Drug Release from a Lipophilic Ointment Base as Influenced by Chain Length of Added Surfactant

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Abstract □ The release of sulfathiazole and salicylic acid from white petrolatum containing ethoxylated surfactants of varying ethylene oxide chain length was evaluated by the dialysis method. The rate of release of the drugs increased with the ethylene oxide number of the added surfactant.

Keyphrases □ Ointment bases, lipophilic—effect of ethoxylated surfactant chain length on drug release □ Lipophilic ointment bases—effect of ethoxylated surfactant chain length on drug release □ Drug release from lipophilic ointment bases—chain length effect of added ethoxylated surfactant

The rate of release of drugs from ointment bases has received considerable attention during the last 10–15 years and interesting reviews are now available on the subject (1–13). Looking closely into the literature, however, one notes that if some aspects of this phenomenon have been extensively studied and are now well understood, others have been only partially explored. One such area is the effect of surfactants on lipophilic ointment bases.

This paper reports an attempt to verify how the variation of the length of the ethylene oxide chain of an added nonionic surfactant could influence the rate of release of water-soluble drugs from a typical lipophilic base such as white petrolatum. It was also thought that such simple systems would provide a good model to verify the possibility that a correlation exists between the rheological parameters of the ointments and the rate of liberation of drugs incorporated in them (14).

EXPERIMENTAL

The dialysis method (7) is a simple and convenient way to study the rate of diffusion of drugs in ointment bases. The significance of the information provided by that method has also been critically examined (15). In the present investigation, the setup suggested by Billups and Patel (9) was used with some modifications: *(a)* the receiving compartment of the dialysis cell was a double-walled beaker through which water could be circulated, permitting temperature maintenance of the aqueous solution (100 ml) of the receiving compartment at 25 ± 0.1°; *(b)* a small cavity was formed in the bottom of the beaker for a stirring bar with the beaker resting on a magnetic stirrer; and *(c)* the size of the jars was such that a relatively large area (~25 cm^2) of ointment (covered with cellulose paper) could be in contact with the aqueous phase. By proceeding in this way, the aliquots removed for analysis could be read directly on a spectrophotometer and then returned to the cell, thus eliminating the necessity of making volume corrections.

The absorbance of sulfathiazole was determined at 283 nm, and that of salicylic acid was determined at 302 nm. (In the acidic form, salicylic acid shows two peaks of absorbance at 237.5 and 302 nm; in both cases, Beer's law is obeyed.) As expected (16), spectrophotometric analysis failed to reveal any trace of surfactant which might have diffused along with the drugs.

The first drug, sulfathiazole[1] (mp 200–201°), was dialyzed into a phosphate buffer solution of pH 6.0 and ionic strength (μ) = 0.1. The second drug, salicylic acid[2], was dialyzed into a buffer solution of pH 1.85 (hydrochloric acid plus sodium chloride to μ = 0.1). In this second case, the conditions were, of course, far from being physiological but they permitted comparison of both drugs in the same conditions with respect to the proportion of nonionized drug in the aqueous solution (~93%). Since these drugs are weak acids, the buffer systems seemed mandatory so that the conditions in the receiving compartment would not change during an experiment. The aqueous solubilities of the nonionized portion of sulfathiazole and salicylic acid were evaluated at 25° (at pH's where less than 1% of the drugs was ionized).

The nonionic surfactants studied were some alkylaryl polyether alcohols[3]. They were completely dehydrated before incorporation into the melted bases[4] at a concentration of 1.592×10^{-3} mole/100 g of base (this value corresponds to 1 g/100 g in the case of the surfactant containing 9–10 ethylene oxide units[5]). The drugs were passed through a screen (BP 100) and were also dehydrated; this step was essential with sulfathiazole. Then they were dispersed into the bases, with a mortar and a pestle, at room temperature. Great care was exerted always to proceed in the same way (with respect to the agitation brought by the magnetic stirrer, the position of the inverted cup, *etc.*) so that the results could be compared.

For the rheological studies, a cone-plate rotational viscometer[6] was used. The experimental conditions adopted were similar to those used by Boylan (17) in his rheological study of white petrolatum.

