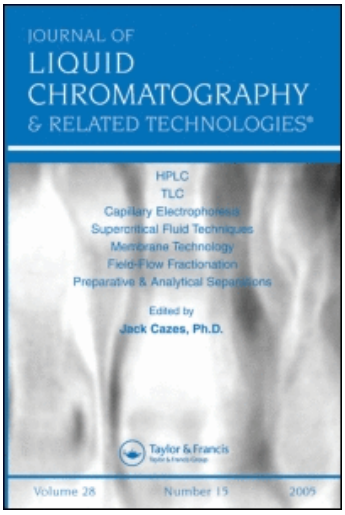

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DIRECT SEPARATION OF D- AND L-SOTALOL MANDELATE AND HYDROCHLORIDE SALTS BY HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

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ABSTRACT

A method was developed specifically to determine the purity of d- and l-sotalol mandelate salts during resolution of the racemic mixture. This procedure provides a useful means of monitoring directly the purity of the salt and the composition of the mother liquors at each step of purification.

INTRODUCTION

Interested in d-sotalol as a reference compound for pharmacological studies on antiarrhythmics, we prepared it from

racemic sotalol according to the method described by A. Simon and al.[1]. The optical purity of the d-sotalol obtained by this method is not indicated. Moreover, any comparison based on the specific rotation is hampered by the fact that neither the concentration of the compound nor the solvent used for this measurement is given.

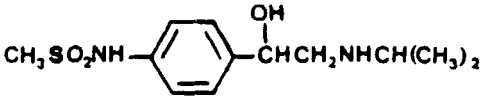
Consequently, we investigated the possibility of separating the d,l mixture by HPLC in order to check the optical purity of the enantiomers prepared. Several indirect methods of separating the enantiomers of sotalol by HPLC have been published, e.g. via the 2,3,4,5,6-tetra-O-acetyl-beta-D-glucopyranosyl isothiocyanate derivative[2] or the tartaric acid monoester[3]. However, these methods are cumbersome and unsuitable for routine use. We therefore developed a method permitting direct determination of the optical purity of each enantiomer.

MATERIALS AND METHODS

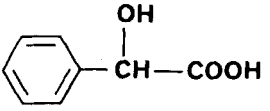
Chemical Resolution of D and L-Sotalol with L and D-Mandelic acid

The chemical structures are given below :

d,l sotalol



d,l mandelic acid



39 g of racemic sotalol (0.143 mole) and 21.8 g (0.143 mole) of l-mandelic acid were dissolved in 300 ml of 2-propanol. After standing overnight 30.5 g enriched in d-sotalol mandelate salt were collected mp = 137°C, $(\alpha)_D$=-20°2 (C=4, CH_3OH). A second

crystallisation in 300 ml of 2-propanol afforded 20 g, mp = 148°C, $(\alpha)_D$=-13°1 (C=4, CH_3OH). The third crystallisation in 400 ml of 2-propanol gave 12 g of d-sotalol mandelate salt mp = 155°C, $(\alpha)_D$=-7°7(C=4, CH_3OH).

The mother liquors from the three crystallisations were evaporated, the residue was taken up in aqueous ammonia and the free base was extracted with ethyl acetate. The organic phase was washed with water, dried on sodium sulfate then evaporated to give 23 g of a mixture of d and l sotalol.

This amount and 12.9 g (0.085 mole) of d-mandelic acid were dissolved in 350 ml of 2-propanol. After standing overnight 21 g enriched in l- sotalol mandelate salt were collected mp = 141°5C, $(\alpha)_D$=+14°8 (C=4, CH_3OH). A second crystallisation in the same conditions gave 15 g, mp = 146°C $(\alpha)_D$=+11°2 (C=4,CH_3OH) and finally the third crystallisation yielded 13 g, mp = 149°C $(\alpha)_D$=+8°8 (C=4, CH_3OH).

The l and d-sotalol mandelates were converted to their hydrochloride salts by dissolving them in 2-propanol and adding the stoechiometric amount of hydrochloride acid in ethanol.

Analytical Resolution of D and L-Sotalol by Direct HPLC

Each step of enantiomeric chemical resolution and crystallisation was monitored by chiral high performance liquid chromatography (H.P.L.C.) of the crystals and mother liquors obtained.

The optical purity of the salts was checked by HPLC, determining the ratio of peak heights on chromatograms and comparing these ratios with the ratio obtained for racemic d,l-sotalol. The instantaneous melting point and specific rotation at 25°C were determined on each salt (C=4, methanol).

H.P.L.C. Method

The sotalol enantiomers were separated by high performance liquid chromatography on an alpha$_1$-acid glycoprotein column (Enantiopac, LKB) 100 x 4.6 mm. The mobile phase was 0.05 M hexanoic acid in 0.02 M phosphate buffer (0.01 M NaH_2PO_4 + 0.01 M Na_2HPO_4) pH = 7.2.

