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Short Communication

Spectrophotometric determination of alkyl salicylate from the mixture of phenyl and alkyl salicylates by the use of the selective reactivity of phenyl salicylate toward secondary amines

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Introduction

Salicylate esters have been used as topical analgesics where an alcoholic component acts as the solvent. Phenyl salicylate, for example, is used in salol aqueous cream which contains a cream base with 5% propylene glycol. Recently, Irwin *et al.* [1–3] have shown the occurrence of transesterification of salicylate esters in alkaline alcoholic medium which could lead to serious problems in such pharmaceutical formulations. The kinetic studies on these transesterification reactions carried out by Irwin *et al.* [1–3] involve the high-performance liquid chromatographic (HPLC) technique. Recently, the author observed that piperidine is highly reactive toward phenyl salicylate and completely nonreactive toward methyl and ethyl salicylates [4, 5]. This selective reactivity of piperidine toward phenyl salicylate could be used to quantitatively estimate the alkyl salicylate (formed when phenyl salicylate is mixed with alkanol) by using an alternative spectrophotometric technique. The details of the method, and its use in the estimation of the 2-hydroxyethyl salicylate formed in the reaction of phenyl salicylate with 1,2-ethanediol, are described in this paper.

Experimental

Materials

Reagent grade chemicals such as dimethylammonium chloride and pyrrolidine were obtained from Aldrich, phenyl salicylate (PSH), 1,2-ethanediol and acetonitrile were obtained from BDH and piperidine as well as *N*-methylpiperazine were obtained from Fluka AG. Methyl salicylate (MSH) and ethyl salicylate (ESH) were synthesized as

described elsewhere [5, 6]. All other chemicals used were also of reagent grade. The stock solutions of PSH, MSH and ESH were prepared in MeCN.

Quantitative estimation of the product, 2-hydroxyethyl salicylate, produced in the alkaline reaction mixture of PSH and 1,2-ethanediol

In a typical kinetic run, the reaction mixture of total volume of 49 ml containing the required amounts of NaOH and $HOCH_2CH_2OH$ was equilibrated at 30°C for about 10 min. The reaction was then initiated by adding 1.0 ml of 0.02 M PSH solution prepared in MeCN. An aliquot of 2.0 ml was withdrawn periodically and added quickly to 2.0 ml of 0.5 M Me_2NH solution to arrest the transesterification reaction. The absorbance of the resulting reaction mixture was measured at 340 nm using a Hitachi 100-50 double-beam UV–visible spectrophotometer. It took less than 4 min for unreacted PSH to be completely converted to *N,N*-dimethyl salicylamide, as revealed by the leveling off of the absorbance. The absorbance values measured at less than 4 min were considered to be due to only 2-hydroxyethyl salicylate, because the molar absorptivities of *N,N*-dimethyl salicylamide and the phenolate ion are negligible compared to that of 2-hydroxyethyl salicylate at 340 nm in an alkaline medium.

Determination of the molar absorptivities of ionized PSH, MSH and ESH at 340 nm

In order to determine the molar absorptivities (at 340 nm), ϵ, of ionized PSH, MSH, and ESH, a series of solutions containing known amounts of ester and NaOH were prepared. The absorbance values of all solutions were obtained quickly at 340 nm. In order to minimize the error caused by possible hydrolysis of salicylate ester in alkaline medium, the required amounts of esters were added to the aqueous solutions containing 0.02 M NaOH just before the measurement of absorbance values. There was always a lapse of less than 60 s between the time of addition of salicylate ester to aqueous alkaline solution and the time at which its absorbance was recorded. During this period, the hydrolysis of the salicylate ester was considered to be negligible because the values of the first-order rate constants are 21.6×10^{-3} min $^{-1}$, 8.33×10^{-3} min^{-1} and 8.61×10^{-3} min^{-1} for hydrolyses of PSH,* MSH [6], and ESH [5], respectively, under such experimental conditions. The observed absorbance values, A_{obs}, were found to fit reasonably Beer's law. The linear least squares technique was used to calculate molar absorptivities, (ϵ), and the results are summarized in Table 1. Samples containing known and equal concentrations of both PSH and MSH were also used to calculate ϵ ($\epsilon = \epsilon_1 + \epsilon_2$ where ϵ_1 and ϵ_2 are the molar absorptivities of PSH and MSH, respectively). The observed value of ϵ [$(13.10 \pm 0.10) \times 10^3$ M^{-1} cm^{-1}] is comparable with the sum of ϵ_1[$(7.39 \pm 0.06) \times 10^3$ M^{-1} cm^{-1}] and ϵ_2[$(5.78 \pm 0.03) \times 10^3$ M^{-1} cm^{-1}] within the limits of the experimental uncertainty.