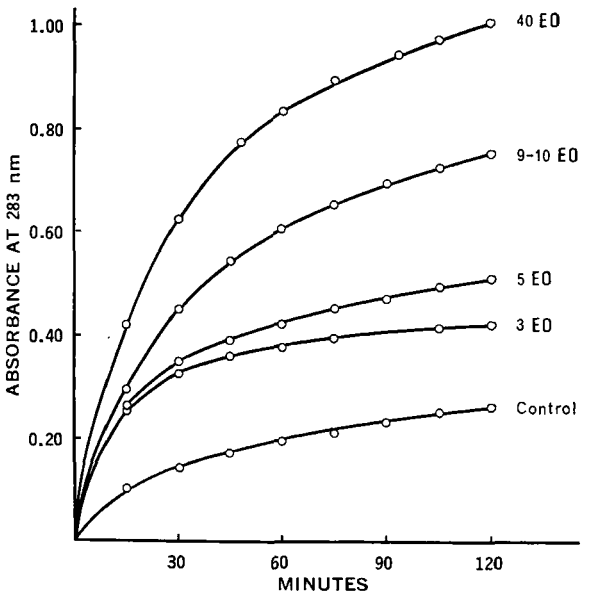

Figure 1—*Absorbance of sulfathiazole in the receiving compartment of the dialysis cell as a function of time (0.2 absorbance = 0.275 mg sulfathiazole/100 ml). Key: EO, ethylene oxide units of the added surfactant; and control, no surfactant added.*

[1] Matheson, Coleman & Bell.

[2] Analar, BDH Chemical Ltd.

[3] Tritons of the X-series, supplied by Rohm and Haas, West Hill, Ontario, Canada. The ethylene oxide units referred to in this investigation correspond to those given by the manufacturer.

[4] They were left overnight in an oven at 70° and then stored in a vacuum desiccator until their weight was found to be constant.

[5] Triton X-100.

[6] Ferranti-Shirley.

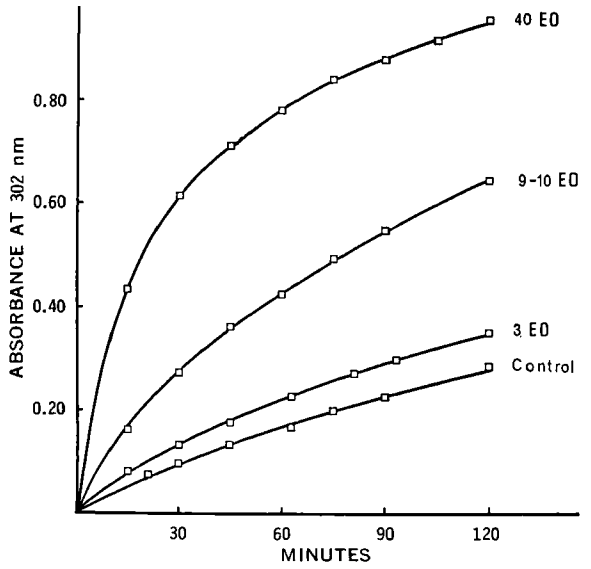

Figure 2—*Absorbance of salicylic acid in the receiving compartment of the dialysis cell as a function of time (0.2 absorbance = 0.80 mg salicylic acid/100 ml). Key: EO, ethylene oxide units of the added surfactant; and control, no surfactant added.*

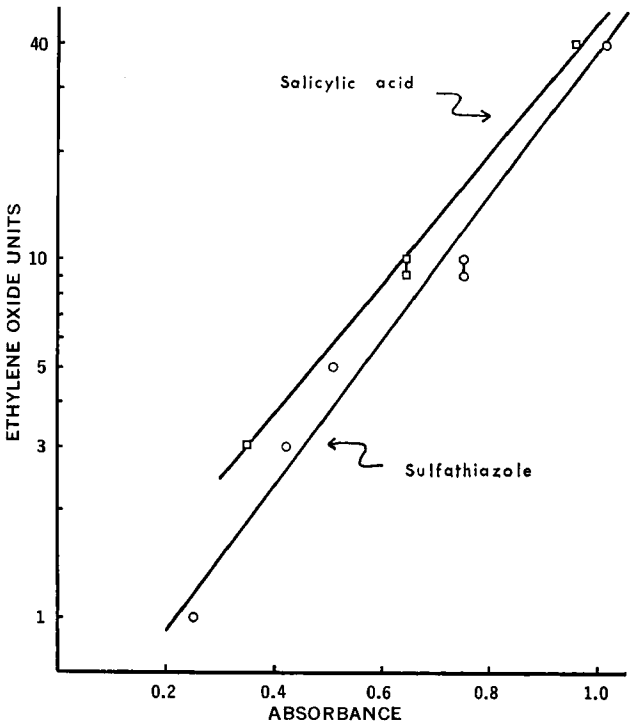

Figure 3—*Ethylene oxide number of the added surfactant (on a logarithmic scale)* versus *absorbance of the drug in the receiving compartment of the dialysis cell.*