The flow rate was 0.20 ml/min, the temperature was maintained at 20°C and the sample loading was 1 nanomole. The enantiomers were diluted in the mobile phase and detected at 230 nm.

RESULTS AND DISCUSSION

The results obtained for each step of resolution of d-sotalol and l-sotalol are given in Table 1 and Table 2 respectively. For d-sotalol and l-sotalol, we obtained an optical purity of 98 % and 95 % respectively.

The results obtained for d-sotalol hydrochloride (specific rotation = +39°9 and melting point = 213°C) are in good accordance with those given by Simon and al.[1] (specific rotation = + 36°0 and melting point = 204°-205°5 C). The specific rotation of l-sotalol hydrochloride (=-36°3) was not found in the literature but the measured value complies well with that of d-sotalol hydrochloride.

Simultaneous monitoring of the mother liquors and the crystalline salts permitted us to check the increase of the opposite enantiomer at each step and to stop the crystallisation when no further significant increase of the opposite enantiomer in the mother liquor was evident.

A previous study [5] permitted us to determine the best HPLC conditions for the resolution of racemic sotalol. Schill and

TABLE 1

D-Sotalol Salt Monitoring Values

Salt	Optical purity by H.P.L.C. D %	L %	Specific rotation (degree) (C=4, methanol)	Melting point (°C)
mandelate 1st crystallisation	80	20	- 20.2	137
mandelate 2nd crystallisation	93	7	- 13.1	148
mandelate 3rd crystallisation	97	3	- 7.7	155
hydrochloride	98	2	+ 39.9	213

TABLE 2

L-Sotalol Salt Monitoring Values

Salt	Optical purity by H.P.L.C. L %	D %	Specific rotation (degree) (C=4, methanol)	Melting point (°C)
mandelate 1st crystallisation	88	12	+ 14.8	141.5
mandelate 2nd crystallisation	93	7	+ 11.2	146
mandelate 3rd crystallisation	95	5	+ 8.8	149
hydrochloride	95	5	- 36.3	211

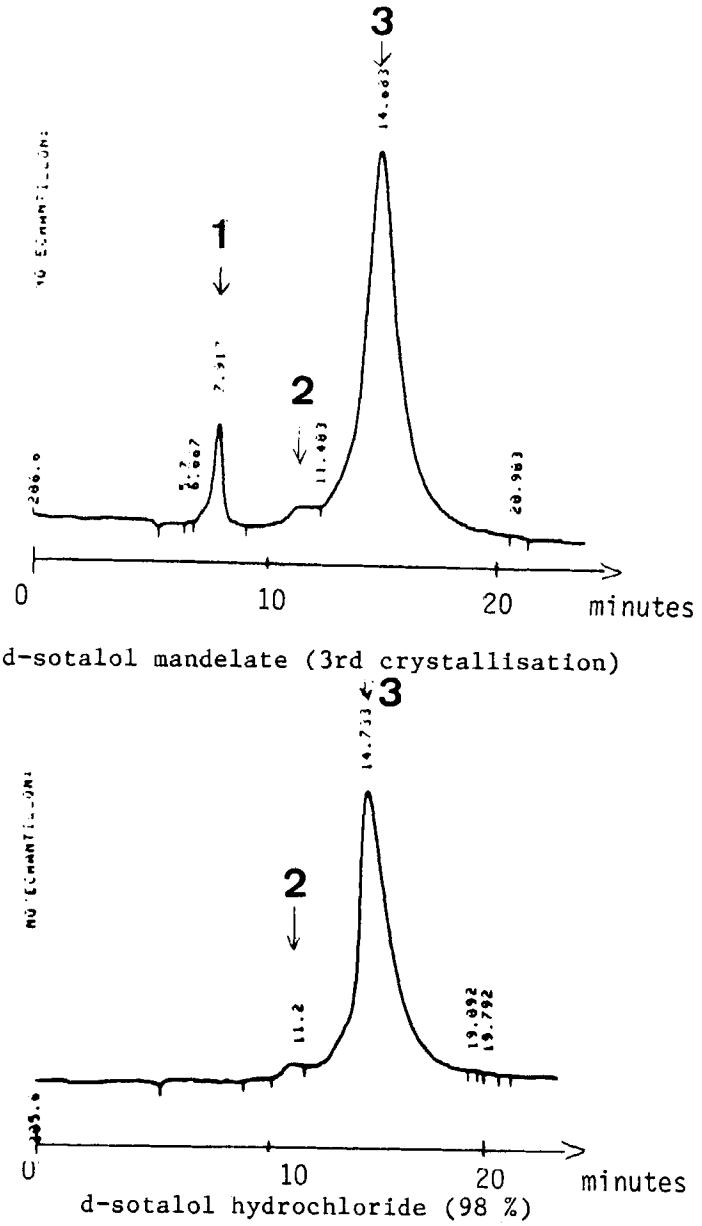
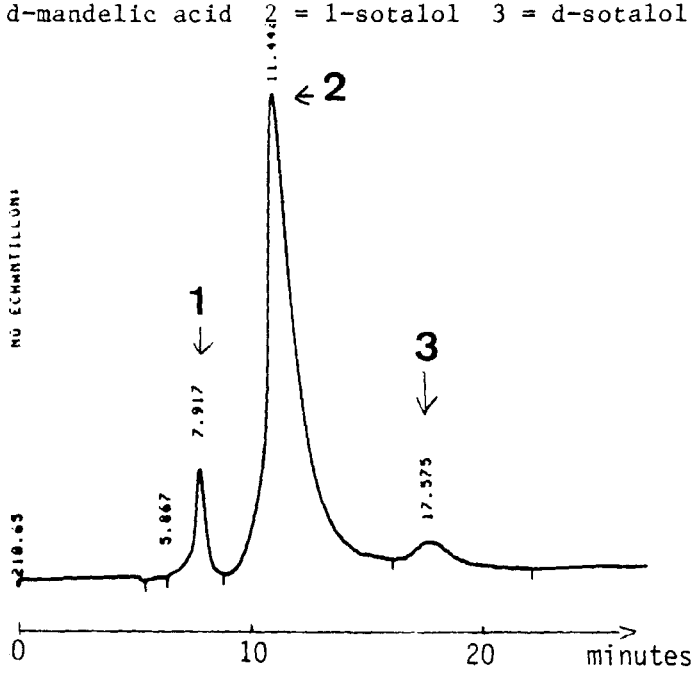


