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Release of sorbic acid from ointment bases

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Summary

The rate and extent of release of sorbic acid from 6 ointment bases were assessed. The amount of drug released depended on the composition of the base and the concentration of sorbic acid employed. The rate of release decreased in the following order: water soluble > o/w emulsion > oleaginous > hydrophobic > w/o emulsion base. The rate of diffusion from the ointment bases was pH dependent. The data obtained may be useful in the formation of topical sorbic acid formulations.

Introduction

The release of medication from a vehicle plays an important role in percutaneous absorption, especially when the skin is in a damaged state due to disease or injury (Mckenzie and Stronghton, 1962). One of the main functions of a semisolid dosage form base is the control it exerts over the release and hence the therapeutic activity of the drug (Paulson et al., 1968; Ayres and Laskar, 1974; Ostrenga et al., 1971). The pharmacokinetics of percutaneous absorption have been reviewed by Webster and Maibach (1983), while Idson (1983) has summarized the vehicle effects in drug release and absorption.

Percutaneous absorption of most drugs occurs by passive diffusion of the undissociated fraction across the lipoidal barrier (Wagner, 1961; Marcus et al., 1970). Among other factors, the absorption of a drug from a vehicle depends on the solubility of the drug in the vehicle and the partition of the drug between vehicle and skin. Factors such as pH and drug concentrations can influence the interaction between drug, vehicle and skin (Anderson and Keller, 1984). For example, Blank and Gould (1961) observed an increase in the absorption of sodium laurate from solutions in contact with excised human skin at reduced pH. They attributed this increase to the formation of undissociated lauric acid. The chief driving force for diffusion and penetration of a drug is the thermodynamic activity which for a weakly acidic drug is inversely proportional to the term 10^{pH} (Higuchi, 1960). Various investigators have used diffusion experiments to evaluate the release of drugs from semisolid dosage forms (Ayres and Laskar, 1974; Brochu and Paiement, 1975; DiColo et al., 1980).

Sorbic acid falls into a group of short-chain organic acids which together with their salts have been shown to exhibit antimicrobial properties

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(Bell and Borg, 1959; Wyss, 1948). This study was conducted to investigate an influence of the type, composition and pH of the ointment base and concentration of sorbic acid in the base on the rate and extent of sorbic acid release using a simple dialysis method.

Materials and Methods

Materials

Sorbic acid, cholesterol and sodium dihydrogen orthophosphate were obtained from E. Merck (Darmstadt, F.R.G.), and used as supplied. Cetyl alcohol, sodium lauryl sulfate, polyethylene glycol 400, polyethylene glycol 4000 and span 80 were purchased from Searle (Chadwell Health, Essex, U.K.). White beeswax, yellow soft paraffin, propylene glycol and borax were obtained from B.D.H. Chemicals (Poole, U.K.) while anhydrous lanolin was procured from Riedel-DeHaem (Hannover, F.R.G.).

Preparation of ointments

The ointments were prepared by fusion or trituration on a pill tile using a spatula on a weight/weight basis. Six different ointment bases were prepared, and the compositions of these bases are presented in Table 1. The final apparent pH's of certain ointment bases was fixed at 3.0, 4.5 or 8.0 using phosphate buffer according to the procedure of Marcus et al. (1970). The sorbic acid was then incorporated at a level of 2 or 4% w/w.

Methods

Porcelain jars with an exposed surface area of

TABLE 1

COMPOSITION AND TYPE OF OINTMENT BASES USED

Ointment	% Sorbic acid	Type of base	Composition	
A_1	2	Water soluble	Polyethylene glycol 4000	47.5 g
			Polyethylene glycol 400	47.5 g
A_2	4		Cetyl alcohol	5 g
B_1	2	o/w Emulsion	White beeswax	1 g
			Cetyl alcohol	15 g
			Propylene glycol	10 g
B_2	4		Sodium lauryl sulfate	2 g
			Water	72 g
C_1	2	Oleaginous	Wool fat	5 g
			Hard paraffin	5 g
C_2	4		Cetyl alcohol	5 g
			Yellow soft paraffin	85 g
D_1	2	w/o Emulsion	Liquid paraffin	45 g
			White beeswax	10 g
			Wool fat	2 g
			Borax	8 g
D_2	4		Water	41 g
			Sorbitan monooleate	1 g
E_1	2	Hydrophilic	Cholesterol	3 g
			Cetyl alcohol	3 g
E_2	4		White beeswax	8 g
			Yellow soft paraffin	86 g
F	2	w/o Emulsion	Wool fat	70 g
			Water	30 g

