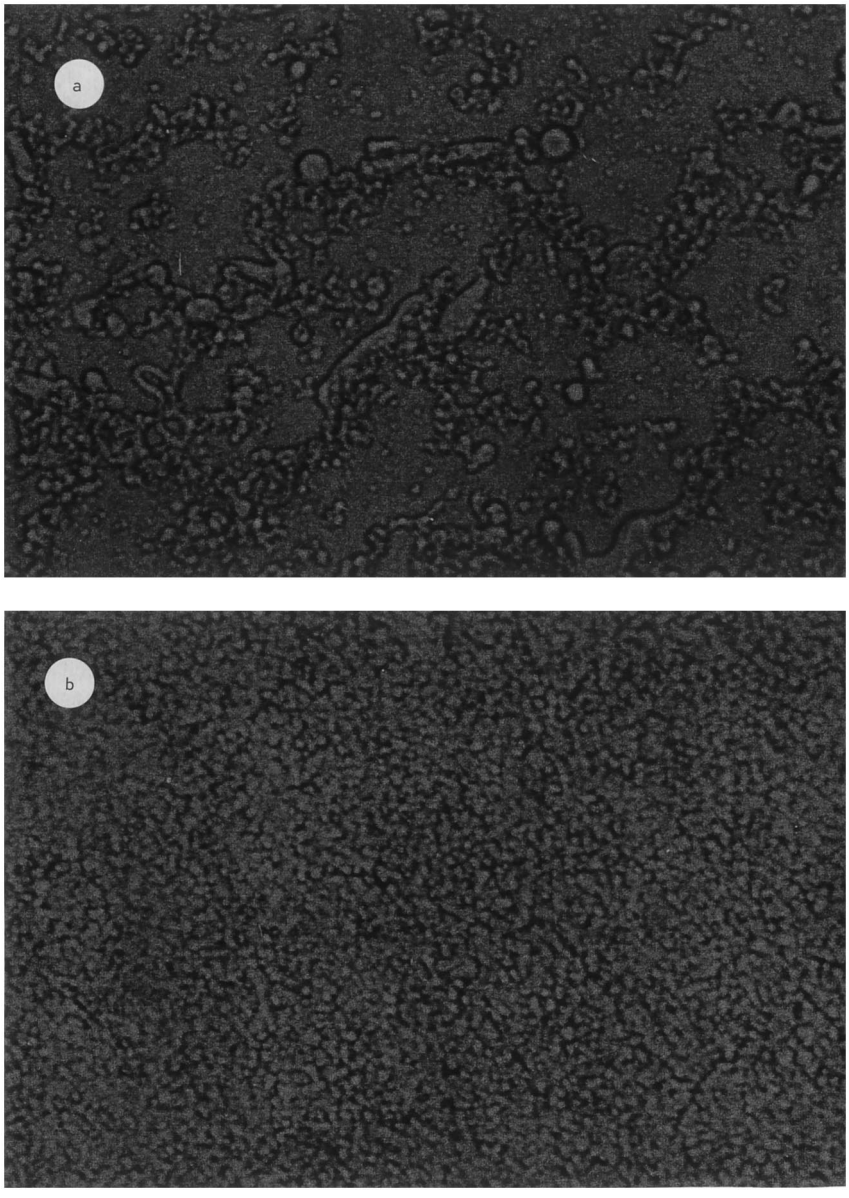

Fig. 4. Photomicrographs (100 × magnification) of poloxamer 407 gels containing: (a) 0% (w/v) lecithin; and (b) 2% (w/v) lecithin. The photomicrographs were magnified 4 × for reproduction.

amer 407 forms viscous isotropic liquid crystal gels consisting of micelles (Attwood et al., 1985), it is likely that the drug is released by diffusion through the extramicellar water channels of the gel matrix. The presence of micelles of lecithin could be changing the equilibrium of the drug in the gel matrix, thus modifying its release mechanism and rate. We found that the presence of lecithin in poloxamer 407 gels not only decrease the flux of a lipophilic drug through the skin, but also increased its skin retention: 25.3, 45.3, 70.4 102.3 and 240.7 μg g^{-1} skin for the preparations containing 0, 1, 2, 4 and 8% w/w lecithin, respectively. The skin retention and flux (J) of TA in the

presence of 2, 4 and 8% w/w lecithin were significantly greater ($p < 0.05$) than the control (0% w/w lecithin).

Fig. 4 shows photomicrographs of the poloxamer gels in the presence of lecithin (2% w/v). Aggregates of liquid paraffin can be seen very poorly dispersed in the isotropic gel structure of the gel. The addition of lecithin (2% w/v) permitted the formation of smaller and more uniform micelles. These microphases may account for the observation made in our previous work (Bentley et al., 1997).

Thus, it is suggested that lecithin provides an additional micellar structure in the polymeric gel thereby improving the characteristics of the formulations for topical delivery drugs.

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