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Study on the release properties and stability of o/w emulsions containing salicylic acid and zinc oxide

M.E. Carlotti*, L. Battaglia, E. Ugazio, M. Gallarate, F. Debernardi

Dipartimento di Scienza e Tecnologia del Farmaco, Università degli Studi di Torino, Via Pietro Giuria n° 9, 10125 Torino, Italy
*Correspondence: eugenia.carlotti@unito.it

o/w emulsions with zinc oxide and salicylic acid were prepared at a pH between 4.0 and 5.2 in order to determine the best pH at which both molecules are simultaneously present in the system. The emulsion's structure and the presence of zinc oxide crystals were investigated by optical microscopy. Zinc oxide caused a slight increase in pH of the emulsions over time. The emulsion that had the most stable pH was that at pH 4.6. Salicylic acid diffusion from these systems, studied as a function of pH and the amount of zinc oxide crystals, was maximal at pH 4.6 and was found to be unrelated to the apparent partition coefficient or to the un-dissociated molar fraction of salicylic acid. Zinc oxide decreased the diffusion of salicylic acid from all emulsions.

Key words: Salicylic acid – Zinc oxide – Diffusion of salicylic acid – o/w emulsion.

Salicylic acid has been used in many different bases to treat acne, psoriasis, icthiosis and other hyperkeratotic disorders [1]. Hydroxy acids, in particular salicylic acid, are also recommended to treat solar skin damage, because they lead to desquamation, giving the skin a youthful appearance. The bioavailability of salicylic acid topical formulations has been evaluated in terms of their keratolytic effect and clinical efficacy. Very little research has been done to address the mechanism and extent of salicylic acid absorption into human skin or to the relationship between local salicylic acid concentration and pharmacological activity. A tape-stripping method, used to evaluate the effect of skin absorption of salicylic acid on the binding forces within the stratum corneum, allows a comparison to be made of the release of salicylic acid to the stratum corneum from different formulations [1].

Poly (2-hydroxyethyl metacrylate) gels have been evaluated as drug delivery systems at different pH values, using salicylic acid as a model drug, for which loading is possible at both high and low pH [2]. Fatty acids have been used as potential carriers for drug delivery systems; they are biocompatible, biodegradable, inexpensive and have low toxicity [3]. Salicylic acid has also been incorporated in chitosan films. A sustained release of salicylic acid from high viscosity chitosan films was found to be due to the drug-polymer interaction [4].

Salicylic acid is an irritant and it is used at low concentrations in the cosmetic field [5]. Zinc oxide, a constituent of many commercial preparations, can decrease this irritation and as a calamine has long been recognized for its healing properties; its value in treating nappy rash, bed sores, venous ulcers and skin wounds is also well-recognized [6].

Macro-pigments are frequently introduced into cosmetic products, where they have traditionally been viewed as light scatters, but they can also absorb UV radiation. Zinc oxide, titanium oxide and iron oxide have an absorption optical band at wavelengths slightly below that of visible light and have photo-catalytic activity [7]. However, some problems must be overcome when cosmetic or dermatological systems are formulated with these oxides. In preparing cosmetics with pigments, it is very important to achieve an uniform dispersion of the pigment throughout the finished product, as this improves the efficacy of the formulation. With zinc oxide, there are also other considerations, as the solubility of zinc oxide in water increases markedly below pH 6.0. As a result, zinc oxide is usually incorporated in the oil phase, but as a consequence of its hydrophilic nature, it tends to migrate to the water phase with an increase in pH, owing to the formation of alkaline zinc complexes. Several ways of limiting this have been suggested [8], but there is often still some migration and a consequential effect on the pH. A change in pH could lead to instability and loss of efficacy or to an irritant reaction on the skin. An example of a problem of formulating with zinc oxide is its incompatibility with AHAs (alpha hydroxy acids).

In this study we formulated o/w emulsions with zinc oxide as a lenitive molecule, and salicylic acid for its keratolytic action; we examined their compatibility and interactions through the presence of crystals of zinc oxide, as well as their efficacy via the diffusion of salicylic acid through a synthetic membrane.

The role of pH on product stability and the diffusion of salicylic acid from the vehicles was investigated. The pH values, ranging from 4.0 to 5.2, were studied to determine the pH at which there was a simultaneous presence of zinc oxide and un-dissociated salicylic acid.

I. MATERIALS AND METHODS

1. Materials

Materials used in the study were obtained as follows: 1-decanol, 1-dodecanol, and hydrochloric acid were from Fluka; citric acid, cetearyl alcohol, dimethycone (350 mPas), and sodium hydroxide were from Acef; cellulose nitrate filter (cut-off 0.1 μm) was from Sartorius; dialisers lauch whisking was from Roth GmbH; and tri-sodium citrate di-hydrate was from Carlo Erba. Hydroxyethyl cellulose (Natrosol 250 MR) was from Acef, and salicylic acid was from Merck. Octyl octanoate (Dragoxat EH) was a donation from Dragoco Gerberding and

Co.; methyl isothiazolinone and chloromethyl isothiazolinone (Kathon CG) were donations from Sinerga; Peg-8-laurate and Peg-8-arachidate (Xalifin 15) were donations from Vevy Europe; and microfine zinc oxide was a donation from Sunsmart.

