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Research Article

Release of Lonapalene from Two-Phase Emulsion-Type Ointment Systems

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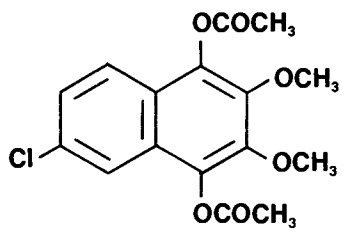
The *in vitro* release of lonapalene, a novel nonsteroidal antipsoriatic agent, was studied from two-phase emulsion-type ointment systems into a perfect sink of propylene carbonate at 32°C. Lonapalene was completely solubilized in the ointments consisting of an internal phase of propylene carbonate (PC)–propylene glycol (PG) mixture dispersed within an external phase of a petrolatum base. The PC:PG ratio was varied to investigate separately the effects of (1) the initial concentration of lonapalene, (2) its saturation level, and (3) the volume fraction of the internal phase. The release profile consisted of an initial release rate which was higher than the ensuing diffusion-controlled release rate. The initial rate was attributed to the release of lonapalene from the surface globules of internal phase directly into the sink. Both rates increased with increasing lonapalene initial concentration in the ointment. For ointment systems in which the saturation level of lonapalene was kept constant, neither release rate was affected by the increasing volume fraction of the internal phase up to 12%. Further increase in this volume fraction to 25% afforded a significantly higher initial rate, while the diffusion-controlled rate was unchanged. However, an increase in the volume fraction of the internal phase with a concomitant decrease in the saturation level of lonapalene in the ointment resulted in a decrease in the initial rates and, to a lesser degree, the diffusion-controlled release rates. The diffusion coefficient in the external phase, calculated from the effective diffusion coefficient, was $(2.68 \pm 0.24) \times 10^{-9}$ cm²/sec.

KEY WORDS: nonsteroidal antipsoriatic agent; two-phase emulsion-type ointment; volume fraction; level of saturation; diffusion; release.

INTRODUCTION

Lonapalene, which is chemically 6-chloro-1,4-diacetoxy-2,3-dimethoxynaphthalene (I), is a novel topical antipsoriatic agent (1–3). Its efficacy has been demonstrated in a pilot clinical study for the topical treatment of psoriasis (4). A two-phase emulsion-type ointment system (5) has been developed for further clinical investigation. During the development of the ointment formulation, several factors that may influence the release of lonapalene from the ointment were studied with the goal of optimizing the release rate.



Scheme I

The availability of a drug from a topical dosage form depends on the percutaneous absorption of the drug. This process involves two consecutive steps, i.e., drug release from the vehicle and subsequent drug penetration through the skin barrier. Drug release depends on several physicochemical factors, such as the drug's concentration, solubility, and diffusion coefficient in the vehicle. At a given concentration, drug release from a vehicle, in which the drug is completely solubilized with the minimum required amount of solvent, is faster than that from a suspension-type vehicle (6). Furthermore, drug release is also affected by the partition coefficient between the vehicle and the receptor phase (7), the latter being the skin barrier for the *in vivo* situation. The correlation found between *in vitro* drug release and *in vivo* response demonstrated the usefulness of *in vitro* release studies in the design of topical dosage forms (6,8–11).

Release of a solubilized drug from emulsion-type creams or ointments depends on the drug's initial concentration, diffusion coefficient in the external phase, and partition coefficient between the internal and the external phases, as well as the volume fraction of internal phase. One difficulty encountered in studies of the effect of one formulation factor on the release of drug from these systems is keeping the other formulation factors constant. For example, in the study of the effect of drug initial concentration, increasing the initial concentration must be concomitant

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with either of the two following factors in order to keep the drug in solution at the same saturation level, which is the ratio of the drug concentration to its solubility in the vehicle: (a) the increase in the volume fraction of the internal phase if the drug is dissolved mainly in the internal phase or (b) the change in the solvent composition of the external phase if this is the phase in which the drug is mainly soluble. Two formulation factors are involved in either case. Therefore, the conditions of each release study must clearly be defined.

In the present study, lonapalene was dissolved mainly in the internal phase of the ointment, which consisted of a mixture of propylene carbonate and propylene glycol. Since the solubility of lonapalene is dependent on the composition of the mixture, this composition was altered to provide additional conditions under which the effect of formulation factors on the release rates could be investigated. Thus, this report is concerned with the study of the separate effects of (i) the initial concentration of lonapalene, (ii) its saturation level, and (iii) the volume fraction of internal phase, on the release of lonapalene under various clearly defined conditions.

