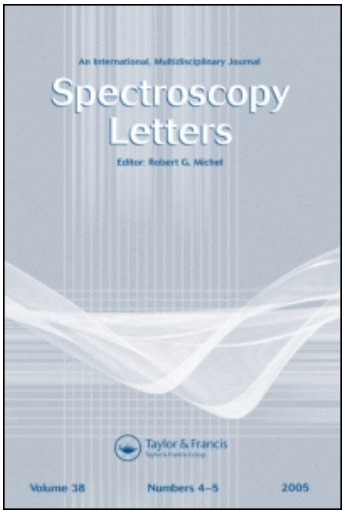

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Simultaneous Derivative Spectrophotometric Quantification of Diethylamine Salicylate and Methyl Nicotinate in Ointments

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SIMULTANEOUS DERIVATIVE SPECTROPHOTOMETRIC QUANTIFICATION OF DIETHYLAMINE SALICYLATE AND METHYL NICOTINATE IN OINTMENTS

Key words: Diethylamine salicylate, methyl nicotinate, ointments, spectrophotometry (derivative).

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ABSTRACT

A direct derivative, D_1 i.e. $dA/d\lambda$, spectrophotometric procedure for simultaneous determination of diethylamine salicylate and methyl nicotinate in their binary mixtures and in ointments has been investigated. Good percent mean recoveries, 99.68 ± 0.58 & 99.71 ± 0.27 and 100.85 ± 0.21, could be obtained for diethylamine salicylate at 303 nm & 236 nm and methyl nicotinate at 224 nm, in order, added to ointment. The band overlapping in the first order due to the coexisting parabens, main additive, and the water-washable ointment base occurs sufficient away from those wavelengths chosen for the direct D_1-measurement of both drug substances.

INTRODUCTION

Diethylamine salicylate is a topical analgesic with high penetrative value commonly prescribed for the pains of fibrosis, muscular and arithretic rheumatism.[1,2] Methyl nicotinate is a

vasodilator usually used for its rubefacient action[3], and it can sustain the analgesic value of the salicylate leading to prolonged analgism.[2,3] Ointments are the most common pharmaceutical formulation for such type of local treatment with the drug substances in admixtures. Among the methods recommended for the analysis of both drugs in heparin-containing analgesic are quantitative TLC, on silica gel F_{254} with acetonitrile-methanol-water (45:5:1) and scanning at 254 nm, in addition to the utility of HPLC, on LiChrosorb RP-18 column with acetonitrile-water (55:45) and detection at 258 nm.[4] Coupling of TLC-separation, on silica gel GF_{254} with benzene-diethyl ether-methanol-ammonia solution (60:30:8.5:1.5), and UV-measurement at 297 nm and 264 nm for diethylamine salicylate and methyl nicotinate, in order, has been investigated to quantify both ester components in ointments (5). However, the problem concerning the determination of diethylamine salicylate in admixture with methyl nicotinate may arises from the fact that the with dispensed additives, such as emulsifiers, stabilizers and/or preservatives, in the gel or ointment bases are interfering factors. As a result, the investigated procedures[4,5] for quantification of diethylamine salicylate and methyl nicotinate need preliminary drug separation or sample clean-up, which might require long time to do complete analysis of such two drug components in dosage formulations for topical use.

The present work gives the chance for simultaneous quantification of diethylamine salicylate and methyl nicotinate in the presence of methyl and propyl parabens in ointments. The advantages of the undertaken investigations appear in the simplicity, in being rapid, so a complete analysis of an ointment sample containing both drug substances needs only 3-5 minutes in a batch analysis. The accuracy and

sensitivity of the proposed procedure show the probability for its acceptance in the routine pharmaceutical analyses, considering the good analytical practice (GAP) rules, or it can be pharmacopoeially adopted for accurate quantification of both drug substances with or without added parabens.

EXPERIMENTAL

Apparatus

A UV/visible Varian DMS90 double-beam spectrophotometer with matched 1-cm quartz cells, was attached to a Hewlett-Packard 7015B X-Y chart recorder.

Materials and Pharmaceutical Preparations

Diethylamine salicylate, Givaudan Corp., New York - U.S.A., BN J14, was used as supplied; the purity was 98.80 ± 0.20% as determined according to the BP 1988-method.[6]

Methyl nicotinate, Les Etablissements Livaucan Lasirotte, Lyan-F., BN 85.031.01, was utilized without further treatment; the purity was 99.15 ± 0.15% as determined by titration in non-aqueous medium according to the BP 1988-method.[7]

Water means freshly bidistilled.

