J. Pharm. Pharmacol. 1995, 47: 455–457
Received November 2, 1994
Accepted November 28, 1994

Percutaneous Absorption of Indomethacin from Pluronic F127 Gels in Rats

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Abstract

Thermally reversible gels of the poly(oxyethylene)-poly(oxypropylene)-(polyoxyethylene) triblock copolymer, Pluronic F127, were evaluated as vehicles for the percutaneous administration of drugs using indomethacin as a model drug.

In-vivo percutaneous absorption studies using a rat model suggest that a 20% w/w aqueous gel of Pluronic F127 may be of practical use as a base for topical administration of the drug. The addition of isopropyl myristate or (+)-limonene to the gel formulation significantly improved percutaneous absorption, particularly when the gel was applied using an occlusive dressing technique.

Indomethacin has been widely used as a potent non-steroidal drug having anti-inflammatory and anti-pyretic effects. However, the oral administration of indomethacin using conventional dosage forms can cause serious systemic side-effects and gastric irritation, and the possibility of the administration of this drug by topical application is currently under examination. Indomethacin applied directly onto the inflamed site would offer the advantage of delivering the drug directly to the disease site, so producing high local drug concentrations.

Pluronic F127 is a commercially available poly(oxyethylene)-poly(oxypropylene)-(polyoxyethylene) triblock copolymer of general formula E_{106} P_{70} E_{106}, which contains approximately 70% ethylene oxide with an average molar mass of 13 000. Thermally reversible gels of this copolymer have been investigated as drug delivery systems for ophthalmic (Miller & Donovan 1982), rectal (Miyazaki et al 1986), nasal (Jain et al 1991), and subcutaneous use (Morikawa et al 1987). The low toxicity and skin irritancy of Pluronic F127 (Henry & Schmolka 1989) have led to the evaluation of the potential dermatological applications of these gels (Schmolka 1972), particularly in the treatment of burns (Nalbandian et al 1987). Their use in the topical application of drugs in cancer treatment was reported by Miyazaki et al (1984, 1992a). The anti-inflammatory activity of a F127 gel containing ketoprofen has been evaluated using the carrageenan-induced rat paw oedema method (Chi & Jun 1990).

In this study, a gel formulation prepared using F127 was evaluated for its potential use as a vehicle for the topical administration of indomethacin. The efficiency of percutaneous absorption was determined by the measurement of drug concentration in rat plasma following topical application of the gel. Many reports have described attempts at increasing the skin permeability of indomethacin using a range of compounds including alcohols, urea, dimethyl sulphoxide, isopropyl myristate, azone and (+)-limonene. In this study the influence of two enhancers, isopropyl myristate and (+)-limonene has been examined. Isopropyl myristate has been widely studied as an absorption promoter for percutaneous absorption of drugs. (+)-Limonene is readily available as the main component in orange and lemon oils; its toxicity and skin irritancy are considered to be low (Okabe et al 1989).

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Materials and Methods

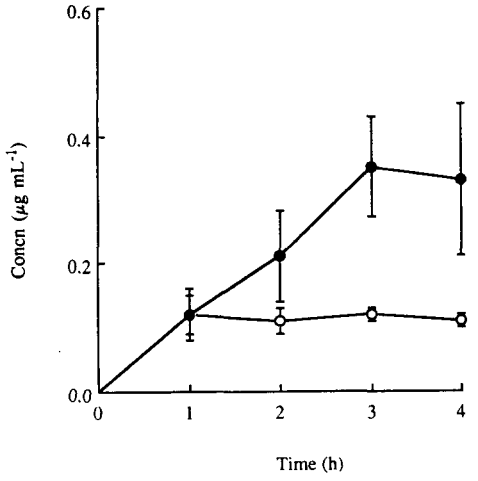
Materials

The following compounds were used as received from the suppliers without further purification: Pluronic F127 (BASF Corporation, USA); indomethacin (Sigma Chemical Company, St Louis, MO); propylene glycol and (+)-limonene (Wako Pure Chemical Industries Company, Tokyo, Japan); isopropyl myristate (Tokyo Kasei Industries Company, Tokyo, Japan).

Table 1. The influence of penetration enhancers on the AUC values for the percutaneous absorption of indomethacin from 20% w/w Pluronic F127 gels.