12.6 cm^2 were filled with the ointments and covered with cellophane membranes (John E. Harcourt, U.K.) which were previously allowed to hydrate in distilled water for at least 2 h. After the membrane was secured in place with a rubber band, the dialysis cell was inverted in 200 ml distilled water contained in a 400 ml beaker and the system was maintained at 37.5 ± 0.5°C. The water was stirred at approximately 500 rpm with a magnetic stirring bar during the entire 150 min incubation. Samples of 5 ml were withdrawn at 25 min intervals and replaced with an equal volume of distilled water at 37.5°C. The samples were then analyzed spectrophotometrically at a wavelength of 262 nm for sorbic acid concentration. Polyethylene glycol, which diffuses across the membrane and was present in ointments A_1 and A_2, does not give an absorbance at 262 nm. Due to dissolution of some ointment vehicle, particularly with polyethylene glycol, swelling of the membrane was observed.

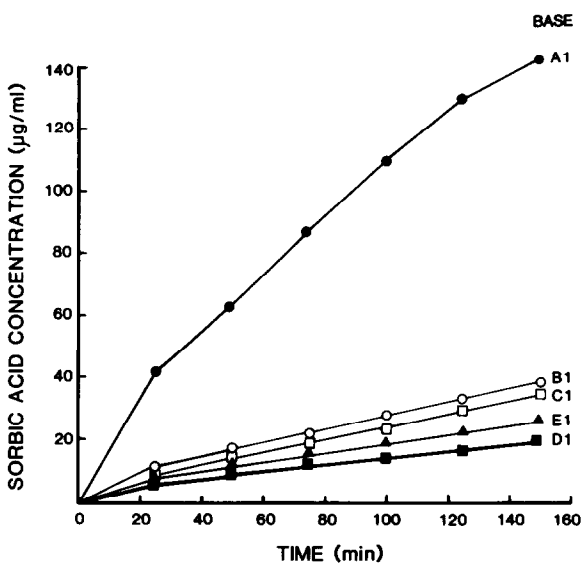

Fig. 1. Influence of ointment base composition on the release of sorbic acid from ointments containing 2% w/w drug. For composition of the bases see Table 1. Each point is the mean of 3 determinations.

Results and Discussion

The release of a drug from an ointment can be altered by modifying the composition of the vehicle (Idson, 1983). Fig. 1 depicts the dissimilarity in sorbic acid release from different ointment bases containing 2% w/w of the drug. The rate of release decreased in the following order: water soluble > o/w emulsion > oleaginous > hydrophilic > w/o emulsion base. Relatively small differences existed in the rates of release of sorbic acid from the hydrophobic (E_1), w/o emulsion (D_1), oleaginous (C_1) and o/w emulsion (B_1) bases as compared to the water soluble (A_1) base. After 120 and 150 min incubation times, the release of sorbic acid from the oleaginous (C_1) and o/w emulsion (B_1) bases was significantly greater than from the w/o emulsion (D_1) base. The release of sorbic acid from the o/w emulsion (B_1) base was also significantly greater than from the hydrophobic (E_1) base. Standard deviation bars were not included due to the tight grouping of some of the points.

A general rule in ointment formulation is that if the drug is held firmly by the vehicle the rate of release of the drug is slow (Barr, 1962). At 20°C, sorbic acid is soluble to the extent of 0.16% in water, 5.5% in propylene glycol, 14.8% in alcohol, and 0.52% in vegetable fat (Furia, 1972). These differences in solubility may explain the differences in the diffusion of sorbic acid from the various bases.

The high diffusion rate of sorbic acid from the water soluble ointment base (A_1) that contains mainly polyethylene glycol may be due to diffusion of water through the cellophane membrane and formation of water–polyethylene glycol solution which increases the solubility and thus the rate and extent of release of sorbic acid. Similar observations involving the use of polyethylene glycol based ointments have been made with respect to the release of salicylic acid (Billups and Patel, 1970) and benzocaine (Ayres and Laskar, 1974).

The higher release of sorbic acid from the o/w emulsion base (B_1) than from w/o emulsion base (D_1) (Fig. 1) may be due to the formation of a continuum from the external phase of the o/w emulsion with the water in the beaker (Nakano and Patel, 1970). Furthermore, the greater solubility of sorbic acid in the oil phase than in the water phase may cause a decrease in the rate of release of the drug.