2. Instruments

The instruments used were: homogenisers Silverson SL 2 and Ultra Turrax T 25 basic (IKA Labortechnik); DLS microstirrer (VELP); centrifuge model 5417 (Eppendorf); centrifuge model 4225 (ALC); centrifuge model Allegra 64 R (Beckman Coulter); conductivity meter Mod. 101 (Orion Research); optical microscope (Leitz); sonicator Sonica 2200 ETH ultrasonic cleaner (Soltec); submicron particle analyser N4 MD (Coulter); UV-Vis Lamda 2 spectrophotometer (Perkin Elmer); HI 9321 microprocessor pH-meter (Hanna Instruments); and digital viscometer Mod. DV-II (Brookfield), equipped with small adapter chamber SC 21, SC 29.

3. Determination of the molar absorbivity (ε) of salicylic acid

The ε value for salicylic acid in water (3475) at 298 nm (mean of three determinations) was not influenced by the pH.

4. Partition coefficient of salicylic acid

The o/w apparent partition coefficient of salicylic acid derives from the relationship:

$$P = [\text{salicylic acid}]_{oil}/[\text{salicylic acid}]_{\text{aqueous buffer solution}}$$

0.1 M citrate buffer solutions of 3.62×10^{-4} M salicylic acid were shaken in a separating funnel with equal volumes of octyl octanoate for 10 min. The apparent partition coefficient was obtained from the ratio of the molar concentration of salicylic acid in oil and of that in water after shaking (mean of three determinations). To relate P to the pH, the partition coefficient was determined at four pH values (3.6, 4.0, 4.6, 5.2).

5. Characterization of aqueous dispersion of zinc oxide with laser light scattering

Laser light scattering was employed to examine zinc oxide particles at pH 4.0, 4.6 and 5.2. Each determination was the mean of three runs, performed by unimodal analysis and SDP. Measurements were done on slightly turbid aqueous dispersions, with an excess of zinc oxide over the saturated solution. Small amounts of zinc oxide were added to the buffer, dissolving it by a sonicator, until the dispersion became slightly turbid.

6. Preparation of emulsions

Xalifin 15, cetearyl alcohol, Dragoxat EH and dimethycone were heated to 65-75°C. Salicylic acid (0.025 or 0.5% w/w) was dissolved and zinc oxide (1.5% w/w) was dispersed in aqueous buffer (0.1 M citrate) at pH 4.0, 4.6, 5.2 and heated to about 80°C. The aqueous phase was then added under homogenisation to the lipid phase, the emulsion was brought to 25°C under stirring and the preservative (Kathon CG) was added. Zinc oxide (1.5%) was alternatively dispersed in the lipid phase before homogenisation of the two phases to obtain emulsions at the desired pH. Owing to a light increase of the pH of the emulsions over time, the pH of the emulsions was adjusted finally to the desired value with 2 N HCl, checking its stability over time (weekly).

7. Preparation of hydroxy ethyl cellulose gels with 0.025% w/w salicylic acid and 1.5% w/w ZnO

Salicylic acid was dissolved in cold aqueous buffer solutions (pH 4.0, 4.6, 5.2) and heated to 80-90°C. Hydroxyethyl cellulose was dispersed in the hot aqueous solutions under stirring. The gels were brought to 25°C under stirring and the preservative added. ZnO was then dispersed in the gels under homogenisation.

8. Characterization of emulsions and gels

8.1. Microscopic analysis

Emulsions and gels were observed by optical microscopy and under polarized light. The preparations were observed at 1250 x without dilution and microphotographs were taken.

8.2. Conductivity

The conductivity of the emulsions was determined over time at 80 Hz in order to verify the stability of the preparations at 25 ± 0.5°C.

8.3. pH

The pH of the preparations was monitored over time.

8.4. Viscosity and flux rheograms

The flux rheograms were determined for emulsions 24 h after preparation using a rotational viscometer (Brookfield DV-II with small adapter chamber and spindle SC 4-21 and SC 4-29) at 25.0 ± 0.5°C. For all formulations, the viscosity was determined 24 h after preparation at two shear rates before studying the rheological flux.

8.5. Accelerated stability test

The emulsions were centrifuged at 6000 rpm for 30 min to check their stability. They were also stored at 40°C for 15 days, after which conductivity, pH, and viscosity were measured and rheograms determined.

9. Permeation of salicylic acid through double membrane

A Sartorius apparatus with a cell for creams was used, with a double membrane composed of cellulose nitrate foil soaked in a mixture of 1-decanol and 1-dodecanol (1:1 w/w ratio) versus the receiving phase and a membrane of hydrophilic cellulose versus the donor phase. The volume of the donor phase was 2.0 ml for experiments with aqueous buffer solutions and 7.85 ml for experiments with semi-solid preparations. The runs were repeated three times.

At scheduled times, a small sample of the receiving phase was withdrawn and analysed spectrophotometrically for salicylic acid determination. After determination, the samples were returned to the receiving phase.

10. Salicylic acid diffusion rate constant

The salicylic acid diffusion rate constant was calculated from *Equation 1*:

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$$k_d = (C_{r2} - C_{r1})/(t_2 - t_1) \times 1/C_{d0} \times V_r/A \qquad \textbf{Eq. 1}$$

where C_r is the molar concentration of salicylic acid at different times in the receiving phase, V_r is the volume of the receiving phase (ml), t is the time at which the receiving phase was removed (min), C_{d0} is the concentration of salicylic acid in the donor phase at time 0, A is the effective area of the membrane and k_d is the diffusion rate constant of salicylic acid through the double membrane(cm/min) [9, 10].

