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Transesterification of salicylate esters used as topical analgesics

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Summary

Salicylate esters undergo reversible transesterification in alcoholic solutions in which the ester radical differs from that of the alcohol. The reactions are base-catalyzed and the predominant pathway involves a concerted solvent attack upon the salicylate anion. Competitive hydrolysis of both ester components also follows this mechanism at moderate pH values but rates increase under strongly alkaline conditions as direct hydroxide attack becomes significant. In contrast, transesterification is independent of base concentration once full ionization is accomplished. Equations are presented to model the time-profile of reactant and product concentration. The process may affect the integrity of pharmaceutical formulations and a gel formulation is shown to degrade rapidly.

Introduction

Salicylates have long been used as topical analgesics in the relief of inflammatory pain. More recently, intradermal aspirin has been shown to alleviate UV-induced erythema (Snyder and Eaglstein, 1974) due to its inhibitory action on prostaglandin

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synthetase (Robinson and Vane, 1974) and the percutaneous delivery of indomethacin has been successful (Naito and Tsai, 1981). Most topical analgesics, however, are still based upon salicylate esters. These range from menthyl salicylate, the essential component in oil of Wintergreen, through glycol salicylate to methyl and phenyl salicylate. These structural variations modify the physicochemical properties of the drug which control release from formulations and the subsequent transdermal delivery (Roberts, 1983; Al-Khamis et al., 1982; Delonca et al., 1977; Plakogiannis and Yaakob, 1977). This is reflected in the use profile of these compounds. The short-chain and more polar esters (methyl, glycol) undergo rapid percutaneous absorption (Al-Khamis et al., 1982; Cotty, 1960; Brown and Scott, 1934) whereas the larger, less polar compounds (menthyl, phenyl) display more substantivity and are used in sun-screen preparations.

The salicylates are hydrolabile (Capon and Ghosh, 1966; Pal et al., 1974; Pekkarinen and Tommila, 1959) and in addition to their potential instability in semi-solid and liquid formulations, the possibility also exists that these compounds are substrates for cutaneous esterases (Pannatier et al., 1981) and may undergo metabolic conversion during absorption. Our interest in this field (Hempenstall et al., 1983; Mroso et al., 1982; Irwin et al., 1983, 1984; Li Wan Po et al., 1983; Yip et al., 1983) has led us to examine the stability of salicylate esters in aqueous and hydro-alcoholic systems and to note that transesterification may be a significant degradation pathway.

Experimental

Apparatus

Analyses were performed using a high-performance liquid chromatograph constructed from an Altex 100A dual-reciprocating, constant-flow solvent-metering pump, a Rheodyne 7120 injection valve fitted with a 20 μl loop and a Pye LC3 variable wavelength ultraviolet monitor, equipped with an 8 μl flow cell and operated at a wavelength of 235 nm with a sensitivity of 0.16–0.64 AUFS. Chromatography was performed using a Shandon 10 cm $\times$ 4.6 mm i.d. stainless steel column packed with ODS-Hypersil (5 μm) reversed-phase material. Pre-filtered mobile phase (0.45 μm), consisting of acetonitrile–water–phosphoric acid (52 : 47 : 0.1; pH = 2.15) for the methyl and ethyl esters and (60 : 40 : 0.1; pH 2.15) for propyl salicylate, was delivered at a flow rate of 1 ml $\cdot$ min^{-1}.

Mass spectra were determined by the direct insertion technique using a Micromass MM12 mass spectrometer operated with an accelerating voltage of 4 kV, a trap current of 100 μA and a source temperature of 250 °C. ^{1}H nmr spectra were determined in deuterochloroform solution with tetramethyl saline as internal standard using a Varian EM360A spectrometer operating at 60 MHz.

Calculations were undertaken using the BASIC programs: LINREG (calibration data and first-order kinetics), NONISO (non-isothermal kinetics), NONREG (non-linear least-squares regression analysis) and IONSTREN (ionic strength). A FORTRAN version of NONLIN was also used for non-linear regression analysis.

Methods

Stock solutions of methyl, ethyl and propyl salicylate were prepared in the corresponding alcohol (10 mM). 10 ml aliquot of these solutions were diluted with an appropriate aqueous alcohol to give 90 ml of a diluted solution which was incubated at the appropriate temperature (usually 37 °C) in a thermostatic water-bath together with a 0.1 M sodium hydroxide solution. 10 ml aliquots of the alkali solution were dispensed into each of the reaction vessels and the contents were mixed thoroughly by vigorous shaking for a few seconds. The final concentration of the reaction mixtures were 1 mM and 10 mM with respect to the ester and NaOH with the alcohol concentration ranging from 10–90%. 3 ml aliquots of the sample were withdrawn immediately and at various intervals samples were withdrawn over a period of 2–12 h, depending on the rate of the reactions. To minimize the analytical effect of alcohol concentration in the sample solvent (Williams et al., 1980), samples were diluted 1 : 1 (10–40% alcohol) or 1 : 2 (50–90% alcohol) with the aqueous alcohol to yield an alcohol concentration of 20%.