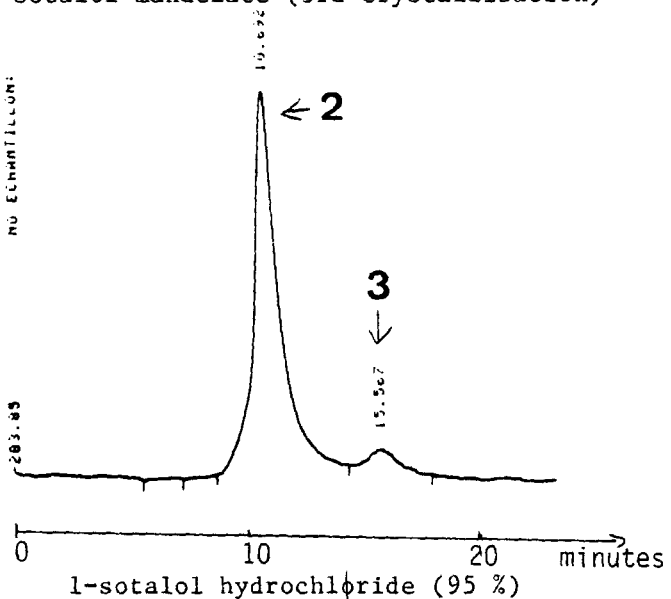
FIGURE 1

Resolution of l-sotalol salt

1 = d-mandelic acid 2 = l-sotalol 3 = d-sotalol



l-sotalol mandelate (3rd crystallisation)



l-sotalol hydrochloride (95 %)

FIGURE 2

al. [4] showed that the retention and stereoselectivity of the Enantiopac column are based on an ion-pairing mechanism. The choice of mobile phase modifier is important and for the resolution of d and l sotalol, we showed that hexanoic acid gives the best result (resolution factor = 1.88).

For the sotalol mandelate salt, we had to slightly modify the H.P.L.C. conditions to separate mandelic acid from l-sotalol (the first enantiomer eluted). This resulted in a resolution factor of 1.62 between l and d sotalol. The capacity factors k' and retention times RT for mandelic acid, l-sotalol, d-sotalol were k'_1 = 0.4, 0.98, 1.73 and RT = 8 min, 11 min and 15 min respectively. Examples of chromatograms are given in Figure 1 for the resolution of d-sotalol and in Figure 2 for the resolution of l-sotalol.

CONCLUSION

Each enantiomer of d,l sotalol was obtained by differential salt crystallisation with mandelic acid.

The resolution of d and l sotalol mandelates and hydrochloride salts was assessed during the chemical process by direct H.P.L.C. with a commercially available chiral stationary phase containing $alpha_1$-acid glycoprotein on silica (Enantiopac, LKB). The optical purity by HPLC of each step was determined directly on the salt obtained without any derivatisation or extraction of free base. Several factors were carefully adjusted to give optimal conditions for the resolution of mandelic acid, d-sotalol and l-sotalol.

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