II. RESULTS AND DISCUSSION

1. Partition coefficients

Figure 1 shows the variation of the apparent P of salicylic acid with the pH of the aqueous buffer solution; the apparent P decreases with the increase in pH of the aqueous solutions.

2. Determination of zinc oxide particles sizes

The particles size of zinc oxide determined by unimodal analysis was 465 ± 100 nm; it was 466 ± 140 nm with SDP analysis.

3. Preparation of emulsions with 0.025% w/w salicylic acid and 1.5% w/w zinc oxide in 0.1 M citrate buffer

o/w emulsions were prepared at different pHs, as this can influence the partition of salicylic acid between the lipid and aqueous phases and may allow the simultaneous presence of zinc oxide crystals. Initially, in order to obtain emulsions with a stable pH in the presence of zinc oxide, 1.5% w/w zinc oxide and only 0.025% w/w salicylic acid were used. This prevented a shift of pH versus low values and the consequent dissolution of ZnO. Xalifin 15 was employed as an emulsifier because of its compatibility with the buffer solutions. *Table I* shows the composition of the emulsions at pH 4.0, 4.6, and 5.2. The pH of these emulsions increased over time owing to the presence of zinc oxide, dispersed either in the lipid or in the aqueous phase. As ZnO probably migrated from the lipid to the aqueous phase, the emulsion pH was thus corrected to the desired value and its stability monitored over time. *Figure 2* shows the pH trend over time in emulsions prepared with zinc oxide in the continuous or in the dispersed phase; pH values of the emulsions increased slightly over time and the most stable pH value was 4.6. The pH of the three emulsions also changed after the accelerated test at 40°C, increasing from 4.0 to 4.9, from 4.6 to 4.7, and from 5.2 to 5.9 (the same increase of pH was obtained by dispersing ZnO in the lipid and aqueous phase). The storage test at 40°C was found to be too drastic.

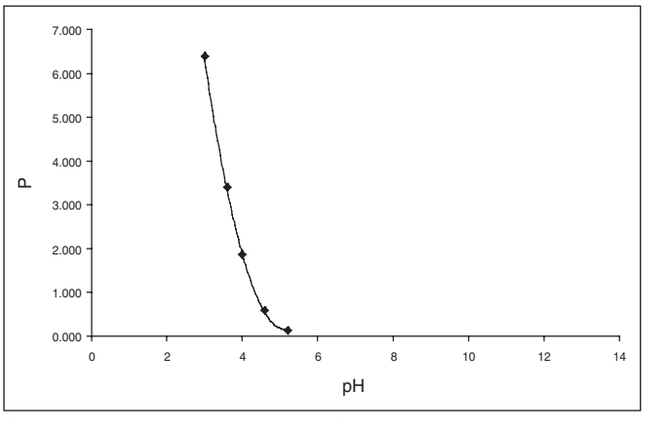

Figure 1 - Variation of the apparent P of salicylic acid with the pH.

4. Preparation of emulsions with 0.5% w/w salicylic acid and 1.5% w/w zinc oxide in 0.1 M citrate buffer

To compare the diffusion of salicylic acid from the different emulsions, systems with higher concentrations of salicylic acid (which could be detected spectrophotometrically) were prepared; with 1.5% w/w ZnO, we tried to obtain systems with comparable viscosity, because the release of salicylic acid can be influenced from the viscosity of the systems. The maximum percentage of salicylic acid that gave a stable system was 0.5% w/w. The composition of the emulsions at pH 4.0, 4.6, and 5.2 was the same as that reported in *Table I* except for the percentage of salicylic acid (0.5% w/w). The pH trend of the emulsions over time was analogous to that of the emulsions with 0.025% w/w salicylic acid and 1.5% w/w zinc oxide, as reported in *Figure 2*. It increased slightly over time, the most stable being that at 4.6. Also, in this case, there was a slight change in the pH of the systems stored at 40°C. The different pH values did not change the viscosities of the emulsions, which remained constant over time. To compare the diffusion of salicylic acid from the emulsions containing salicylic acid and ZnO to that from ZnO-free emulsions, emulsions were prepared without ZnO but otherwise had the same composition (reported in *Table I*), except for the percentage of salicylic acid (0.5% w/w), and the same pH.

Table I - Composition of emulsion with zinc oxide and salicylic acid at different pH.

Components	w/w percentages
Salicylic acid	0.025
Zinc oxide	1.50
Xalifin 15	12.00
Octyl octanoate	20.00
Cetearylic alcohol	0.50
Dimethicone	0.50
Buffer solution	a.s. to 100
Kathon CG	0.30

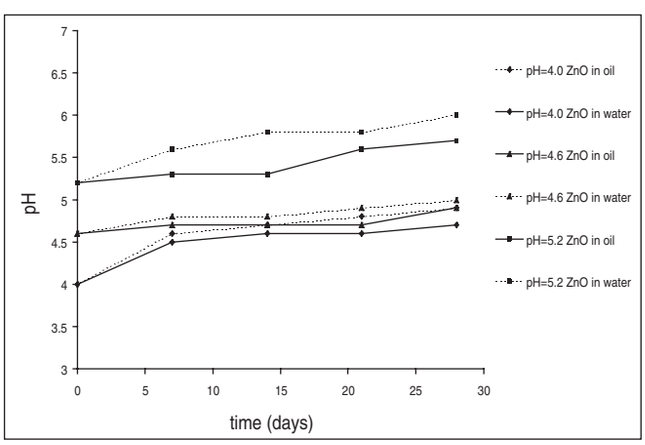

Figure 2 - Trend of the pH of emulsions, prepared with ZnO dispersed in oil or in water, as a function of time.