Both the hydrophilic (E_1) and oleaginous (C_1) ointment bases used in this study contained primarily yellow soft paraffin along with cetyl alcohol and several additional lipoidal constituents. Although cetyl alcohol can associate with water and facilitate diffusion of sorbic acid across the membrane, the high lipid solubility of the drug favors its retention in the base (Furia, 1972). This may explain the slow release of the sorbic acid that is observed.

Fig. 2 shows the release profile of sorbic acid from various bases containing 4% w/w acid. Proportionately larger amounts of sorbic acid were released as compared to the release from ointment bases containing 2% w/w of the drug (Fig. 1). In addition, the rate of release followed the same order, namely, water soluble > o/w emulsion > oleaginous > hydrophilic > w/o emulsion base. Therefore, with 2% and 4% sorbic acid w/w, the amount of drug released with time was dependent upon the concentration of sorbic acid in the bases.

Table 2 summarizes the effect of pH on sorbic acid release from o/w and w/o ointment bases containing 2% w/w sorbic acid. Each value in Table 2 represents an average for 3 experiments.

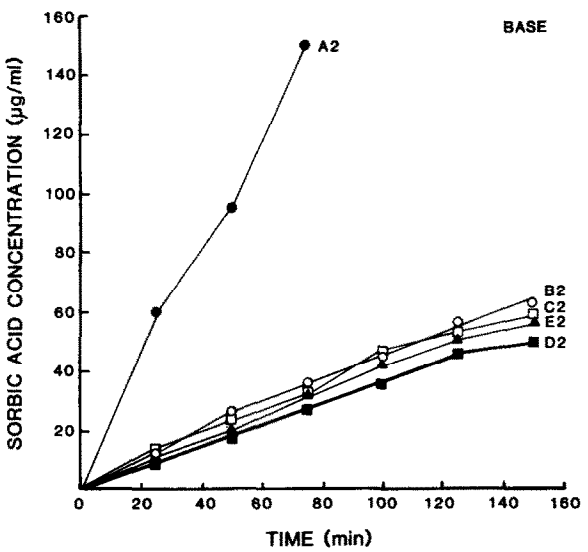

Fig. 2. Influence of ointment base composition on the release of sorbic acid from ointments containing 4% w/w drug. For composition of the bases see Table 1. Each point is the mean of 3 determinations.

The results indicate that the release of sorbic acid is greater at pH 3 than pH 8 for both bases. These findings agree with the observations of Blank and Gould (1961) and Marcus et al. (1970). Decreasing the pH of the vehicle increases the thermodynamic activity of the undissociated form of a weakly acidic drug as sorbic acid (Higuchi, 1960). At pH 4.5, which is about the pK_a of sorbic acid, the results show the highest release of sorbic acid from the o/w emulsion, and again demonstrate greater release from the o/w emulsion as compared to the w/o emulsion. Thus, trends in the release rates are observed, depending on the apparent pH of the preparations being evaluated. The presence of equal amounts of dissociated and undissociated forms of the acid may provide a better balance between solubility and thus availability of the acid and its diffusion capability.

Release studies have long been employed for determining the effects of different factors on drug availability. The data obtained in this investigation may be useful in the formulation of topical sorbic acid preparations. Furthermore, several conclusions can be drawn. The release of sorbic acid from ointment bases depends on the composition of the base and the concentration of the sorbic acid employed. The rate of diffusion of sorbic acid from ointment bases is pH dependent, and a pH which is about equal to the pK_a of the acid gives

TABLE 2

RELEASE OF SORBIC ACID (μg/ml) FROM TWO OINTMENT BASES AT DIFFERENT APPARENT pH VALUES

Base [a]	Time (min)	Apparent pH		
		3.0	4.5	8.0
B_1	15	1.5	2.9	0.6
	30	2.3	3.5	1.1
	45	3.4	4.8	1.5
	60	4.3	7.1	2.2
	75	5.3	8.0	2.8
F	15	0.4	0.5	0.4
	30	0.8	1.0	0.7
	45	1.3	1.5	1.0
	60	1.9	2.0	1.3
	75	2.4	2.5	1.7

[a] For composition of the two bases see Table 1.

the highest release from both o/w and w/o emulsion bases.

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