MATERIALS AND METHODS

Materials. Propylene carbonate, N.F. (Carmona Chemical, San Francisco, Calif.), propylene glycol, U.S.P. (VWR, San Jose, Calif.), glyceryl monostearate, pure (Stepan Chemical, Northfield, Ill.), white wax, N.F. (Frank B. Ross, Jersey City, N.J.), and white petrolatum, U.S.P. (Penreco, Butler, Pa.), were used as received. Lonapalene was obtained from the Institute of Organic Chemistry, Syntex Research, Palo Alto, Calif. The chemicals and reagents used in the high-performance liquid chromatographic (HPLC) assay were reagent grade.

Ointment Preparation. The ointments were prepared by adding a heated solution of lonapalene in propylene carbonate–propylene glycol mixture to a molten petrolatum base (glyceryl monostearate, white wax, and white petrolatum) while stirring constantly. The mixture was then allowed to cool and congeal.

Analytical Method. The reverse-phase HPLC method used to determine the concentration of lonapalene has been fully described elsewhere (12).

Solubility Studies. An excess of lonapalene was added to 2 ml of the propylene carbonate–propylene glycol mixtures being investigated. After 1 min of sonication, the suspension was equilibrated for 4 days with rotary mixing in a 25°C water bath. The suspensions were filtered through an Alpha 200 filter (pore size, 0.2 μm), and the lonapalene concentration was determined by HPLC.

Release Studies. The apparatus and procedure for studying drug release from ointments have been described previously (13), but with the following minor modification. Briefly, 300 mg of the ointment was evenly spread at the outside bottom surface of a Teflon dish. The dish was allowed to float on the surface of the propylene carbonate sink maintained at 32°C. One-milliliter samples were withdrawn from the sink at predetermined time intervals, and the concentrations of lonapalene were assayed by the above HPLC method. The volume of the sink was kept constant throughout the release study by replacing the removed sample with an equal volume of propylene carbonate. Triplicate runs were conducted for each ointment. The results are reported as the average values with standard error of the mean.

Partition Coefficient. The partition coefficients of lonapalene between the internal and the external phases of the ointment systems were determined according to the following method. Six grams of the external phase consisting of glyceryl monostearate, white wax, and white petrolatum was added into a 20-ml tube with screw cap and melted at 70°C. The external phase was then allowed to congeal as a thin layer in the inner wall of the tubes by rotating the tubes horizontally under a stream of tap water. Into each tube was added 6.0 ml of lonapalene solution in the internal phase of propylene carbonate–propylene glycol mixture at a predetermined ratio. The initial concentration of lonapalene was approximately half of its solubility in the respective propylene carbonate–propylene glycol mixtures, i.e., 20, 40, and 80 mg/ml for mixtures containing propylene carbonate–propylene glycol ratios of 2:8, 3:7, and 5:5, respectively. The tubes were shaken to equilibrate in a water bath maintained at 25°C. Samples were taken at 3 and 8 days, and the concentration of lonapalene in the propylene carbonate–propylene glycol mixtures was assayed by HPLC. The concentration of lonapalene prior to equilibration was also determined. Thus, the concentration of lonapalene in the external phase was calculated from the results before and after equilibration of the internal and external phases.

RESULTS AND DISCUSSION

In the present study, lonapalene was completely solubilized in the two-phase emulsion-type ointment systems. Microscopic examination using cross-polarized light showed no drug crystal present in any of the ointments. While most of the lonapalene was dissolved in the internal phase of propylene carbonate (PC)–propylene glycol (PG) mixtures, a fraction was also solubilized in the external phase of the petrolatum base. Thus, lonapalene was in equilibrium between the two phases. Table I shows the solubility of lonapalene in the internal phase of PC–PG mixtures, and its partition coefficient between the mixture and the external phase of the ointment. Lonapalene solubility increases with increasing ratios of PC to PG. The same is true for its partition coefficient since the composition of the external phase was similar in all of the ointments. The use of this two-component solvent mixture allows the lonapalene concentration in the ointment to be increased while the same volume fraction and saturation level are maintained by simply increasing the PC:PG ratio to increase the solubility of lonapalene.

Data on lonapalene release from these emulsion-type ointments can be treated as the data from emulsions containing drug in solution by the following "square-root" approximations (14,15):

$$Q = 2C_0\sqrt{\frac{D_e t}{\pi}} \qquad (1)$$

where Q is the amount of drug released per unit area of application, C_0 is the initial concentration of drug in the ointment, D_e is the effective diffusion coefficient of the drug in the ointment, and t is the time after application.