5. Preparation of hydroxy ethyl cellulose gels

Table II shows the composition of hydroxyethyl cellulose gel at pH 4.0, 4.6 and 5.2.

6. Characterization of emulsions with 0.025% w/w salicylic acid and 1.5% w/w zinc oxide

6.1. Optical microscopy

The microphotograph of the emulsion prepared at pH 5.2 with zinc oxide in the lipid phase is shown in *Figure 3*. There was some difficulty in seeing the crystals of ZnO in these systems. The amount of zinc oxide crystals decreased markedly as the pH decreased, the maximum amount being present at pH 5.2. The emulsion droplets showed regularity and low polydispersion.

The microphotograph in *Figure 4* shows a large amount of crystals in the gel with salicylic acid and ZnO at pH 5.2, where the crystals were more evident than in the emulsions.

6.2. pH

The pH trend over time of the gels with zinc oxide was different from that of the emulsions, being stable in all cases. The pH stability difference between emulsions and gels probably depends on the presence of a dispersed phase in the emulsions that partially incorporates the zinc oxide and, acting as a reservoir, slowly delivers it to the continuous phase, determining an increase in pH.

Table II - Composition of hydroxyethyl cellulose gel with salicylic acid and zinc oxide.

Components	w/w percentages
Salicylic acid	0.025
Hydroxyethyl cellulose	1.50
Aqueous solution	a.s. to 100
Zinc oxide	1.50
Kathon CG	0.05%

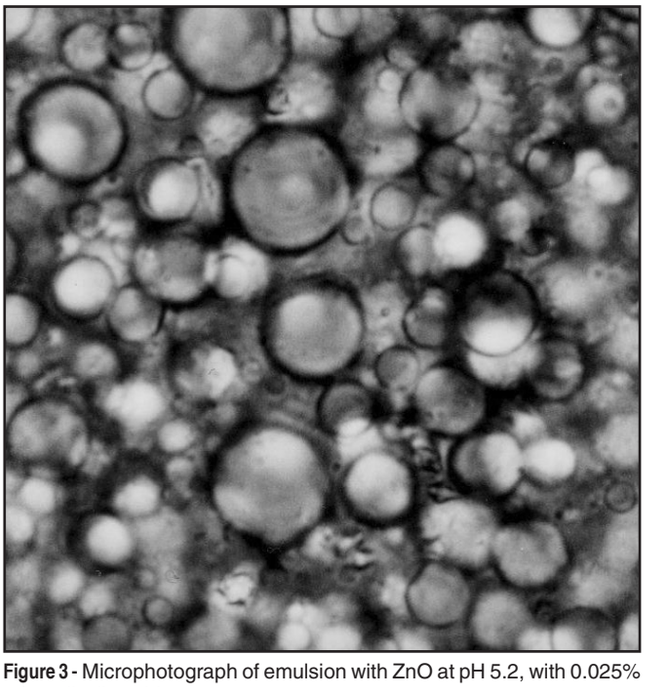

Figure 3 - Microphotograph of emulsion with ZnO at pH 5.2, with 0.025% w/w salicylic acid.

6.3. Conductivity

The relatively high conductivity (1.32-1.60 mS) of the emulsions denoted a continuous aqueous phase, and its constancy (1.27-1.54 mS) after the accelerated test at 40°C demonstrated that there was no phase inversion over time.

6.4. Viscosity and rheograms

The viscosity values, reported in *Table III*, were fairly similar for all the emulsions. The viscosity of emulsions stored at 40°C for 15 days was partially modified, indicating a low instability of the preparations. *Figure 5* shows, as an example, the rheograms of the emulsion at pH 5.2, 24 h after preparation and after the test at 40°C. The rheograms indicated a shear thinning and thixotropic flux; they changed when the emulsions were warmed to 40°C.

6.5.Test of stability by centrifuge

A slight separation of the emulsions occurred, with sedimentation of zinc oxide, after centrifuging the samples 24 h after their preparation at 6000 rpm for 20 min. This separation also occurred in those heated to 40°C.

7. Characterization of emulsions with 0.5% w/w salicylic acid and 1.5% w/w zinc oxide

The microphotographs of these emulsions were analogous to those of the emulsions with 0.025% w/w salicylic acid; they showed regular droplets with low polydispersion and a large amount of crystals of ZnO at pH 5.2. The pH of these emulsions also changed over time, from pH 4.0 to pH 4.8, from pH 4.6 to 5.2, and from pH 5.2 to 5.8, respectively. The conductivity values remained unaltered after the test at 40°C (0.72 mS). The high conductivity indicated a continuous aqueous phase. The viscosity values of the different emulsions were similar. There was a slight drop in viscosity after storage at 40°C. The rheograms of the emulsions denoted systems with shear thinning