The diluted samples were added to an equal volume of the internal standard (propyl paraben, 0.25 $mg \cdot ml^{-1}$ for methyl and ethyl salicylate; thymol 0.01 $mg \cdot ml^{-1}$ for propyl salicylate) in 0.02 M HCl giving a final pH of about 1.2. 20 μl of this solution were analyzed by HPLC and concentrations were calculated by interpolation onto a calibration line prepared from the appropriate ester dissolved in 20% alcohol to cover the range 0.025–0.5 mM. Salicylic acid was also included in the calibration solutions so that the total salicylate level was always equivalent to the initial concentration.

Hydrolyses in distilled water were undertaken using 2 mM stock solutions because of the low aqueous solubility of the esters. Reactions were initiated by mixing 50 ml of stock solution with 40 ml of distilled water followed by sodium hydroxide (10 ml, 0.1 M), equilibrated at the appropriate temperature.

Effect of pH on the rate of transesterification of methyl salicylate

0.5 M Britton-Robinson buffer solutions were prepared in the pH range 1.81–11.95 according to Mongay and Cerda (1974). 50 ml of buffer solution and 40 ml of equimolar mixed alcohol (methanol–ethanol 32 : 46 w/w) were mixed together and equilibrated at 50 °C. 10 ml stock solution of methyl salicylate (10 mM in 100% equimolar mixed alcohol) were added to the reaction vessels. Concentrations of the reactant (methyl ester), the intermediate (ethyl ester) and the product (salicylic acid) were determined by the regression analysis of the calibration solutions prepared in 50% mixed alcohol in distilled water.

Non-isothermal degradation of methyl salicylate in 50% aqueous methanol

10 ml of the stock solution of methyl salicylate (10 mM in MeOH), 40 ml of MeOH and 40 ml of distilled water were thoroughly mixed. 0.1 M NaOH and the ester solution were equilibrated with stirring at 25 °C in a thermostatic water-bath (when full-on the heater is capable of increasing the temperature to 80 °C in 2 h). To prevent evaporation, the reaction vessel was well sealed. The reaction was initiated by pouring 10 ml of the alkali solution into the reaction vessel. 3 ml aliquot of the

sample was withdrawn immediately and injected onto the column after 1 : 1 dilution with the internal standard. The water-bath heater was turned full-on. Samples were withdrawn initially at an interval of 5 min (until the temperature reached 40 °C) and then at every 2 min over a period of about 2 h.

Isothermal degradation

A series of isothermal hydrolyses of methyl salicylate in 50% MeOH in water were carried out at 37, 43, 51, 58.4 and 65 °C. Experimental solutions and the samples were prepared as described for the non-isothermal run.

Theoretical

The hydrolysis of salicylate esters in aqueous solutions, or in hydro-alcoholic solutions when the alcohol is that corresponding to the ester, follows first-order kinetics such that:

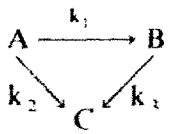
$$A \xrightarrow{k} C \tag{1}$$

where A represents the ester, C salicylic acid and k the first-order degradation rate constant. The concentration A_t at any time t is dependent upon the initial concentration (A_0):

$$A_t = A_0 \cdot \exp(-kt) \tag{2}$$

Irreversible transesterification

When the alcohol does not correspond to that of the ester function, transesterification to produce a second ester B may occur and both esters undergo hydrolysis to salicylic acid (C). This transformation may be represented by:



(3)

The rates of change in concentration of species A, B and C are given by:

$$\frac{dA}{dt} = -A(k_1 + k_2) \tag{4}$$

$$\frac{dB}{dt} = k_1 A - k_3 B \tag{5}$$

$$\frac{dC}{dt} = k_2 A + k_3 B \tag{6}$$

Integration of these equations between time zero and the current time t enables expressions for the instantaneous concentrations of each species to be obtained.Thus:

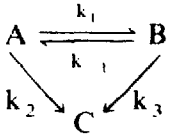
$$A_t = A_0 \cdot \exp(-(k_1 + k_2)t) \tag{7}$$

$$B_t = A_0 \cdot k_1 \cdot \left[\frac{\exp(-k_3 t)}{(k_1 + k_2 - k_3)} + \frac{\exp(-(k_1 + k_2)t)}{(k_3 - k_1 - k_2)} \right] \tag{8}$$

$$C_t = A_0 \cdot \left[1 - \frac{k_1 \cdot \exp(k_3 t) + (k_2 - k_3) \cdot \exp(-(k_1 + k_2)t)}{(k_1 + k_2 - k_3)} \right] \tag{9}$$

Reversible transesterification

When the transesterification reaction is reversible, the reaction scheme is modified to:



(10)

The rates of change in concentration of species A, B and C are now given by:

$$\frac{dA}{dt} = k_{-1}B - A(k_1 + k_2) \tag{11}$$

$$\frac{dB}{dt} = k_1 A - B(k_{-1} + k_3) \tag{12}$$

$$\frac{dC}{dt} = k_2 A + k_3 B \tag{13}$$

Integration of these expressions from time zero to time t allows the concentration of each species at time t to be determined:

$$A_t = A_0 \cdot \left[\frac{(k_{-1} + k_3 - \gamma_1) \cdot \exp(-\gamma_1 t)}{(\gamma_2 - \gamma_1)} + \frac{(k_{-1} + k_3 - \gamma_2) \cdot \exp(-\gamma_2 t)}{(\gamma_1 - \gamma_2)} \right] \tag{14}$$

$$B_t = A_0 \cdot k_1 \cdot \left[\frac{\exp(-\gamma_1 t)}{(\gamma_2 - \gamma_1)} + \frac{\exp(-\gamma_2 t)}{(\gamma_1 - \gamma_2)} \right] \tag{15}$$

$$C_t = A_0 \cdot \left[1 - \frac{(k_1 + k_{-1} + k_3 - \gamma_1) \cdot \exp(-\gamma_1 t) - (k_1 + k_{-1} + k_3 - \gamma_2) \cdot \exp(-\gamma_2 t)}{(\gamma_2 - \gamma_1)} \right]$$

(16)

where γ_1 and γ_2 are quadratic root functions of the various rate constants from $s^2 + s(k_1 + k_{-1} + k_2 + k_3) + k_{-1}k_2 + k_1k_3 + k_2k_3 = 0$ and are given by:

$$\gamma_1 = \frac{(k_1 + k_{-1} + k_2 + k_3) + \sqrt{(k_1 + k_{-1} + k_2 + k_3)^2 - 4(k_{-1}k_2 + k_1k_3 + k_2k_3)}}{2}$$

$$\gamma_2 = \frac{(k_1 + k_{-1} + k_2 + k_3) - \sqrt{(k_1 + k_{-1} + k_2 + k_3)^2 - 4(k_{-1}k_2 + k_1k_3 + k_2k_3)}}{2}$$

Eqns. 7, 8, 9 and 14, 15, 16 were fitted to the measured profiles by non-linear least-squares regression techniques to evaluate the rate constants.

Results and Discussion

The hydrolysis of methyl salicylate in aqueous sodium hydroxide at 37 °C followed first-order kinetics with a degradation rate constant of 1.470×10^{-2} min^{-1} for ester disappearance and of 1.430×10^{-2} min^{-1} when salicylic acid levels were monitored. In aqueous methanolic solutions containing hydroxide first-order kinetics were maintained and a significant reduction in the rate of degradation was observed as the methanol content was increased (Table 1). The stabilization of a charged transition state between two ions, A and B, is influenced by the dielectric constant (ε) of the reaction medium. This may be expressed quantitatively by:

$$\ln k = \ln k_{\varepsilon=\infty} - \frac{KZ_AZ_B}{\varepsilon} \qquad (17)$$

where k is the measured degradation rate constant, $k_{\varepsilon=\infty}$ is the rate constant in a medium of infinite dielectric constant, Z_A and Z_B are the charges on the reacting species and K is a nominal constant holding Avogadro's number (N), electrical charge (e), the interionic distance within the activated complex (r), the gas constant (R) and temperature (T) such that $K = Ne^2/rT$ (Martin et al., 1983).

The rate constants for the methyl ester degradation follow this relationship closely and a least-squares plot of $1/\varepsilon$ against ln k gives:

$$\ln k = -0.06946(\pm 0.0534) - \frac{285.9(\pm 3.3)}{\varepsilon} \quad (r = -0.9995, n = 10)$$

providing a limiting value for $k_{\varepsilon=\infty}$ of 0.4993 min^{-1}. The negative slope indicates that the ions in the transition state have like charges and confirms that the reaction involves an attack of hydroxide upon the salicylate anion (Pal et al., 1974; Irwin et al., 1984). Ethyl and propyl salicylate behave similarly but yield plots which are biphasic and show two linear sections with intersection near 50% alcohol.