Determination of the molar absorptivity of ionized N-piperidinyl salicylamide at 340 nm

The nucleophilic second-order rate constants for the reactions of ionized PSH with piperidine, *N*-methylpiperazine, pyrrolidine and dimethylamine are 13.84 M^{-1} min^{-1} [4], 7.09 M^{-1} min^{-1} [4], 33.0 M^{-1} min^{-1}* and 34.9 M^{-1} min^{-1},* respectively. In order to determine the molar absorptivity of *N*-piperidinyl salicylamide at 340 nm, a series of samples containing known but different amounts of PSH ([PSH] range 2×10^{-5}–1.6×10^{-4}M) were prepared. To each of these samples were added the same

* Unpublished observations.

Table 1
Observed molar absorptivities, ϵ, of salicylate esters and *N*-substituted salicylamide at 340 nm

System	ϵ (M^{-1} cm^{-1})	[Ester(s)] range (M)	Base*	MeCN content range (v/v, %)	Incubation period (min)†
PSH	(7.39 ± 0.06)‡ $\times 10^3$	2.0×10^{-5}–1.4×10^{-4}	0.02 M NaOH	2–14	≤1
MSH	$(5.78 \pm 0.03) \times 10^3$	2.0×10^{-5}–1.8×10^{-4}	0.02 M NaOH	2–18	≤1
ESH	$(5.35 \pm 0.04) \times 10^3$	2.0×10^{-5}–1.4×10^{-4}	0.02 M NaOH	2–14	≤1
PSH + MSH	$(13.10 \pm 0.10) \times 10^3$	1.0×10^{-5}–8.0×10^{-5}§	0.02 M NaOH	2–16	≤1
PSH + Piperidine	300 ± 19	2.0×10^{-5}–1.6×10^{-4}	*ca* 0.3 M Piperidine	2–16	*ca* 2–5
PSH + MSH + Piperidine	$(6.09 \pm 0.7) \times 10^3$	2.0×10^{-5}–1.6×10^{-4}§	*ca* 0.3 M Piperidine	4–32	*ca* 2–5
PSH + MSH + Pyrrolidine	$(5.85 \pm 0.06) \times 10^3$	2.0×10^{-5}–1.6×10^{-4}§	*ca* 0.36 M Pyrrolidine	4–32	*ca* 2–5
PSH + MSH + *N*-Methylpiperazine	$(6.10 \pm 0.06) \times 10^3$	2.0×10^{-5}–1.6×10^{-4}§	*ca* 0.3 M *N*-Methylpiperazine	4–32	*ca* 2–5
PSH + MSH + Dimethylamine	$(5.79 \pm 0.04) \times 10^3$	2.0×10^{-5}–1.6×10^{-4}§	0.3 M Me_2NH	4–32	*ca* 2–5
PSH + ESH + Dimethylamine	$(5.59 \pm 0.04) \times 10^3$	2.0×10^{-5}–1.6×10^{-4}§	0.3 M Me_2NH	4–32	*ca* 2–5

*Concentration of base (NaOH or Secondary amine) in each sample.
†Period during which the absorbance at 340 nm was recorded for each sample.
‡Error limits are standard deviations.
§Concentration range of each ester in the mixture of PSH and MSH or ESH.

known amounts of piperidine which would produce a 0.3 M piperidine concentration into each sample. The absorbance at 340 nm of each sample was found to level off within 5 min. The recorded absorbance at 4 min was considered to be due to the presence of *N*-piperidinyl salicylamide. The absorbance values as shown graphically in Fig. 1 were used to calculate the value of ϵ, and this is shown in Table 1. The calculated value of ϵ indicates that the absorption at 340 nm due to *N*-piperidinyl salicylamide is negligible compared to that of ionized PSH or MSH.

Selective reactivity of secondary amines toward PSH in the mixture of alkyl salicylate and PSH

A series of samples containing various total concentrations of PSH and MSH (but having equal concentrations of PSH and MSH) in a mixed solvent (H_2O–MeCN) were prepared. A constant amount, 0.255 g (0.3 ml) of piperidine was added to each sample, and the absorbance of each sample was then measured at 340 nm within 2–5 min of the addition of piperidine. These absorbance values (as shown graphically in Fig. 1) were used to obtain the values of ϵ shown in Table 1. Similar observations were carried out with pyrrolidine, *N*-methylpiperazine, and dimethylamine, and the calculated values of ϵ are summarized in Table 1. In the case of dimethylamine, 5 ml of 0.6 M Me_2NH solution (freshly prepared) containing 95–100% free base was added to 5 ml of each sample.