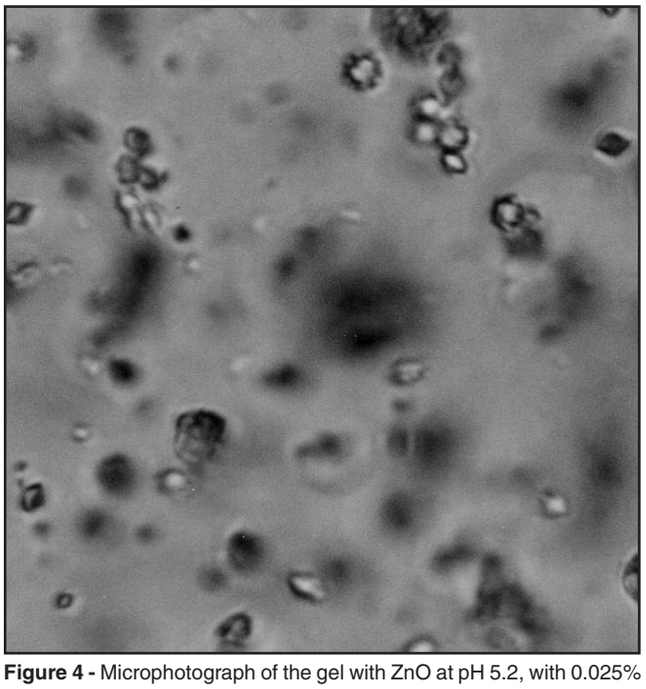

Figure 4 - Microphotograph of the gel with ZnO at pH 5.2, with 0.025% w/w salicylic acid.

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Table III - Values of viscosity of the emulsions with 0.025% w/w salicylic acid and zinc oxide, measured after preparation and after accelerated test at 40°C.

Shear rate (1.25 s^{-1})	Viscosity (mPa.s)	Viscosity after test at 40°C (mPa.s)
Emulsion at pH 4.0, ZnO in water	31400	29000
Emulsion at pH 4.0, ZnO in lipid	25600	26800
Emulsion at pH 4.6, ZnO in water	21200	16400
Emulsion at pH 4.6, ZnO in lipid	32400	34800
Emulsion at pH 5.2, ZnO in water	29400	27800
Emulsion at pH 5.2, ZnO in lipid	25200	25000
Shear rate (2.5 s^{-1})		
Emulsion at pH 4.0, ZnO in water	18000	22000
Emulsion at pH 4.0, ZnO in lipid	15200	13200
Emulsion at pH 4.6, ZnO in water	13800	12000
Emulsion at pH 4.6, ZnO in lipid	20900	19000
Emulsion at pH 5.2, ZnO in water	18000	17700
Emulsion at pH 5.2, ZnO in lipid	14900	14000

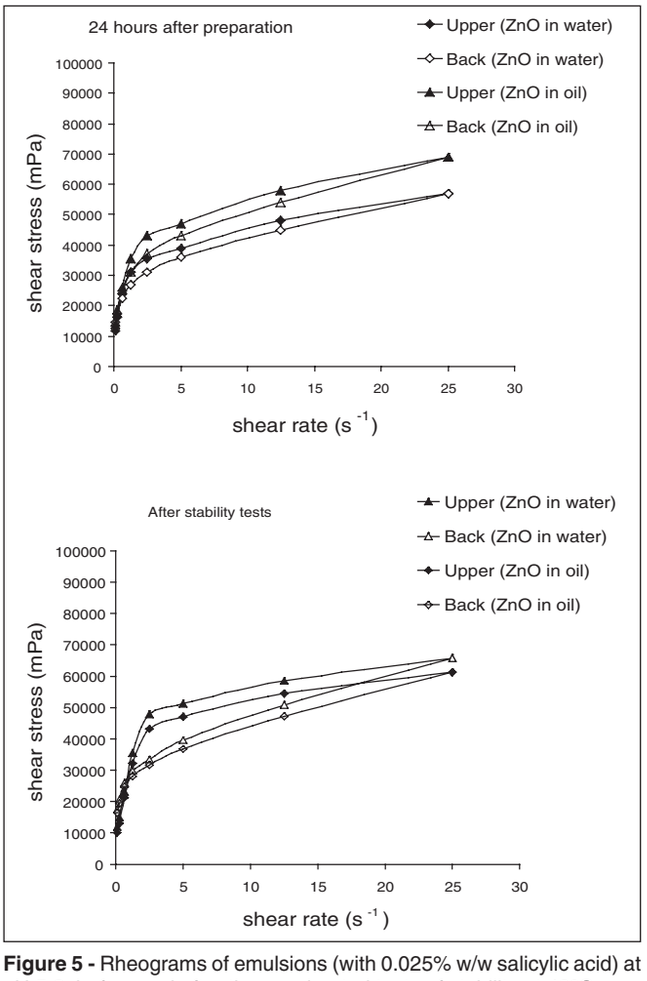

Figure 5 - Rheograms of emulsions (with 0.025% w/w salicylic acid) at pH 5.2, before and after the accelerated tests of stability at 40°C.

and thixotropic flux. A slight change in rheological behaviour indicated a slight instability of the emulsions after the accelerated test at 40°C.

8. Diffusion of salicylic acid from emulsions and solutions at different pH values

The influence of the pH on the diffusion of salicylic acid through the double membrane from buffered emulsions with and without zinc oxide was studied. The diffusion was compared to that from aqueous solutions at the same pH. The emulsions considered were initially those at pH 4.0, 4.6, and 5.2.