Standard and Sample Solutions

Prepare stock solutions, 1 $mg.ml^{-1}$, of each drug substance fresh by dissolving the reference compounds in water by aid of mechanical shaking. Working solutions can be prepared by diluting the stock aqueous solutions with water to get final concentrations of 5-20 $\mu g.ml^{-1}$. Prepare different mixtures containing diethylamine salicylate

and methyl nicotinate, in 5:1 ratio. For drug analysis prepare the sample solutions by taking an aliquot of the homogenized ointment equivalent to 10 mg diethylamine salicylate and 2 mg methyl nicotinate into a 100-ml calibrated flask, add 70-75 ml water, shake mechanically for about 5 minutes, complete to volume with water and filter after well mixing through dry filter paper. Make further 100-times dilutions of each clear filtrate to obtain final concentrations of 100 $\mu g.ml^{-1}$ diethylamine salicylate and 20 $\mu g.ml^{-1}$ methyl nicotinate in water.

Spectrophotometric Procedure

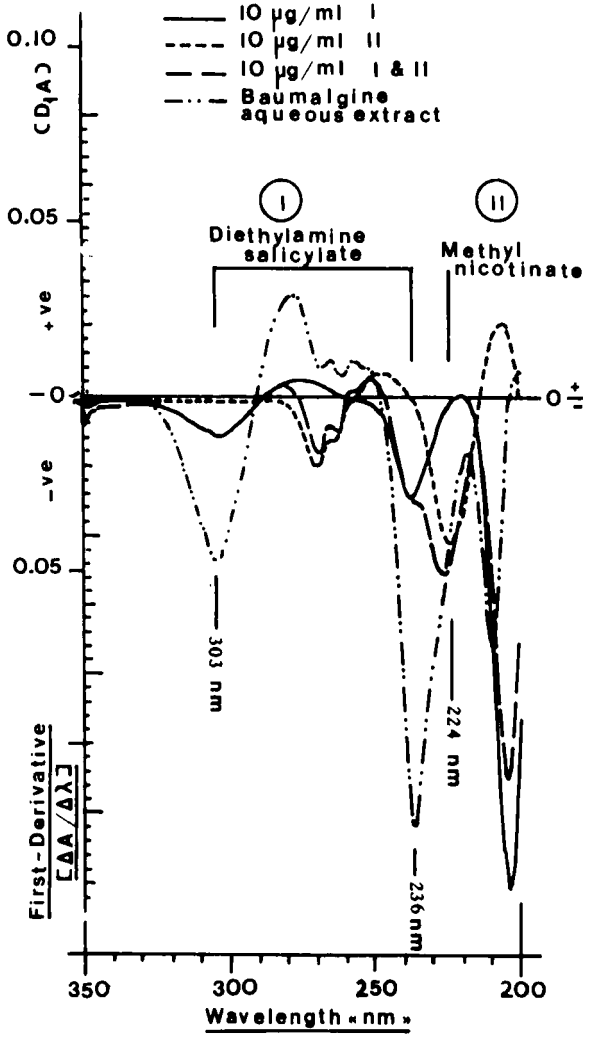
Carry out the D_1-scanning (350-200 nm) against water for each drug solution and their mixtures to demonstrate the absorption patterns of single-component solutions and in binary admixtures. For quantitative determination of individual drug substances in pure, binary mixtures, and dosage formulations, scanne and measure the $d_1A(\Delta A/\Delta\lambda)$-absorption of the aqueous solutions or extracts for diethylamine salicylate at 303 nm & 236 nm and for methyl nicotinate at 224 nm. The amount of each drug component can be directly obtained by sample/standard comparison and/or by taking the $d_1A(1\%,1cm$-values) of each component in the calculation.

RESULTS AND DISCUSSION

The D_0 UV-scanning (350-200 nm) of aqueous solutions of diethylamine salicylate and methyl nicotinate indicates that the light absorption due to diethylamine salicylate occurs maximally at about 295 nm [$A(1\%,1cm$ = 208, ϵ = 4395] and 226 nm [$A(1\%,1cm$ = 407.9, ϵ = 8619]; while the second drug substance has its maximal absorption at about 264 nm [$A(1\%,1cm$ = 313, ϵ = 4292] and 225 nm [$A(1\%,1cm$ = 785.5, ϵ = 10771]. Clear interferences and band overlappings can be observed between the

individual absorption spectra of the two drugs. The presence of the additives such as the emulsifiers and/or stabilizers as well as the preservatives, e.g. methyl and propyl parabens, complicates the pattern of light absorptions; i.e. they appear to be interfering elements. Ointments for topical treatments with diethylamine salicylate and methyl nicotinate usually contain both drugs in 5:1-ratio, as in Baumalgine®, or sometimes more, where the UV-scanning of the binary mixtures in such ratios exhibits a typical maximum of the predominating drug, i.e. diethylamine salicylate, at its λ_{max}, where the absorption due to methyl nicotinate appears mostly in the shoulder form. The observed spectral interferences caused by the ointment matrices complicates the utility of the Vierordt's[8] and the modified Vierordt's calculations for the spectrophotometric quantification of the two component drugs in dosage formulations.[5]