Dimethylamine was also added to samples containing different total concentrations of PSH and ESH, but which contained equal concentrations of PSH and ESH. The observed absorbance values at 340 nm obtained within 2–5 min were found to fit Beer's law with a least squares calculated value of ϵ of 5.59×10^3 M^{-1} cm^{-1}. It is important to mention here that the ionized hydroxyl group of a salicylate ester has been shown to increase its hydrolysis by nearly 10^6-fold [5] by acting as an intramolecular general base catalyst. A significant hydrolysis of alkyl salicylate during the incubation period would result in a significant error in the quantitative estimation of alkyl salicylate. Similarly, an

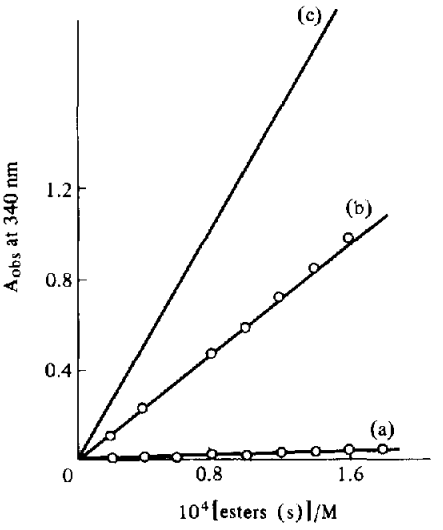


Figure 1
Plots showing the dependence of A_{obs} upon total ester concentration, [ester]. (a) Absorbance of the products of the reaction of phenyl salicylate (PSH) with piperidine (PSH + Piperidine); (b) absorbance of the products of the reaction of piperidine with the ester mixture containing equal concentrations of PSH and methyl salicylate (MSH) (PSH + MSH + Piperidine); (c) expected absorbance of the ester mixture containing identical concentrations of PSH and MSH under alkaline medium and in the absence of piperidine (PSH + MSH + NaOH).

incomplete conversion of PSH into *N*-piperidinyl salicylamide during the incubation period would also cause an error in the estimation of alkyl salicylate. Because of these reasons, care should be taken in establishing the optimum incubation time during which the secondary amine will convert total amount of PSH to the product (*N*-substituted salicylamide), and the intramolecular general base catalyzed hydrolysis of alkyl salicylate will be insignificant. The hydrolyzed products of alkyl salicylate and phenolate ion have essentially no absorption at 340 nm.

Results and Discussion

The observed values of ϵ (Table 1) clearly indicated that during the incubation period of 2–5 min, alkyl salicylates did not demonstrate any detectable reactivity toward the secondary amines. Under the same conditions, almost 100% of PSH was converted to products. This is in agreement with the kinetic studies on these reactions.*

It is interesting to note that several primary amines have been found to react with both PSH [4] and MSH.* Tertiary amines have been found to be nonreactive toward PSH* and presumably alkyl salicylates also.

Kinetics of the reaction of PSH with 1,2-*ethanediol*

The rates of the reactions of PSH with 1,2-ethanediol were studied at 30°C in 5% and 10% 1,2-ethanediol in mixed aqueous solvents containing 0.01 M NaOH. The rate of the production of the intermediate product, 2-hydroxyethyl salicylate, was monitored as described in the experimental section. The observed results are shown in Fig. 2. It has been well established that the neighbouring ionized hydroxyl group in salicylate esters causes a nearly 10^6-fold increase in the hydrolyses of these esters [5, 7, 8]. Thus the

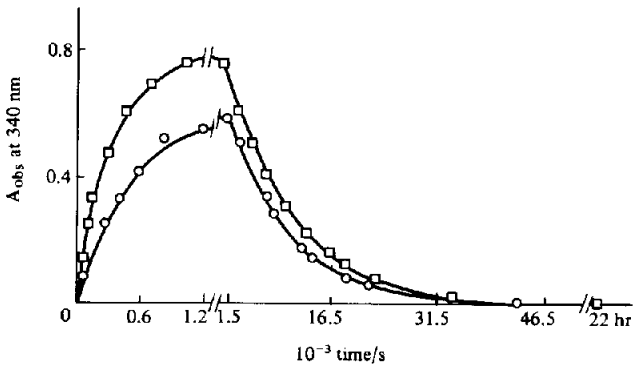
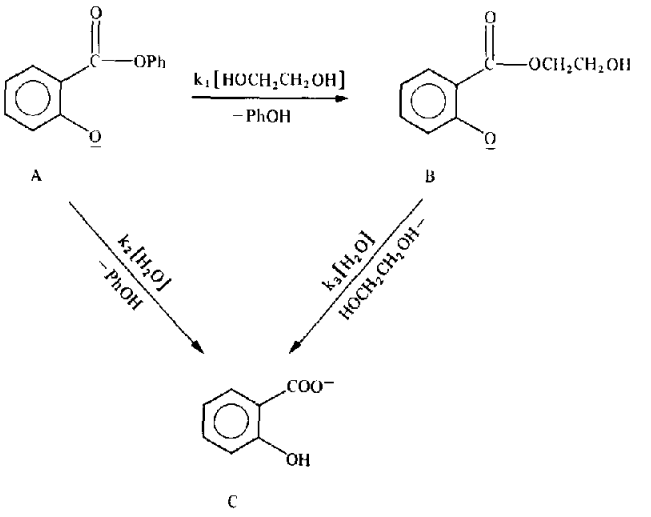