At all the pH values, the diffusion was a curve from the start, because the receiving phase had a larger volume than the donor phase. At the beginning, when there was a large difference in salicylic acid concentration between the donor and receiving phases, the flux was considerable, but there was a small increase of concentration in the receiving phase in spite of a considerable decrease in concentration in the donor phase; this caused an immediate reduction in the difference in salicylic acid concentration between the donor and receiving phases and consequently, in the flux through the membrane.

Figure 6 shows the profile release over time, in moles of salicylic acid, from preparations with zinc oxide at each pH. The highest diffusion rate constant was found at pH 4.6. The diffusion of salicylic acid from emulsions at the same pH but without zinc oxide is reported in *Figure 7*. The composition

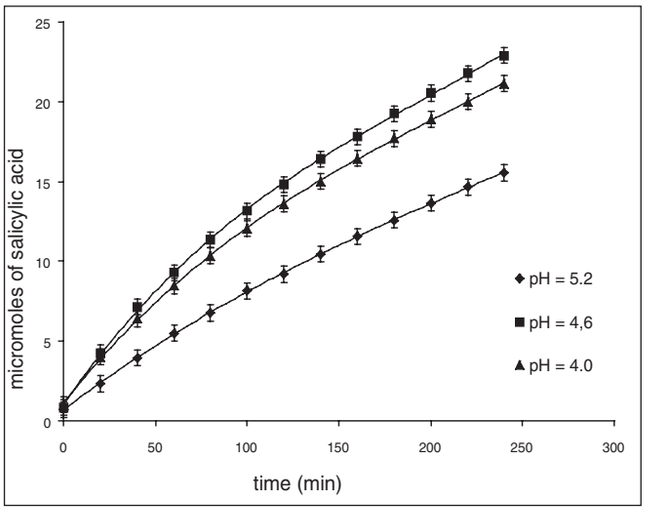

Figure 6 - Diffusion of salicylic acid from emulsion with ZnO at pH 4.0, 4.6, 5.2.

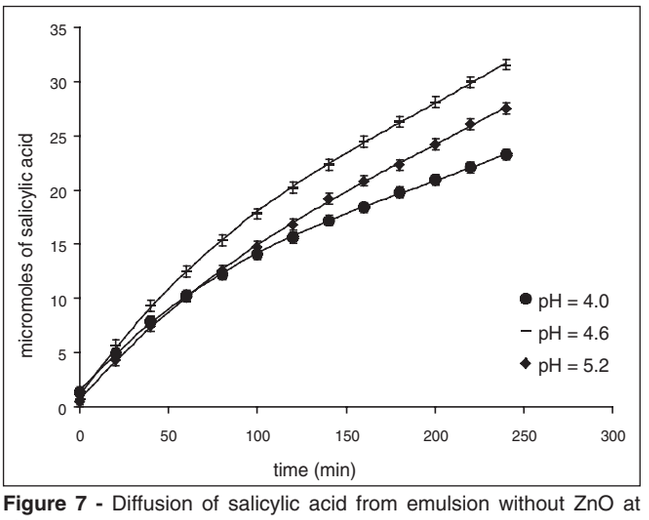

Figure 7 - Diffusion of salicylic acid from emulsion without ZnO at pH 4.0, 4.6, 5.2.

of these emulsions was the same as that reported in *Table I* but without ZnO. For both systems, with and without ZnO, diffusion was lower at pH 4.0, higher at pH 4.6 and intermediate at pH 5.2.

The trend of the release of salicylic acid was not related to the apparent partition coefficient or to the molar fraction of the un-dissociated molecule, as determined at each pH. To verify that the trend of permeation of the acid through a double membrane was correct, two diffusion experiments from emulsions without zinc oxide were performed at pH 4.3 and 4.8, being intermediate pH values among those previously examined. The results are in *Figure 8* and confirm the trend previously seen. The highest diffusion of the acid occurred close to pH 4.6, above which diffusion decreased. This diffusion trend from a two-phase system appears to be rather complex, and may be ascribable to many contemporary equilibria affecting the distribution of salicylic acid between the oil and the buffer solutions of the emulsions, and diffusion of salicylic acid through the double membrane. The diffusion of salicylic acid from the two-phase systems was then compared to that from mono-phase aqueous solutions of 1.81 x 10^{-3} M salicylic acid at pH 4.0, 4.6 and 5.2. The release of salicylic acid from the aqueous solutions in the receiving phase, reported in *Figure 9*, increased with decreasing pH. The molar fraction of un-dissociated salicylic acid in the donor phase was the only factor involved in the diffusion. By recombining the diffusion data for salicylic acid, reported in *Figures 7 and 8*, other graphs were obtained to evaluate the influence of zinc oxide on the diffusion at various pH values. As an example, *Figure 10* shows salicylic acid diffusion at pH 5.2 from emulsions with and without zinc oxide. By comparing the diffusion of salicylic acid in the presence and absence of zinc oxide, the existence of crystals of zinc oxide at each pH was confirmed. In all cases, there was a decrease in salicylic acid diffusion in the presence of zinc oxide; increasing amounts of solid zinc oxide (from pH 4.0 to 5.2) determined a large decrease in salicylic acid diffusion. The decrease in diffusion was largest at pH 5.2. This is in agreement with the microphotographs of the emulsions with salicylic acid and ZnO, where the oxide was more evident at pH 5.2.