The spectral problem of the band overlapping and the presence of the UV-absorbing interferents in our case could be completely solved by adopting the derivative (D_1) spectrophotometry. The equivalent D_1 ($\Delta A/\Delta\lambda$)-scannings of the same solutions of diethylamine salicylate, methyl nicotinate and their binary mixtures exhibit typical resolved spectra. Figure 1 demonstrates the d_1-runnings of aqueous solutions (10 $\mu g.ml^{-1}$) of diethylamine salicylate, methyl nicotinate and their binary equimixture, in addition to the aqueous extract of ointment, which claimed to contain 50 $\mu g.ml^{-1}$ diethylamine salicylate and 10 $\mu g.ml^{-1}$ methyl nicotinate. When diethylamine salicylate shows its characteristic trough at 303 nm [$d_1A(1\%,1cm = 8.24$, $d_1\epsilon = 174$] and 236 nm [$d_1A(1\%,1cm = 23.88$, $d_1\epsilon = 504.5$], the aqueous solutions of methyl nicotinates exhibit a characteristic non-interfering trough at 224 nm [$d_1A(1\%,1cm = 45.52$, $d_1\epsilon = 624$]. At 303 nm and 236 nm diethylamine



D_1 ($\Delta A/\Delta\lambda$) scanning of 10 µg.ml^{-1} aqueous solutions of diethylamine salicylate, methyl nicotinate and binary equimixture compared with aqueous extract of ointment.

salicylate has d_1A responses equivalent to its concentrations, while methyl nicotinate reads almost zero. On the other hand, as the d_1-response at 224 nm is completely due to methyl nicotinate, diethylamine salicylate shows zero-reading. It is obvious that diethylamine salicylate can be quantitatively determined at 303 nm & 236 nm in the presence of methyl nicotinate, which can be quantified also without interference of the other drug substance at 224 nm. The wavelength of 236 nm is preferable to quantify methyl salicylate because of its higher $d_1\epsilon$-value than that at 303 nm, where also some negligible absorbance caused by methyl nicotinate was found. The methyl and propyl parabens, coexisting in the studied ointment, were found to be interfering only in the wavelength ranges between 289-257 nm and 218-200 nm.

The D_1-spectrophotometric measurements for diethylamine salicylate at 303 nm & 236 nm and for methyl nicotinate at 224 nm have been applied to investigated ointment; the results of assay and recovery are collectively summarized in table 1. Good mean recoveries of 99.68 ± 0.58% & 99.71 ± 0.27% of added diethylamine salicylate at 303 nm & 236 nm, in order, and 100.85 ± 0.21% in case of methyl nicotinate at 224 nm, could be obtained.

The investigated derivative spectrophotometric method has the clear advantages over the method of coupling of TLC-separation and UV-measurement in being direct, need no preliminary drug separation or sample clean-up and so more rapid. A pronounced advantage of the proposed method is that the two drug components can be quantified at same time in the same solution of the samples, so automated flow, air-segmented or non-segmented, injection analysis can be easily

TABLE 1

Assay and Recovery of Diethylamine Salicylate and Methyl Nicotinate in Ointment*

Drug substance	Diethylamine salicylate		Methyl nicotinate
measuring wavelength (nm)	(303)	(236)	(224)
Assay, (%)	101.01	100.13	91.43
	99.05	99.93	91.81
	101.01	98.03	88.89
	99.43	98.02	90.91
	99.05	98.69	90.95
	100.95	—	—
X (SD)	100.08(1.00)	98.96(1.02)	90.80(1.13)
CV (n)	1.00(6)	1.03(5)	1.24(5)
Recovery, (%)	99.81	99.67	100.93
	100.19	99.47	101.00
	99.05	100.00	100.61
X (SD)	99.68(0.58)	99.71(0.27)	100.85(0.21)
CV (n)	0.58(3)	0.27(3)	0.21(3)

*Baumalgine® ointment, Misr Co. for Pharm. Ind., S.A.A., El-Mataria, Cairo-ET.; each 1 g of the ointment is labelled to contain 100 mg diethylamine salicylate and 20 mg methyl nicotinate in water-washable base.

established *via* double detection by setting at the selected wavelengths for both drug substances.

As a result of the presented communication, diethylamine salicylate and methyl nicotinate can be quantitatively analyzed in ointments simultaneously by following a simple, direct and rapid spectrophotometric procedure.

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