RESULTS AND DISCUSSION

Figure 1 shows some representative curves for the release of sulfathiazole from white petrolatum containing surfactants of varying ethylene oxide chain lengths. As can be seen, the rate of release of the drug kept increasing up to the most hydrophilic surfactant studied (containing 40 ethylene oxide units). Since salicylic acid had been shown to diffuse best with mixtures of surfactants (sorbitan esters and polysorbates) having a low hydrophilic–lipophilic balance (HLB) value (12), it was thought that that drug would provide a good point of comparison for sulfathiazole. Figure 2 shows that the general pattern of diffusion obtained with salicylic acid was very close to the one obtained for sulfathiazole.

In Fig. 3, the amount of either sulfathiazole or salicylic acid dialyzed after 120 min was plotted as a function of the logarithm of the number of ethylene oxide units of the added surfactant. For sulfathiazole, it was verified that the relation was linear at any time in the dialysis runs so long as the curves had started to flatten. For salicylic acid at dialysis times less than 120 min, the relation was not linear; it can be observed (Fig. 2), however, that some diffusion curves had not then started to flatten.

The effect of surfactants on the release of drugs from hydrophilic ointment bases has been extensively studied (1, 2, 5, 6). Since those systems contained water (~30%), it is expected that oil-in-water or water-in-oil emulsions were formed, depending on the HLB of the mixture of surfactants studied, giving essentially different systems than those studied here. The diffusion behavior of drugs in such emulsified systems has been well explained (11).

In dealing with lipophilic bases modified by nonionic surfactants, it is believed that the comparisons should be made on a "pseudomolar" basis (*i.e.*, a given number of moles of surfactant added to a given weight of base or a given volume of preparation). The reason becomes apparent when one considers, for instance, the case of the following pair: sorbitan monooleate (mol. wt. ~453) and polysorbate 80 (mol. wt. ~1470). One notes then that, at any given percentage (identical for both surfactants), the concentration of the ethoxylated surfactant is, on a molar basis, about four times lower than that of the other. Since the concentration of the added surfactant is also important [the rate of diffusion increases with increasing concentration up to an optimum concentration and then decreases (11)], comparison of the effect of a large molar concentration of a surfactant having, for example, a middle HLB value to that of a low molar concentration of a surfactant having a high HLB value might obscure the real phenomenon.

It is also possible that nonionic surfactants of different classes (*i.e.*, sorbitan esters and ethoxylated surfactants) do not work in the same way (or to the same extent) when added to lipophilic bases. Hence, it has been observed that the addition of sorbitan monooleate to white petrolatum decreased the rate of diffusion of sulfathiazole while the addition of polysorbate 80 increased it (11). These explanations are given as suggestions to account for the fact that the diffusion of some drugs was shown previously to decrease above a certain HLB value of the added surfactants (3, 4, 12) while this phenomenon was not observed here.

In the three figures, the absorbance of the drugs instead of their concentration is presented to emphasize that the *pattern* of diffusion of both drugs is quite similar. However, the concentration of salicylic acid was evaluated using its peak of second maximum absorbance in the UV region (at 237.5 nm, the peak of maximum absorbance, volume corrections would have been necessary). Salicylic acid diffused to a greater extent than sulfathiazole (~3 times more on a molar basis) per unit of time. This observation may reflect that salicylic acid is about three times more soluble than sulfathiazole on a molar basis (87 mg *versus* 55 mg/100 ml with the unionized portions being considered). In conclusion, it is suggested that these solubility considerations and the relation shown in Fig. 3 (this relation will have, however, to be substantiated with other drugs and other surfactant series) might give a clue as to the mode of diffusion of water-soluble drugs in ointment bases containing ethoxylated nonionic surfactants.

In the rheological part of this study, only sulfathiazole preparations were considered. Rheograms were obtained with the modified bases only (without the drug) and with the complete preparations (with the drug). The study was also extended to white petrolatum containing varying concentrations of polysorbate 80 (11), with and without incorporated sulfathiazole. Various parameters [*e.g.*, thixotropy, yield value, and spur value (18)] were examined and compared to verify if a correlation could be found between the rate of release of the drug and any of the parameters. So far, no correlation has been found. It is possible that such correlations could be obtained if the bases investigated are gels made with water-soluble polymers. Further research in that direction is in progress.