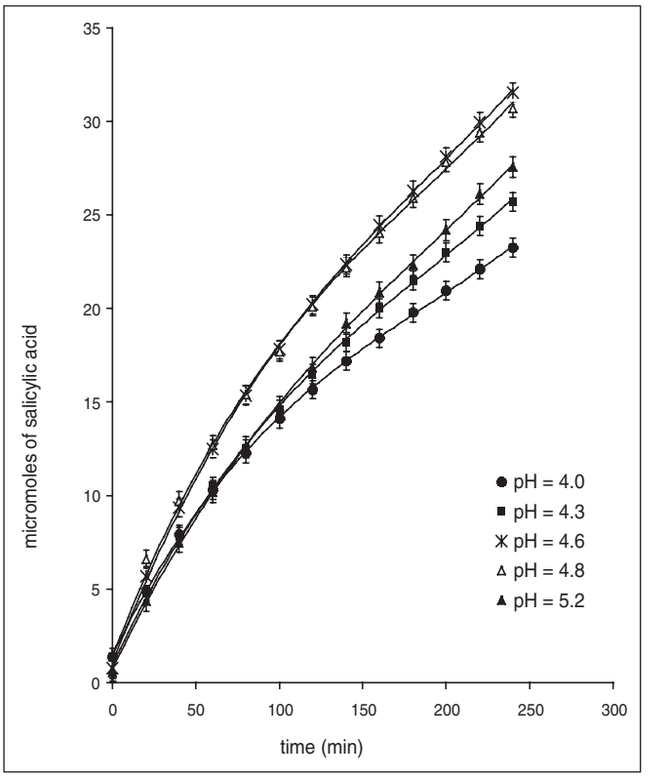

Figure 8 - Complete behaviour of the diffusion of salicylic acid with the pH.

9. Salicylic acid diffusion rate constant

To calculate the diffusion rate constant of salicylic acid, only the linear part of the diffusion graph was considered, which is only that relating to the first hour for emulsions and to the first half hour for the aqueous solutions. The calculated kd values are reported in *Table IV*. The rate constants of diffusion of salicylic acid were much higher from solutions than from emulsions; kd values for solutions were in agreement with the apparent partition coefficient of salicylic acid.

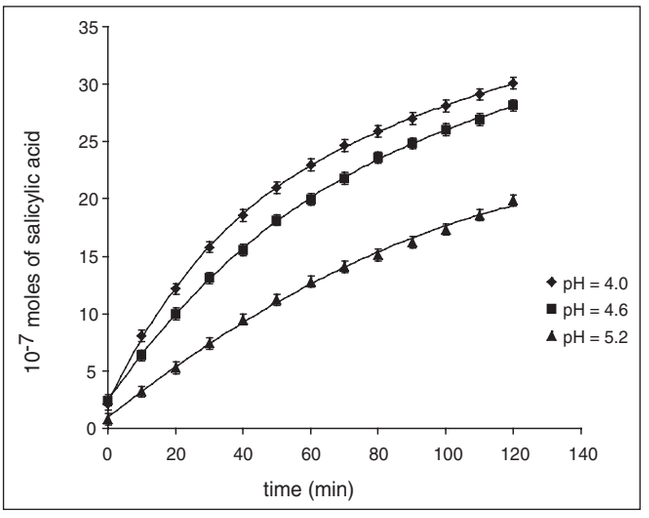

Figure 9 - Diffusion of salicylic acid from aqueous solution at pH 4.0, 4.6, 5.2.

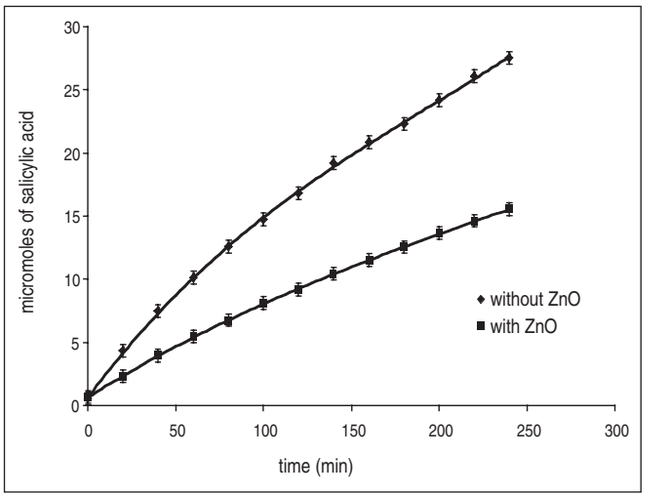

Figure 10 - Diffusion of salicylic acid at pH 5.2 from emulsion with and without ZnO.

Table IV - k_d values of salicylic acid from emulsions and aqueous solutions.

pH	k_d (cm/min)	
	in the presence of zinc oxide	in the absence of zinc oxide
Emulsions		
4.0	0.22×10^{-3}	0.26×10^{-3}
4.3	-	0.29×10^{-3}
4.6	0.25×10^{-3}	0.343×10^{-3}
4.8	-	0.34×10^{-3}
5.2	0.14×10^{-3}	0.28×10^{-3}
Solutions		
4.0	-	2.4×10^{-3}
4.6	-	1.86×10^{-3}
5.2	-	1.16×10^{-3}

10. Determination of the flux values

The flux J, i.e. the number of moles that flow through a permeation membrane in unit time, depends on contact surface, barrier thickness, difference of concentration between the donor and receiving phases and the diffusion of the substance through the barrier. J is calculated from the moles of substance accumulating in the receiving phase over time. In our case, a first order kinetic for the diffusion of salicylic acid was found.