TABLE 1

EFFECT OF ALCOHOL CONCENTRATION ON THE ALKALINE (10 mM NaOH) HYDROLYSIS OF SALICYLATE ESTERS (1 mM) AT 37°C.

System	Alcohol (%)	Dielectric constant (ϵ)	Rate constant ($min^{-1} \times 10^3$)
methyl salicylate in methanol–water	0	80.00	14.66
	10	77.71	12.65
	20	75.15	11.17
	30	72.26	9.34
	40	68.99	7.57
	50	65.24	6.39
	60	60.90	4.33
	70	55.83	3.01
	80	49.82	1.67
	90	42.58	0.60
ethyl salicylate in ethanol–water	0	80.00	13.99
	10	78.35	12.12
	20	76.13	11.44
	40	70.79	7.08
	50	67.26	5.44
	60	62.90	4.72
	70	57.36	3.95
	80	50.09	2.81
	90	40.15	1.32
n-propyl salicylate in propanol–water	10	78.53	15.52
	20	76.79	10.89
	30	74.71	7.00
	40	72.17	5.41
	50	68.99	4.45
	60	64.92	3.86
	80	51.91	3.51
	90	40.58	2.83

Ethyl salicylate

low alcohol: $\ln k = 0.752 - \frac{401.8}{\varepsilon}$ $(r = -0.996, n = 5)$

high alcohol: $\ln k = -3.101 - \frac{140.8}{\varepsilon}$ $(r = -0.999, n = 5)$

Propyl salicylate

low alcohol: $\ln k = 5.558 - \frac{773.6}{\varepsilon}$ $(r = -0.976, n = 5)$

high alcohol: $\ln k = -4.883 - \frac{40.07}{\varepsilon}$ $(r = -0.974, n = 4)$

TABLE 2

EFFECT OF TEMPERATURE ON THE ALKALINE (10 mM NaOH) HYDROLYSIS OF METHYL SALICYLATE IN 50% METHANOL

Temperature	Rate constant (min^{-1})	
	Isothermal	Non-isothermal
37	0.006386	–
38.2	–	0.007243
43	0.01277	0.01278
51	0.02620	0.02409
58.4	0.05690	0.05302
65	0.09240	0.1032
Eact ($kJ \cdot mol^{-1}$)	85.36	83.72
A (min^{-1})	1.464×10^{12}	8.013×10^{11}
r	−0.998	−0.999

The effect of temperature upon reaction rate is closely modelled by the Arrhenius equation and isothermal and non-isothermal methods (Hempenstall et al., 1983; Li Wan Po et al., 1983) are applicable. Typical data are displayed in Table 2.

When the stability is monitored in hydro-alcoholic solution in which the alcohol component differs from the alkyl radical of the ester a more complex profile is exhibited. Fig. 1 illustrates a typical HPLC trace of the fate of methyl salicylate in alkaline aqueous ethanol. The initial trace (t = 0) indicates the presence of methyl salicylate and internal standard alone. After 5 min traces of the hydrolysis product, salicylic acid, are detected but a larger, fourth peak is also present. The retention time of this component is identical to that of ethyl salicylate and suggests that a

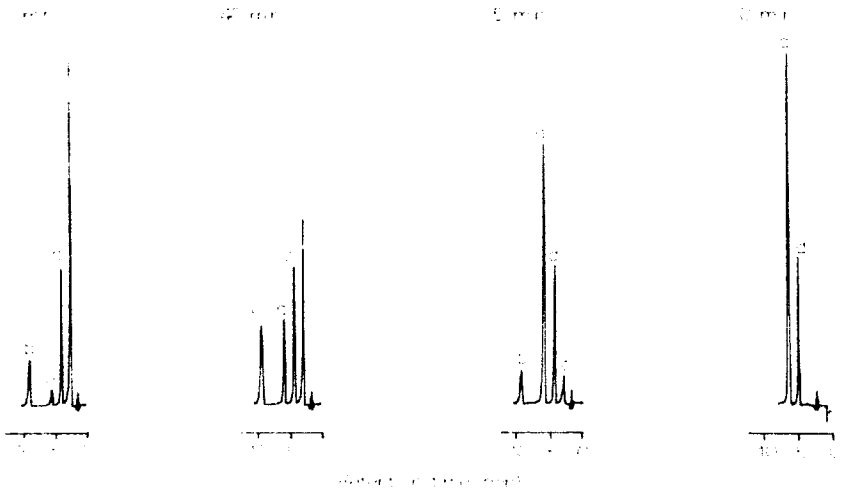


Fig. 1. High-performance liquid chromatogram of methyl salicylate degradation in alkaline aqueous ethanol. a, methyl salicylate; b, ethyl salicylate; c, salicylic acid; d, propyl paraben; 20% ethanol, 0.01 M NaOH, 37 °C.

transesterification process is favoured under these conditions. The identity of this component was confirmed by isolation from a solution of methyl salicylate (0.07 M) in absolute ethanol containing 0.002 M NaOH stored at 37 °C for 5 days. The transesterified material was the only product under these conditions and it displayed ^{1}H nmr absorptions and mass spectral fragmentation identical to those of ethyl salicylate.