Treatment	Concn (w/w)	n	AUC (0–4 h)[a] (μg h mL^{-1})	Enhancement factor[b]
Control	–	4	0·41 ± 0·05	1·0
ODT[c]	–	4	0·84 ± 0·24	2·0
Isopropyl myristate				
	2%	3	0·85 ± 0·09**	2·1
	5%	3	1·11 ± 0·11**	2·7
	10%	3	1·60 ± 0·19*	3·9
(+)-Limonene				
	1%	4	0·88 ± 0·10**	2·1
	2%	4	1·58 ± 0·26**	3·9
	3%	4	2·15 ± 0·24*	5·2
ODT[c] + (+)-limonene				
	2%	3	3·03 ± 0·18*	7·4

[a]Each value represents the mean ± s.e.m. [b]Enhancement factor relative to AUC compared with the control. [c]Occlusive dressing technique. *P < 0·001, **P < 0·01 compared with control, by Student's t-tests.



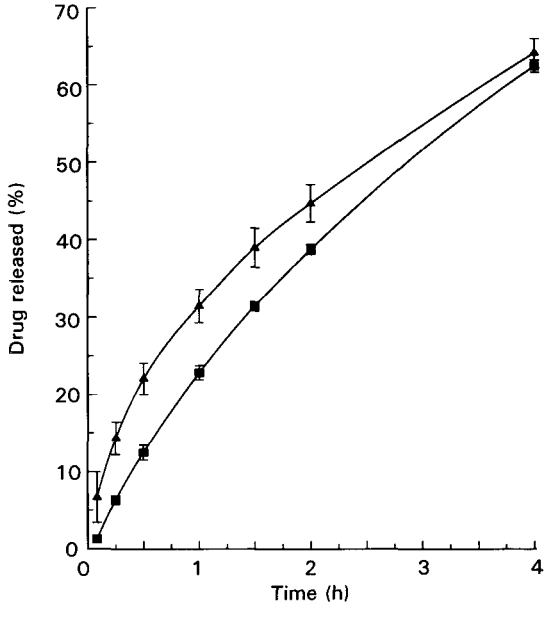


FIG. 1. Percutaneous absorption of indomethacin from 20% F127 gels in rats with (●) or without (○) the use of an occlusive dressing technique. Each value represents the mean ± s.e.m. of four rats.

Preparation of Pluronic F127 gels

Gels containing 20% w/w F127 and 1% w/w indomethacin in phosphate buffer pH 7·4 were prepared as described previously (Miyazaki et al 1986). To study the effect of enhancers on the percutaneous absorption characteristics, gels were formulated as above and either (+)-limonene (1–3% w/w) or isopropyl myristate (2–10% w/w) was added to the final preparation at room temperature using propylene glycol (10% w/w) as a dispersing agent.

In-vivo percutaneous absorption experiments

Male Wistar rats, 200–300 g, were shaved and anaesthetized by intraperitoneal injection of sodium pentobarbitone (40 mg kg^{-1}). The gel formulation (1 g) was applied to a 3-cm diameter circular site on the abdominal skin (Miyazaki et al 1992b). The effect on percutaneous absorption of the application of an occlusive dressing technique was

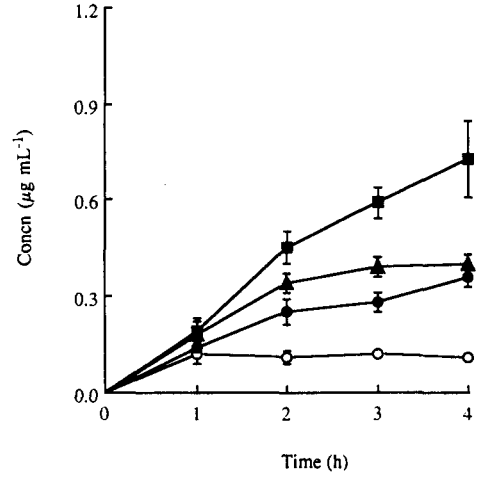


FIG. 2. Effect of isopropyl myristate on the percutaneous absorption of indomethacin from 20% F127 gels in rats. ○ Control, ● 2%, ▲ 5% and ■ 10% isopropyl myristate. Each value represents the mean ± s.e.m. of three rats.

investigated by covering the area around the application site with Saran Wrap film (Asahi-Dow Co., Japan). Blood samples (0·5 mL) were taken from the jugular vein at hourly intervals after drug administration. The plasma samples were analysed by HPLC (Miyazaki et al 1986).