The linear relationship between flux and moles of substance can be therefore expressed by the following equation:

$$J = dn/dt = k\,(n_\infty - n) \qquad \textbf{Eq. 2}$$

where n_∞ is the number of moles of the substance in the receiving phase at infinite time, that is the maximum number of moles that can be released from the donor system in conditions of equilibrium. By integrating and rewriting *Equation 2*, we obtained *Equation 4*, which describes the release in the receiving phase over time:

$$dn/(n_\infty - n) = k\,dt \qquad \textbf{Eq. 3}$$

$$n = n_\infty\,(1 - e^{-kt}) \qquad \textbf{Eq. 4}$$

Equation 5 was then obtained, which describes the behaviour of the flux versus time:

$$dn/dt = n_\infty\,k\,e^{-kt} \qquad \textbf{Eq. 5}$$

To obtain the values of n_∞ and k, flux values were determined at different times by dividing the experimental Δn by the corresponding Δt. The straight line obtained for flux versus the number of moles of salicylic acid is described by *Equation 3*.

Both for solutions and for emulsions at all the pH values studied (4.0, 4.5, 5.2), straight lines with a good linear relationship were found.

Figure 11 shows, as an example, the flux of salicylic acid from emulsions at pH 4.0, 4.6, and 5.2 in the presence of zinc oxide at different times, versus micromoles of salicylic acid in the receiving phase.

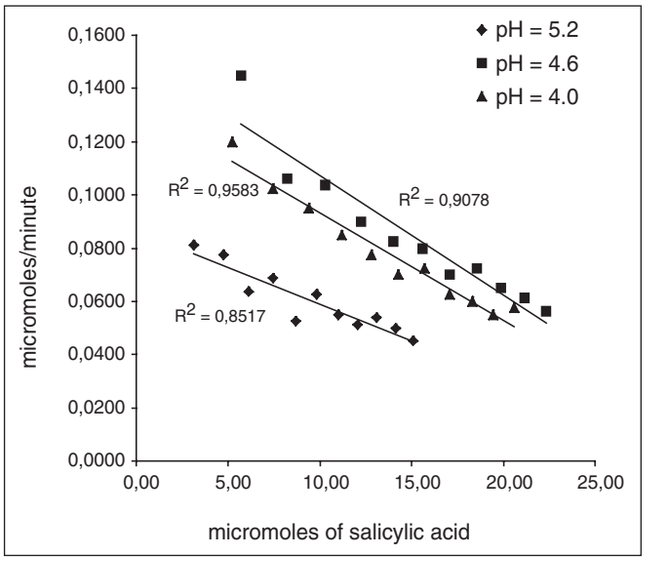

Figure 11 - Flux of salicylic acid versus the moles from buffered emulsion with ZnO.

The values of k and n_∞ were extrapolated from the straight lines and are reported in *Table V*. Taking these values, *Equation 5* was employed to calculate the flux.

The fluxes of the different preparations may be compared; they were calculated at fixed times, being at two hours for emulsions and at 1 h for solutions. The flux per unit area was obtained by dividing the flux from each preparation by the membrane area (15.7 and 10.46 cm^2, respectively, for emulsions and solutions). *Table VI* reports the calculated flux values of

Table V - Values of n_∞ and k for the diffusion of salicylic acid.

pH	Emulsions with ZnO	Emulsions without ZnO	Solutions
n_∞			
4.0	33.35	34.23	3.39
4.3	-	39.26	-
4.6	33.87	49.09	3.36
4.8	-	48.18	-
5.2	30.89	45.51	3.18
4.8	-	0.0039	-
5.2	0.0028	0.0037	0.0079
k (min)			
4.0	0.004	0.0044	0.0172
4.3	-	0.042	-
4.6	0.0045	0.0041	0.0014

Table VI - Flux values (μmoles min^{-1} cm^{-2}) of salicylic acid from emulsions and aqueous solutions.

pH	Emulsions with ZnO	Emulsions without ZnO	Solutions
4.0	5.25×10^{-3}	5.4×10^{-3}	1.99×10^{-3}
4.3	-	6.34×10^{-3}	-
4.6	5.66×10^{-3}	7.84×10^{-3}	1.94×10^{-3}
4.8	-	7.94×10^{-3}	-
5.2	3.94×10^{-3}	6.88×10^{-3}	1.49×10^{-3}

salicylic acid from emulsions and from solutions. The flux followed the same behaviour with regard to the pH that occurred for the release of salicylic acid in the receiving phase.

*
* *

o/w emulsions with 0.025% w/w and 0.5% w/w salicylic acid and 1.5% w/w zinc oxide were difficult to prepare; Xalifin 15 was the best of the emulsifiers used and gave systems with good stability. It was the only emulsifier tested that was compatible with the buffer solutions employed to give emulsions at pHs of 4.0, 4.6 and 5.2. The presence of zinc oxide determined a slight increase of the pH values over time, and the emulsion at pH 4.6 was the most stable.

The variation with pH of the diffusion of salicylic acid from emulsions through a double membrane could not be related to the partition coefficient and was maximum at pH 4.6. The presence of zinc oxide decreased salicylic acid diffusion from emulsions through the membrane, its effect being maximum at pH 5.2, probably owing to the increase of zinc oxide.

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