The reaction profile, showing the fate of reactant and products, is displayed in Fig. 2 and the formation of ethyl salicylate is clearly observed. Under the experimental conditions salicylic acid is not esterified so this product must arise from methyl salicylate by transesterification, involving solvent ethanol, in competition with the hydrolysis reaction. Both esters will suffer depletion by hydrolysis to salicylic acid. Two models may be proposed to describe these events: one involving an irreversible transesterification (Eqn. 3) and one in which the transesterification is a reversible reaction (Eqn. 10). The presence of methyl salicylate in the reversed system, composed of ethyl salicylate in aqueous methanol, clearly demonstrates the reversible nature of this reaction (Scheme 1), but unless mixed alcohol systems are used the reverse rate constant is negligible and model 3 may be used.

The rate constants may be estimated from these equations by fitting to them the measured profiles by non-linear least-squares regression techniques (NONREG, NONLIN) and a typical fit is shown in Fig. 3 for the reaction of methyl salicylate in equimolar methanol–ethanol (50%). The reversible nature of the transesterification is further indicated by the degree of fit of the two models used. The correspondence between theoretical and measured data is much poorer for the irreversible model (Fig. 3B) and clearly shows that the reversible model (Fig. 3A) is appropriate in this case.

Transesterification appears to be a general reaction of salicylates under these

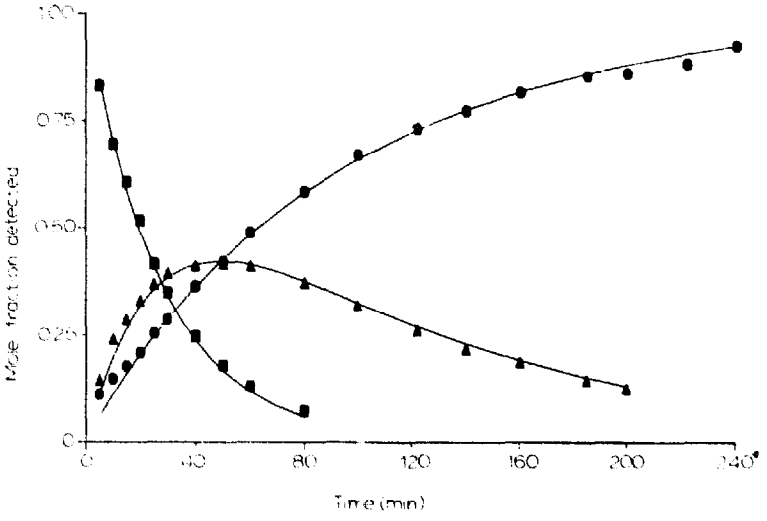
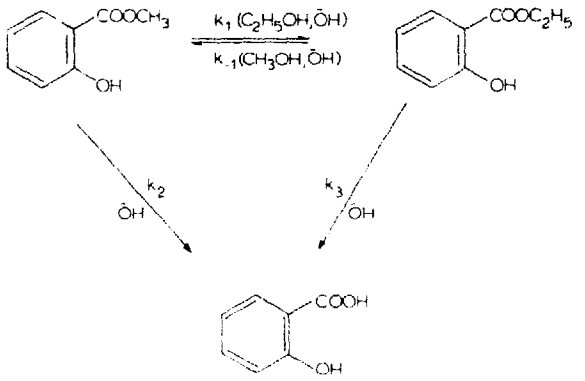


Fig. 2. Reaction profile of methyl salicylate degradation in alkaline aqueous ethanol. ■, methyl salicylate; ▲, ethyl salicylate; ●, salicylic acid. 20% ethanol, 0.01 M NaOH, 37 °C; $k_1 = 0.0245$ min^{-1}, $k_2 = 0.0117$ min^{-1}, $k_3 = 0.0099$ min^{-1}.

conditions and Scheme 1 is also followed by ethyl salicylate in methanol, and propyl salicylate in methanol and ethanol. The rate constants calculated from these systems with varying amounts of alcohol are displayed in Table 3. The rate of transesterification depends markedly upon the concentration of alcohol and a parabolic relationship is observed (Fig. 4).

