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Determination of methyl salicylate in pharmaceutical preparations

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A method based on gas-liquid chromatographic technique is described for the determination of methyl salicylate in pharmaceutical preparations. 10% carbowax 20M is used as a stationary phase to resolve mixtures containing amyl, ethyl and methyl salicylates, menthol and camphor. The determinations are based on the area triangulation method against a diphenyl reference standard.

ALTHOUGH many methods have been described for the estimation of methyl salicylate (Garratt, 1935; Hatfull, 1948; Haslam, Grossman, Squirrell & Loveday, 1953; Valsman & Benderskaya, 1958; Gengrinovich & Kadyrov, 1958; Benzuglyi & Dmitrieva, 1959; Bloom, P., personal communication), the use of gas chromatography appeared to offer a more elegant technique than any previously used. It promised to be more specific, accurate and time saving. The application of this technique to complex mixtures has been described by Domange & Longuevalle (1958) but no quantitative results on methyl salicylate were reported.

The work now reported covers the investigation of the conditions leading to the separation of methyl salicylate from a range of pharmaceutical formulations.

Experimental

Apparatus and running conditions. An F & M model 720 gas chromatograph incorporating a katharometer detector was used for the experiments. Stainless steel columns, measuring 2 ft. × ¼ in. O.D. were packed with 10% carbowax 20M on 60/80 mesh Celite. The carrier gas was helium flowing at 60 cc/min. Temperatures used were: oven, 150° isothermal; detector, 300°; injection port, 250°. The katharometer bridge current was 150 mA and the chart speed: 2 inches/min.

Under these conditions the methyl salicylate was well separated from those compounds with which it is commonly associated in pharmaceutical preparations.

The retention times of camphor, menthol, methyl salicylate, and amyl salicylate were 1·9, 2·7, 4·8 and 14·2 min respectively. To resolve methyl and ethyl salicylate where both were present it was necessary to increase the column length to 6 ft. and to programme the temperature from 140 to 200° at 1°/min.

The peak areas of the chromatogram were calculated by the area triangulation method: area × 2 = height × base (Birchfield & Storrs, 1962). The base of the triangle is obtained by drawing tangents at the points of inflection on the peak and measuring the distance between the points of intersection of the tangents and the base line. The height

From Smith Kline & French Laboratories Limited, Welwyn Garden City, Hertfordshire.

measurement is the vertical distance in the same units from the intersection of the tangents to the base line.

Selection of an internal standard. The compounds investigated as possible internal standards (Ray, 1954) were: diphenyl, naphthalene, diphenylmethane and diphenylethane. Diphenyl with a retention time of 10·5 min was chosen because of its complete resolution from all compounds likely to be encountered. The reagent grade material was checked to ensure it yielded a single peak under test conditions. A *standard diphenyl solution* was prepared by accurately weighing approximately 4 g into 100 ml graduated flask and making up with toluene.

Detector response to methyl salicylate and diphenyl. This was linear over a volume range of 0·02 to 3·0 μl. The minimum detectable quantity of methyl salicylate was 0·02 μl.

Calibration curve. Mixtures of methyl salicylate and diphenyl in varying proportions were prepared and the peak areas of their chromatograms measured.

The calibration plot of methyl salicylate area/diphenyl area against the percentage w/w methyl salicylate gave a straight line passing through the origin and corresponding to the expression $y = mx$ where $m = 2 \times 0{\cdot}58 = 1{\cdot}16$ since the peak area of the diphenyl internal standard was halved to assist in the plotting of the ratio of the methyl salicylate area against diphenyl area.

DETERMINATION OF METHYL SALICYLATE IN PHARMACEUTICAL PREPARATIONS

Accurately weigh an amount of ointment containing approximately 80 mg methyl salicylate into a 10 ml graduated flask. Pipette 5 ml standard diphenyl solution into the flask together with about 2 ml toluene. Shake the flask mechanically until the ointment has completely dissolved or has been uniformly dispersed. Dilute the solution to 10 ml with toluene. If the preparation yields any insoluble matter, the mixture should be centrifuged. Inject approximately 50 μl of the clear toluene extract by means of a Hamilton syringe on to the column. Calculate the peak area ratio of methyl salicylate against diphenyl and from the calibration curve determine the weight of methyl salicylate and hence its concentration in the original sample.

A solution of the sample in toluene, clarified as before but without diphenyl should be similarly examined to establish that no peaks from the sample interfere with the use of diphenyl as a reference standard.

With oil in water formulations which are immiscible with toluene, the preparation should be dissolved in absolute ethanol: the diphenyl standard solution should then be similarly prepared.

Reproducibility of method. To establish the reproducibility, a series of replicate analyses were made on a proprietary ointment for which the determinations gave 4·9% (s.d. 0·13).

Recovery experiments. A series of experiments were carried out in which the methyl salicylate concentration in a plain iodine ointment base was varied from 5 to 55% w/w. The method gave a mean recovery of 99·5% (s.d. 0·63).

Results

The method has been applied to a range of official and proprietary formulations with the results shown in Tables 1 and 2.

TABLE 1. DETERMINATION OF METHYL SALICYLATE IN OFFICIAL PREPARATIONS

	Stated content % w/w	% w/w*	
		by B.P.C. method	by G.L.C. method
1. Ointment of Methyl Salicylate B.P.C.	50	45·0 45·2	53·6 52·4
2. Ointment of Methyl Salicylate Comp. B.P.C. ..	50	46·1 46·3	50·2 51·5
3. Ointment of Iodine and Methyl Salicylate B.P.C.†	5·9	5·2 5·2	5·9 5·8
4. Liniment of Methyl Salicylate B.P.C.	≡30	31·4 31·4	31·6 31·8

Note. The results are individual analyses. However, the preparation† contained some dross so the solution of the ointment was centrifuged before injection. In these instances the methyl salicylate was between 5·8 and 5·9% w/w.

TABLE 2. DETERMINATION OF METHYL SALICYLATE IN PROPRIETARY PREPARATIONS

	Samples tested	Methyl salicylate % w/w	
		Stated contents	Found
Ointments	6	5·0	4·7–5·0
	2	2·3	2·1
	1	1·3	1·5
Liniment	2	≡3·74	3·6, 3·7
Balm	1	1·15	0·9
	2	12·8	11·7, 11·8
	2	12·39	11·7
Balsam	2	15·0	15·8, 15·9

The method provides reproducible results in a relatively short time and in its application to the analysis of ointments appears to meet a recent criticism of Garratt (1964) that no really satisfactory method for the determination of methyl salicylate in ointments has yet been described.

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