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ACKNOWLEDGMENTS AND ADDRESSES

Received September 6, 1974, from the *School of Pharmacy, Laval University, Quebec, Canada G1K 7P4.*

Accepted for publication December 2, 1974.

Supported by the Medical Research Council, Ottawa, Canada.

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Antitubercular Activity of Substituted 5-Oxo-1-thiocarbamoyl-3-pyrazoline-4-alkanoic Acid Derivatives

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Abstract □ Several novel pyrazolin-5-ones prepared by the cyclization of variously substituted thiosemicarbazone derivatives of ethyl formylsuccinate, ethyl acetylsuccinate, and ethyl acetylglutarate were tested for antitubercular activity against *Mycobacterium tuberculosis*, human type, strain H37Rv, by a tube dilution technique. Minimum inhibitory concentrations (MIC) for these derivatives ranged from 0.05 to 100 μg/ml. The most active compound was ethyl 3-methyl-1-methylthiocarbamoyl-5-oxo-3-pyrazoline-4-acetate (MIC = 0.05–0.1 μg/ml).

Keyphrases □ 5-Oxo-1-thiocarbamoyl-3-pyrazoline-4-alkanoic acid derivatives—synthesis, antitubercular activity □ Pyrazolin-5-one derivatives—synthesis, antitubercular activity □ Antitubercular activity—synthesis and screening of substituted 5-oxo-1-thiocarbamoyl-3-pyrazoline-4-alkanoic acid derivatives

Various classes of thiosemicarbazones have been of interest to clinicians for their therapeutic value as antitubercular, antiviral, antileprotic, and antifungal agents (1–3). Recently, the synthesis of a group of variously substituted 5-oxo-1-thiocarbamoyl-3-pyrazoline-4-alkanoic acid derivatives (II*a*–II*l*), which were prepared by the cyclization of open-chain thiosemicarbazones (I) of diethyl formylsuccinate, diethyl acetylsuccinate, and diethyl acetylglutarate, was described (4). Spectral evidence indicates that these compounds also exist in their tautomeric 5-hydroxypyrazole form (II′*a*–II′*l*). Several of these derivatives were tested for their overall therapeutic value as anti-infective agents and were found to possess substantial antitubercular activity against *Mycobacterium tuberculosis*, human type. A summary of the biological test results in relation to chemical structure is reported here.

EXPERIMENTAL[1]

The open-chain thiosemicarbazones (I) were prepared by heating ethyl formylsuccinate, ethyl acetylsuccinate, or ethyl acetylglutarate with 1 equivalent of a suitably substituted thiosemicarbazide (Scheme I). Ring closures of these derivatives were carried out by warming the various thiosemicarbazones in ammonium hydroxide solution followed by acidification; the title compounds were obtained (Table I). The esters were readily converted to the corresponding acids by hydrolysis using sodium hydroxide solution.

Synthesis—The following example typifies the method used to prepare the title compounds. Further preparative details as well as the chemistry and spectral analyses for other compounds were previously published (4).

Diethyl Acetylsuccinate Thiosemicarbazone (I)—A mixture of 10.8 g of diethyl acetylsuccinate and 4.56 g of thiosemicarbazide in 250 ml of ethanol was heated under reflux for 17 hr. The ethanol solution was cooled in ice, and cyclohexane was added to precipitate the product. The product amounted to 13.1 g, mp 98–102°. The analytical sample (mp 98–100°) was obtained by recrystallization from ethanol–cyclohexane; IR (KBr): 2.90, 3.00, 3.12 (NH), 5.72, and 5.79 (ester C=O) μm.

Anal.—Calc. for $C_{11}H_{19}N_3O_4S$: C, 45.66; H, 6.62; N, 14.52; S, 11.08. Found: C, 45.64; H, 6.58; N, 14.65; S, 11.42.

Ethyl 3-Methyl-5-oxo-1-thiocarbamoyl-3-pyrazoline-4-acetate (IIa)—A mixture of 10 g of diethyl acetylsuccinate thiosemicarbazone and 250 ml of concentrated ammonium hydroxide solution was heated on a steam bath for approximately 30 min, at which

[1] Melting points were determined with a Thomas-Hoover capillary melting-point apparatus and are uncorrected. The IR spectra were determined in potassium bromide disks using a Perkin-Elmer model 21 spectrophotometer.