The mechanism of both hydrolysis and transesterification may be revealed by the dependence of reaction rate upon base concentration. Fig. 5 holds data for the degradation of methyl salicylate in alkaline aqueous methanol–ethanol in the pH range 7–12. Each curve describing an individual rate constant is sigmoid with little degradation appearing below pH 8. Above this value the rate of reaction increases rapidly up to pH 11 when a plateau is observed. The rapid increase in degradation rate corresponds directly with the increase in salicylate anion concentration (pK_a = 10.4; pK_a in 50% aqueous methanol–ethanol = 11.4) and indicates that the reaction of this species with solvent in a concerted attack (Scheme 2, weakly alkaline pathway) is the dominant process. This is confirmed by the linearity of plots of anion percentage [A^-] vs observed rate constant (k′) which follow closely the



Scheme 1. Transesterification and hydrolysis of methyl salicylate in alkaline aqueous ethanol.

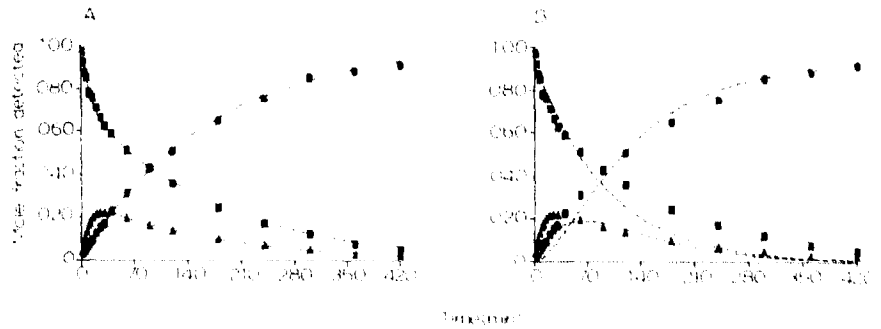


Fig. 3. Reaction profile for the degradation of methyl salicylate in aqueous methanol–ethanol. Correspondence to theoretical model. A: reversible model, $k_1 = 0.026$ min^{-1}, $k_2 = 0.0072$ min^{-1}, $k_3 = 0.002$ min^{-1}, $k_{-1} = 0.071$ min^{-1}. B: irreversible model, $k_1 = 0.0091$ min^{-1}, $k_2 = 0.0016$ min^{-1}, $k_3 = 0.022$ min^{-1}. Symbols are measured data, lines are generated by the appropriate model; ■, methyl salicylate; ▲, ethyl salicylate; ●, salicylic acid.

TABLE 3

EFFECT OF ALCOHOL CONCENTRATION ON THE TRANSESTERIFICATION AND HYDROLYSIS RATES OF SALICYLATE ESTERS AT 37 °C

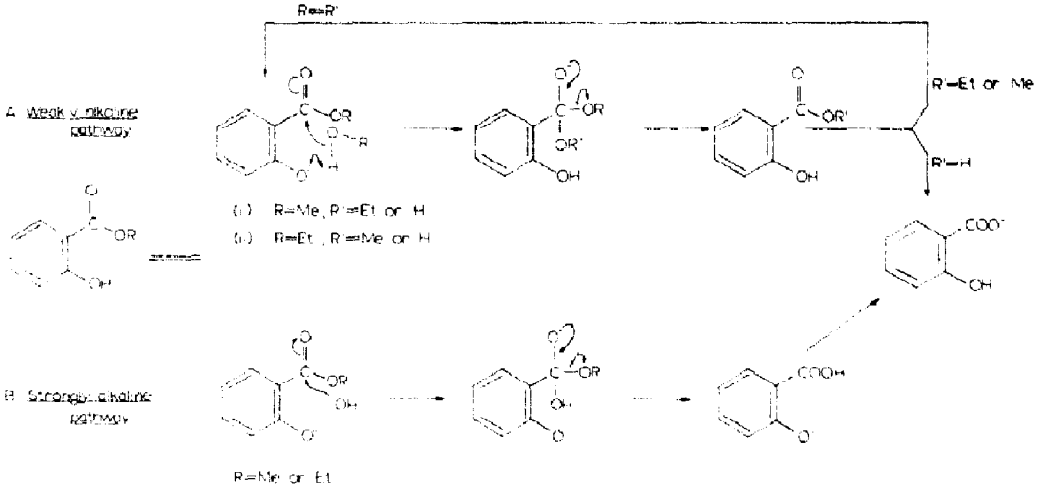
Alcohol (%)	Methyl salicylate in ethanol (k/min)×10^3			Ethyl salicylate in methanol (k/min)×10^3			Propyl salicylate in methanol (k/min)×10^3			Propyl salicylate in ethanol (k/min)×10^3		
	k_1	k_2	k_3	k_1	k_2	k_3	k_1	k_2	k_3	k_1	k_2	k_3
10	15.0	13.1	12.5	46.3	10.9	13.0	47.1	11.4	13.2	7.51	13.6	9.43
20	24.5	11.7	9.89	114	10.1	11.2	99.1	9.63	11.5	12.8	10.5	7.89
30	31.5	10.8	8.14	115	10.8	8.61	121.0	8.12	9.83	32.2	13.6	8.03
40	37	8.37	6.69	139	8.86	6.92	122	7.43	7.08	17.8	5.84	5.57
50	42.2	7.60	4.82	130	8.79	5.20	135	5.89	5.81	21.7	6.53	4.78
60	48.1	7.48	4.30	137	7.73	3.84	121	3.53	3.96	20.6	5.25	3.89
70	53.1	5.87	3.52	130	4.43	2.80	111	0.215	2.72	26.2	3.17	3.49
80	59.6	4.45	2.06	109	6.77	1.24	106	4.46	1.37	22.6	2.61	2.50
90	55.1	3.56	1.20	135	2.23	0.497	81	0.013	0.590	26.2	2.35	0.930