The release profiles of lonapalene from the ointments are shown in Fig. 1 for a concentration range of 0.25 to

Table I. Solubility of Lonapalene in Propylene Carbonate–Propylene Glycol Mixtures and Its Partition Coefficient Between the Mixture and the External Phase of Ointment, at 25°C

PC:PG[a]	Solubility (mg/ml)	Partition coefficient
2:8	39.0	22.1
3:7	79.2	48.0
5:5	160.0	69.0
7:3	242.7	—
8:2	294.9	—

[a] Weight ratio of propylene carbonate to propylene glycol in mixture.

2.0%. In each of the ointments, the internal phase consisted of the same ratio of PC to PG but the volume fraction was increased to maintain complete solubilization at the same saturation level as the concentration of lonapalene was increased. Figure 2 also depicts the release profiles of lonapalene from ointments containing 0.5 to 2.0% lonapalene. In this study, however, the PC:PG ratio was increased to afford higher lonapalene solubility, and consequently, the volume fraction and saturation level could be kept constant. Both figures show profiles with positive intercepts if the linear portions of the plots are extrapolated to zero. These demonstrate an initial release mechanism having rates higher than the ensuing release rates. The latter were linear and thereby adhered to Eq. (1), indicating that the release was controlled by lonapalene diffusion in the ointment. As the internal phase was in equilibrium with the external phase, the former served as a reservoir for the diffusing drug. The slopes of the linear portion of the plots give the release rates from which the effective diffusion coefficients (D_e) can be calculated. The correlation coefficients of these linear regression lines are mostly greater than 0.99.

The following diffusion equation has been derived for a small volume fraction of the internal phase (15):

$$D_e = \frac{D_1}{V_1 + KV_2}\left[1 + 3\,V_2\left(\frac{KD_2 - D_1}{KD_2 + 2D_1}\right)\right] \qquad (2)$$

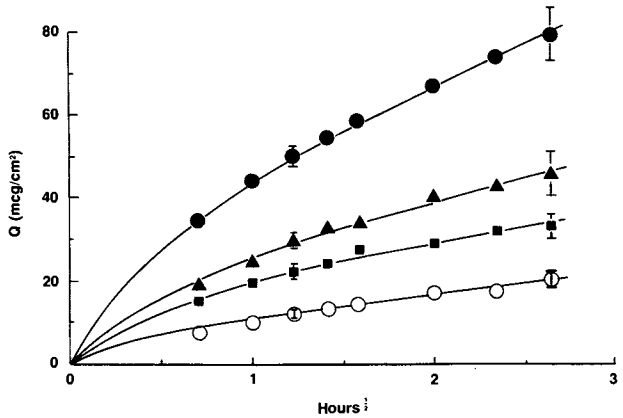

Fig. 1. Lonapalene release from two-phase emulsion-type ointments containing 0.25% (○), 0.5% (■), 1.0% (▲), and 2.0% (●) lonapalene. The volume fraction of the internal phase was proportionally increased to maintain solubilization at the same level of saturation.

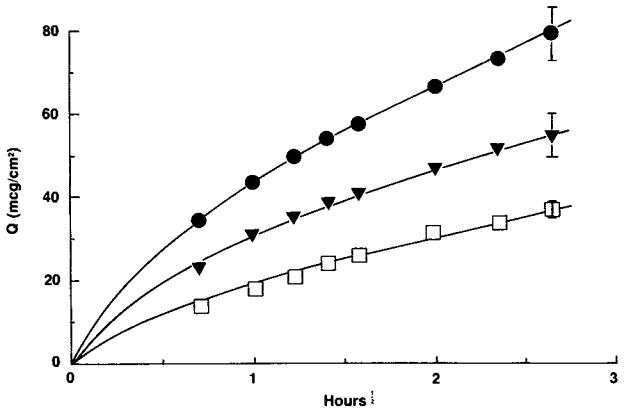

Fig. 2. Lonapalene release from two-phase emulsion-type ointments containing 0.5% (□), 1.0% (▼), and 2.0% (●) lonapalene. The volume fraction of the internal phase and the level of saturation were kept constant by increasing the ratio of propylene carbonate to propylene glycol in the internal phase.

where D_e is the effective diffusion coefficient; D_1 and D_2 are the diffusion coefficients in the external and internal phase, respectively; V_1 and V_2 are the volume fractions of the external and internal phase, respectively; and K is the partition coefficient between the internal and the external phases.

For the present ointment systems in which $D_2 \gg D_1$, the above equation reduces to

$$D_e = \frac{D_1(1 + 3V_2)}{V_1 + KV_2} \qquad (3)$$

Therefore, the diffusion coefficient in the external phase (D_1) can be calculated from Eq. (3) after D_e is obtained from the release studies.