Results and Discussion

Fig. 1 shows the mean plasma levels of indomethacin obtained following administration of gels prepared from 20% w/w F127 at pH 7·4 and containing 1% w/w indomethacin. This formulation was shown from preliminary in-vitro experiments to provide a maximum flux of the drug. Table 1 summarizes the AUC value (Yamaoka et al 1981) up to 4 h post-administration. Fig. 1 shows that indomethacin was detected in rat plasma 1 h after the percutaneous administration of the F127 gel; plasma indomethacin levels reached a constant value of approximately 0·1 μg mL^{-1} after that time. A thin, smooth film was formed on application to the skin, due to evaporation of water from the gel. Prevention of water loss by the occlusive dressing technique resulted in a threefold increase of indomethacin plasma concentration after 4 h and a twofold increase of AUC (see Table 1).

The effect of the isopropyl myristate concentration in the gel on the absorption of indomethacin is seen from Fig. 2. All concentrations of added isopropyl myristate caused higher indomethacin plasma levels compared with the control; an increase of plasma concentration and AUC (see Table 1) was noted with increase of isopropyl myristate concentration. The effect of esters, including isopropyl myristate, on the flux of indomethacin is thought to involve direct interaction of the ester with the skin (Inagi et al 1981). It is probable that the isopropyl myristate in the administered gel enhances the skin permeation of indomethacin by accelerating conformational changes of the lipid of the stratum corneum.

Fig. 3 and Table 1 show a progressive increase in the enhancement of the absorption of indomethacin with

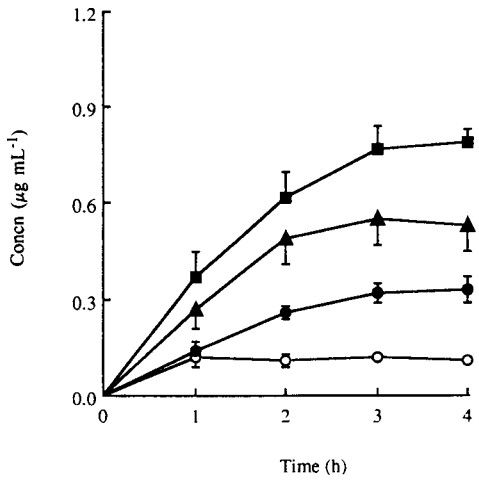


FIG. 3. Effect of (+)-limonene on the percutaneous absorption of indomethacin from 20% F127 gels in rats. ○ Control, ● 1%, ▲ 2% and ■ 3% (+)-limonene. Each value represents the mean ± s.e.m. of four rats.

increase in the concentration of (+)-limonene added to the gel up to a concentration of 3% w/w. Further enhancement of absorption was achieved by the use of an occlusive dressing technique in combination with (+)-limonene (2% w/w) (see Table 1). The mechanism by which (+)-limonene improves percutaneous absorption is not fully understood. It is known that some terpenes are effective penetration enhancers for lipophilic oestradiol (Williams & Barry 1991). The terpenes interact with the highly-ordered lipid structure of the stratum corneum, fluidizing the crystalline structure and thus increasing membrane diffusivity (Williams & Barry 1989). The precise mechanism of enhancement for the formulation used in the present investigation, which contains both (+)-limonene and propylene glycol, requires further elucidation.

Pluronic F127 has potential as a gel vehicle for transdermal formulation due to its low toxicity and irritancy, its compatibility with a wide range of chemical compounds and its reversible sol-gel characteristics, which permit gel formation on the skin by application of a cool solution of the gel. Although attempts were not made in this study to optimize the formulations, it is clear from the results that the percutaneous absorption of indomethacin can be enhanced by the addition of isopropyl myristate or (+)-limonene to the F127 gel base, and the use of an occlusive dressing technique.

Acknowledgements

This study was supported by the Japan Society for the Promotion of Sciences (JSPS). The authors are grateful to BASF Wyandotte Co. for the generous gift of Pluronic F127. We are also indebted to Miss Fumiko Nose of Health Science University of Hokkaido for her assistance.

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