relationship:

$$k' = k'_s + k''_s[A^-] \quad (18)$$

where k''_2 is the specific rate constant for attack of solvent on the anion and k'_s is the corresponding value for attack on the salicylate molecule.
viz:

$$k'_1 = 0.00449 + 0.000556\,[A^-] \quad (n = 9, r = 0.937)$$
$$k'_{-1} = 0.00423 + 0.00109\,[A^-] \quad (n = 9, r = 0.973)$$
$$k'_2 = 0.00166 + 0.000250\,[A^-] \quad (n = 9, r = 0.954)$$
$$k'_3 = 0.00098 + 0.000200\,[A^-] \quad (n = 9, r = 0.896)$$



Scheme 2. Mechanism of methyl salicylate degradation in alkaline aqueous ethanol.

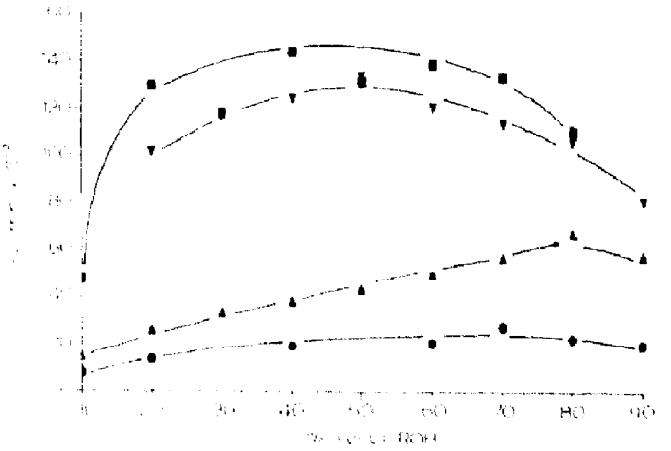


Fig. 4. Effect of alcohol concentration on the transesterification of salicylate esters in alkaline aqueous alcohol. ▲, methyl salicylate in ethanol; ■, ethyl salicylate in methanol; ▼, propyl salicylate in ethanol; ●, propyl salicylate in methanol.

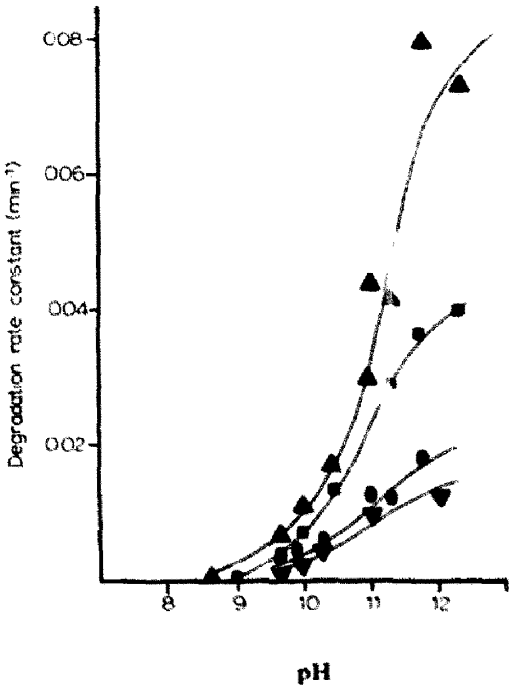


Fig. 5. Effect of pH on the transesterification and hydrolysis of methyl salicylate in 50% aqueous methanol–ethanol. ▲, k_{-1}; ■, k_1; ●, k_2; ▼, k_3.