The effect of the lonapalene initial concentration on its release is summarized in Table II, based on the data obtained from Fig. 1 (set A) and Fig. 2 (set B). The release of lonapalene can be categorized into two distinct rates, i.e., initial and diffusion-controlled rates. The initial rates, estimated as the amount of lonapalene released during the initial 30 min, are higher than the ensuing diffusion-controlled rates. This phenomenon is due to the large transfer of lonapalene from the surface globules of internal phase directly into the sink. The initial release rates are an important part of the process that provides immediate availability of the drug for absorption. In set A, the ointments contained the same ratio of PC to PG in the internal phase. When the concentration of lonapalene was increased from 0.25 to 2.0%, the volume fraction of the PC–PG internal phase was increased proportionally not only to keep the drug in solution but also to maintain the same saturation level. Because the concentration and volume fraction were altered in this set of studies, the release rates were affected by both. In set B, despite the increase in the lonapalene concentration, the volume fraction of the internal phase was kept constant, but the PC:PG ratio was increased to maintain complete solubilization at the same saturation level. In this case, the two factors altered were concentration and partition coefficient. As listed in Table II, under both conditions, the initial and diffusion-controlled release rates increased with increasing concentrations of lonapalene, while the effective diffusion coefficient (D_e) decreased accordingly. The diffusion coefficient in the

Table II. Release Characteristics of Lonapalene from Two-Phase Emulsion-Type Ointments Containing Various Initial Concentrations

Set	C_0^a (%, w/w)	V_2^b	PC:PG[c]	Release rate ($\mu g/cm^2/hr^{1/2}$)		Diffusion Coefficient[d] (cm^2/sec)	
				Initial[e]	Diffusion controlled	$D_e \times 10^9$	$D_1 \times 10^9$
A	0.25	0.014	5:5	10.9	5.85 (0.95)[f]	1.63	3.02
	0.50	0.028	5:5	21.0	9.12 (2.22)	0.98	2.60
	1.0	0.056	5:5	27.2	13.4 (2.16)	0.51	2.10
	2.0	0.115	5:5	48.6	21.2 (1.45)	0.31	2.03
B	0.5	0.119	2:8	20.5	11.0 (0.85)	1.38	3.57
	1.0	0.113	3:7	33.3	14.6 (1.10)	0.59	2.78
	2.0	0.115	5:5	48.6	21.2 (1.45)	0.31	2.03

[a] Initial concentration in the ointment.
[b] Volume fraction of the internal phase.
[c] Weight ratio of propylene carbonate to propylene glycol in the internal phase.
[d] D_e is the effective diffusion coefficient; D_1 is the diffusion coefficient in the external phase.
[e] Estimated at the initial 30 min.
[f] ±95% confidence interval.

external phase (D_1) was relatively independent of the change and was calculated to be $(2.68 \pm 0.24) \times 10^{-9}$ cm^2/sec ($N = 6$).

Table III shows the release rate data of 0.5% lonapalene ointment, and Fig. 3 shows the release profiles of 1.0% lonapalene ointment, each containing various volume fractions of internal phase. When the volume fraction was increased, the PC:PG ratio was reduced to maintain the same saturation level by decreasing the solubility of lonapalene in the PC–PG mixture. For each of the two concentrations, the initial release rates were not affected by the volume fraction up to 12%. However, there was a significant increase in the initial rate when the volume fraction was increased to 25% (Fig. 3). This tends to indicate that, in addition to the release of lonapalene from the surface globules of internal phase, the release from the external phase had significant contribution to the overall initial rates. At much larger volume fractions of the internal phase (e.g., 25%), it is possible that a channeling effect, caused by close proximity of the internal phase globules, contributed to the greater initial burst of the drug from the vehicle. The diffusion-controlled release rates were unaffected by the volume fraction of the internal phase up to 25%, as evidenced by the parallel slopes of the release profiles. This represented the condition under which the increase in the volume fraction of internal phase V_2 was offset by the decrease in the partition coefficient K, such that the effective diffusion coefficient D_e [Eq. (3)] and, thus, the diffusion-controlled release rate were unchanged. The results lead to the following conclusions: (a) the diffusion of lonapalene in the external phase was the rate-limiting process, and (b) the internal phase served as a reservoir in which lonapalene was highly soluble.