Figure 2
Plots of A_{obs} versus time for the formation and decay of 2-hydroxyethyl salicylate in the reaction of PSH with 1,2-ethanediol. (○) 2×10^{-4}M PSH, 0.01 M NaOH, 5% 1,2-ethanediol, 2% MeCN and 93% H_2O and (□) 2×10^{-4}M PSH, 0.01 M NaOH, 10% 1,2-ethanediol, 2% MeCN and 88% H_2O. The solid lines are drawn through the least squares calculated points using equation (5) as described in the text.

* Unpublished observations.

hydrolysis of PSH along with its transesterification cannot be completely ruled out. The complete reaction scheme is therefore proposed to be:



The rate of change of concentration of 2-hydroxyethyl salicylate (B) may be expressed as

$$\frac{d[B]}{dt} = k_1 [A] - k_3 [B], \tag{1}$$

where [A] represents the concentration of PSH. Also, the rate of change of concentration of PSH (A) may be expressed as

$$-\frac{d[A]}{dt} = (k_1 + k_2) [A]. \tag{2}$$

Equation (3) can be easily derived from equations (1) and (2) [9]:

$$[B] = \frac{[X]_0 k_1}{k_1 + k_2 - k_3} (e^{-k_3 t} - e^{-(k_1 + k_2)t}), \tag{3}$$

where $[X]_0$ represents the concentration of A at $t = 0$. Since the molar absorptivities of *N,N*-dimethyl salicylamide, the salicylate ion, phenolate ion and 1,2-ethanediol at 340 nm are negligible compared to that of the 2-hydroxyethyl salicylate ion, it is reasonable to assume that the observed absorbance (A_{obs}) at 340 nm is due only to species B. Thus

$$A_{obs} = \epsilon_B [B], \tag{4}$$

where ϵ_B represents the molar absorptivity of B.

From equations (3) and (4), one obtains:

$$A_{obs} = \frac{[X]_0 \epsilon_B k_1}{k_1 + k_2 - k_3} (e^{-k_3 t} - e^{-(k_1 + k_2)t}). \tag{5}$$

The value of ϵ_B for $(5.42 \pm 0.17) \times 10^3$ M^{-1} cm^{-1} was calculated from the A_{obs} values obtained at 8–12 min from several kinetic runs carried out within an 1,2-ethanediol content range of 20–90% (v/v) in 0.01 M NaOH and at 30°C. Under such experimental conditions, k_1 is expected to be larger than k_2 and k_3 by factors of 10 and 40, respectively. The observed value of ϵ_B is comparable with those of MSH and ESH (Table 1). The rate constants k_1, k_2 and k_3 were calculated from equation (5) using the nonlinear least squares technique with known values of ϵ_B and $[X]_0$. The respective values of k_1, k_2 and k_3 thus obtained were:

$(1.07 \pm 0.03) \times 10^{-3}$ s^{-1}, $(5.42 \pm 0.33) \times 10^{-4}$ s^{-1} and $(1.15 \pm 0.03) \times 10^{-4}$ s^{-1} at 5%, and
$(2.18 \pm 0.03) \times 10^{-3}$ s^{-1}, $(5.63 \pm 0.28) \times 10^{-4}$ s^{-1} and $(1.07 \pm 0.02) \times 10^{-4}$ s^{-1} at 10% 1,2-ethanediol.

The goodness of the fit in the observed data by equation (5) is evident from the plots in Fig. 2 where solid lines are drawn through the least squares calculated points and the agreement is good.

Conclusion

Various secondary amines have been found to react selectively with PSH in the mixture of PSH and alkyl salicylate. This selective reactivity of the secondary amines toward PSH formed the basis of the present technique which might be used in the quantitative estimation of the degradation of a drug containing a phenyl salicylate moiety in it and dissolved in an alkanol solvent. Although the HPLC technique used by Irwin *et al.* [1–3] in monitoring the degradation of PSH in an alkaline alcoholic medium is more versatile, the present technique is probably more convenient to use in the quantitative estimation of the degradation of PSH of the specific pharmaceutical formulations which involve an alcoholic component as the solvent.

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