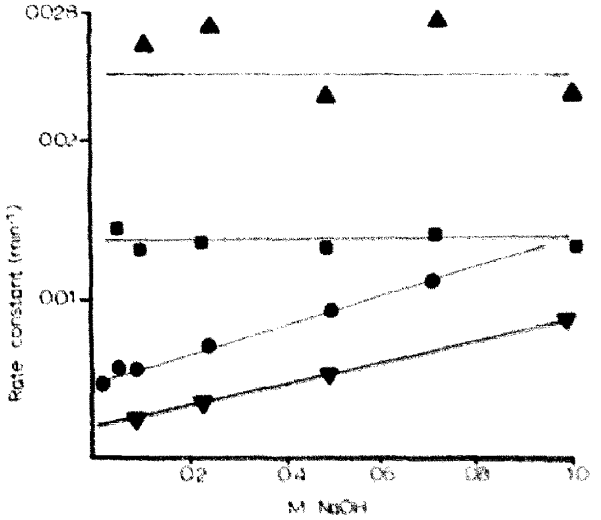


Fig. 6. Effect of hydroxide concentration on the transesterification and hydrolysis of methyl salicylate in 50% aqueous methanol–ethanol. Symbols as in Fig. 5.

As the hydroxyl ion concentration increases further the direct attack by hydroxide also becomes a significant degradation pathway. The decomposition is represented by both pathways in Scheme 2 and the observed rate of reaction (k) is dependent upon both solvent (k′) and hydroxyl (k″) rate processes (Irwin et al., 1984):

$$k = k' + k''[OH^-] \tag{19}$$

Degradation with 0.01–1 M NaOH in aqueous methanol–ethanol follows this scheme closely and linear regression of the hydroxyl ion concentration against each observed rate constant is displayed in Fig. 6. This reveals that the transesterification processes are independent of hydroxide concentration, once complete ionization of salicylate ester is achieved, whereas hydrolysis proceeds by both concerted solvent attack and by direct hydroxide involvement.

Although transesterification is of clear importance in analysis and kinetic work, the question arises as to whether this process may threaten the integrity of pharmaceutical formulations. Fig. 7 records an HPLC trace from a salicylate gel which has been stored for 30 days. The transesterified components involving the glycol base are clearly seen and serve as a cautionary indicator that these processes may affect the availability of esters from bases containing hydroxylic vehicles such as glycols and their polymers.

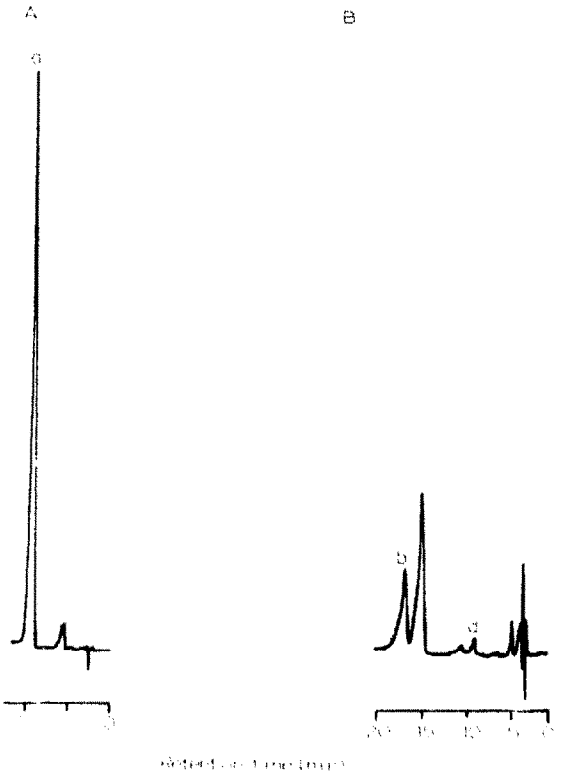


Fig. 7. HPLC of methyl salicylate gel. Methyl salicylate, 0.25 g; propylene glycol, 40 g; carbopol, 1 g; 0.5 M NaOH, 16 ml; pH = 6.66. a, methyl salicylate; b, 2-hydroxypropyl salicylate; c, 1-hydroxymethylethyl salicylate; d, salicylic acid. Mobile phase: A, 45% acetonitrile (pH = 2.0); B, 25% acetonitrile (pH = 2.0)).

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