Another condition to study the effect of increasing volume fractions of internal phase V_2 was carried out by maintaining the same PC:PG ratio and, thus, the same partition coefficient K. Equation (3) predicts that, if K is constant and since $K \gg 3$, D_e will decrease with increasing V_2. But the effect on the diffusion-controlled release rate is less than that on D_e. This is because, according to Eq. (1), the release rate is dependent on the square root of D_e and, therefore, V_2. As shown in Table IV, the diffusion-controlled release rate did decrease when the volume fraction of internal phase was increased by four- or eightfold for the 0.5 or 0.25% lonapalene ointments, respectively. The effect of a twofold increase in the volume fraction was not observed for the 1% ointment, although Eqs. (1) and (3) predict a 20% decrease in the rate. This could be due to the approximation made in the derivation of the equations. In addition, the partition coefficient K would change slightly at different levels of saturation, leading to inaccuracy in the above prediction.

Poulsen *et al.* (7) have shown that the release of steroid

Table III. Release Rates of Lonapalene from Two-Phase Emulsion-Type Ointments Containing Various Volume Fractions of the Internal Phase[a]

V_2	PC:PG	Release rate ($\mu g/cm^2/hr^{1/2}$)	
		Initial	Diffusion controlled
0.028	5:5	21.0	9.12 (2.22)
0.056	3:7	19.1	11.2 (0.85)
0.119	2:8	20.5	11.0 (0.85)

[a] Initial concentration is 0.5% (w/w).

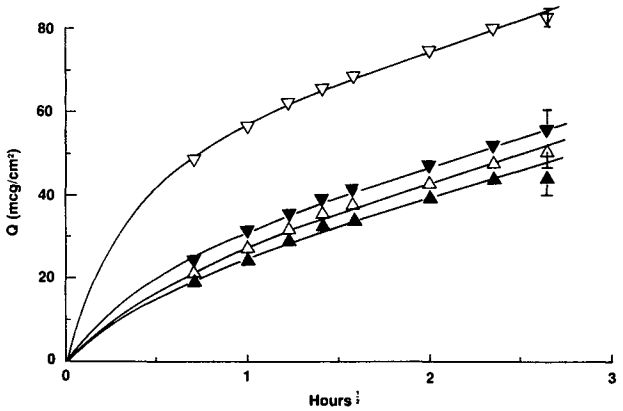

Fig. 3. Lonapalene release from two-phase emulsion-type ointments containing 1.0% lonapalene and increasing volume fractions of the internal phase, i.e., 3.0% (△), 5.6% (▲), 11.3% (▼), and 25% (▽). The same level of saturation was maintained by decreasing the ratio of propylene carbonate to propylene glycol in the internal phase.

Table IV. Release Rates of Lonapalene from Two-Phase Emulsion-Type Ointments Containing Various Volume Fractions of the Internal Phase and Levels of Saturation[a]

Set	C_0 (%, w/w)	V_2	Relative level of saturation[b]	Release rate ($\mu g/cm^2/hr^{1/2}$) Initial	Diffusion controlled
A	1.0	0.056	1.0	27.2	13.4 (2.16)
A′	1.0	0.114	0.56	21.9	13.8 (0.96)
B	0.5	0.028	1.0	21.0	9.12 (2.22)
B′	0.5	0.113	0.34	11.4	7.65 (0.08)
C	0.25	0.014	1.0	10.9	5.85 (0.95)
C′	0.25	0.113	0.23	5.9	3.78 (0.29)

[a] PC:PG weight ratio of 5:5 was maintained.
[b] A′, B′, and C′ relative to A, B, and C, respectively.

is dependent on the composition of the solvent mixture in the gel vehicle. The vehicles that contain cosolvent in excess of that required to dissolve the steroid, i.e., reduced saturation level of steroid, have a strong affinity for the steroid and therefore reduce its release rates. In the present study of emulsion-type ointment systems, the external phase had similar composition and thus solubilizing capacity for lonapalene. However, a volume fraction of the internal phase in excess of that required to dissolve lonapalene was formulated into the ointments to study the effect of a reduced saturation level of lonapalene in the internal and also external phases.

The effect of the saturation level on the initial release rate of lonapalene is listed in Table IV. For a given concentration, the volume fraction was increased while the solubility was maintained by using the same ratio of PC to PG. As a result, the saturation level of lonapalene in the ointments decreased to 0.56, 0.34, or 0.23 of the original level when the volume fractions were increased by two-, four-, or eightfold for the 1.0, 0.5, or 0.25% lonapalene ointments, respectively. The data show that the initial rate decreased with decreasing saturation levels. The decrease in the saturation level of lonapalene in the internal phase will result in the same decrease in the external phase, as lonapalene was equilibrated between the two phases. These conditions led to the unfavorable partitioning of lonapalene into the sink, or a slower initial release rate.

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