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Hydrogen Bonding Studies in Menthol and Methyl Salicylate in Drug Formulations by Vibrational Spectroscopy

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The infrared spectral investigation on the pure samples and formulations containing menthol and methyl salicylate showed the presence of intramolecular hydrogen bond in methyl salicylate and intermolecular hydrogen bond in menthol but there is no hydrogen bonding between the two drug molecules in the compound mixture.

INTRODUCTION

Many topical preparations in the form of combinations containing methyl salicylate and menthol have been marketed in the form of external irritant ointments. While methyl salicylate possesses pain relieving properties, menthol is a rubbing alcohol incorporated to relieve local neuralgia and healing of inflamed areas[1].

Our continued interest in exploring and designing new methods of assay for various types of analgesic and antiinflammatory drug preparations has led us to the above drug combination[2, 3].

A structural examination of the two drug constituents contained in the above stated preparation indicates that while methyl salicylate contains a phenolic —OH group, menthol contains an alcoholic —OH group. It is a well known fact that —OH group is a highly polar group and associates with other such groups[4, 5]. While the infrared spectra of the two individual compounds are known, no hydrogen bonding studies in the individual drugs and no vibrational assignments on the compound preparation have been reported[6–10]. The objective of this research has been to examine if there is any type of interaction in the form of hydrogen bonding between the two drug constituents and its effect if any on the absorption and distribution through the skin.

In the present work we describe in detail the results of the infrared spectral investigation on the pure samples of methyl salicylate and menthol, on the pure mixture as well as on the commercial (ointment) preparations.

EXPERIMENTAL

All infrared spectral studies were performed on infrared JASCO REPORT-100 autoscan spectrophotometer.

Method

The infrared spectra were taken at room temperature in the form of solutions in the region between 4000–600 cm^{-1} on the pure samples ranging from 0.1–2.1 mL of methyl salicylate in 10 mL of chloroform giving the concentrations of 1% to 21%; from 0.1006 g to 2.10006 g of menthol in 10 mL of chloroform giving concentrations ranging from 1% to 21%; from 0.1 to 2.1 mL methyl salicylate in 10 mL of carbon tetrachloride giving concetrations of 1% to 21%; from 0.1013 to 2.1002 g of menthol in 10 mL of carbon tetrachloride giving concentrations of 1% to 21%.

The observed frequencies were calibrated with frequencies of polystyrene film. For the determination of infrared spectra on the ointment preparation, the latter (2 g) was removed from the container and transferred to a 100 mL conical flask and extracted 3 times with 5 mL of diethyl ether. The ether layers were combined and evaporated to dryness. The drug mixture obtained after extraction and dryness from the ointment preparation was examined in the neat form and in carbon tetrachloride.

SPECTRAL INTERPRETATIONS

(A) Methyl Salicylate

Absorption between 4000–600 cm^{-1}: The spectrum of methyl salicylate taken in different concentrations of chloroform showed an intense band at 3194 cm^{-1} which can be assigned to bonded —OH stretching vibrations. However no absorption bands were observed at any of the higher frequencies indicating that no free —OH is present in the molecule (Fig. 1).

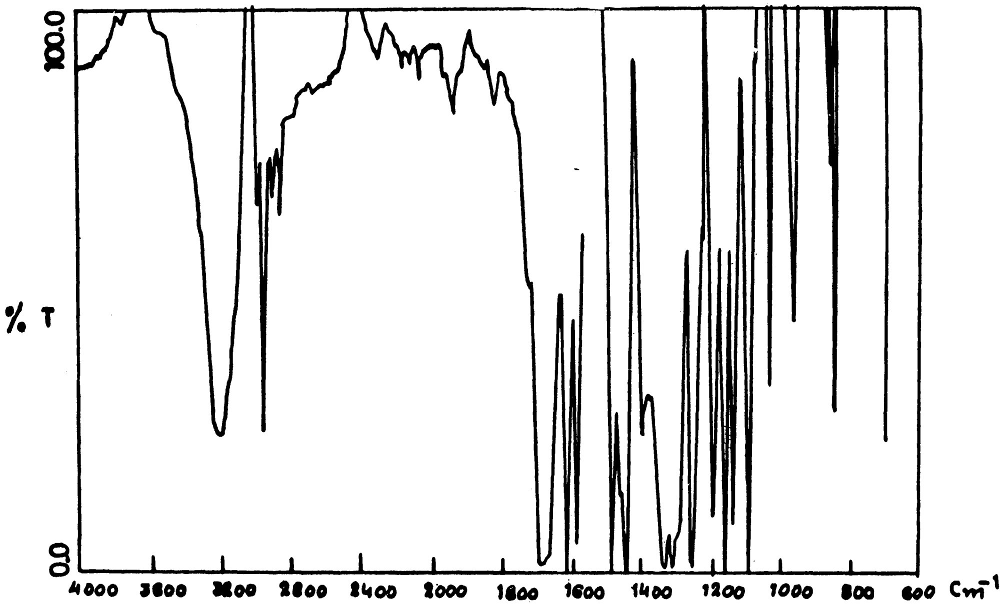

Fig. 1 IR spectrum for methyl salicylate in 9% chloroforn.

The infrared spectrum also showed frequencies at 1395 and 1327 cm^{-1} indicating the presence of in-plane bendings due to —OH group. A number of strong absorption bonds were noted in the range from 1303 to 1033 cm^{-1} indicating presence of —C—O—C— as well as —C—C—O— symmetrical vibrations due to the presence of the ester of the aromatic acid. The presence of the aromatic ring was established from the bands located at 2994, 965, 865, 849 and 702 cm^{-1}, the last three frequencies confirmed the presence of ring C—H out of plane bending abscrptions and *ortho* distribution.

When the infrared spectrum of methyl salicylate was determined in different concentrations of carbon tetrachloride, strong bands were located at 3196, 3070, 3052, 3026 and 3002 cm^{-1} indicating the absorption due to bonded —OH stretching and C—H (aromatic) stretching vibrations (Fig. 2). There were additional absorption peaks at 1252, 1213, 1212, 1195 cm^{-1} indicating the presence of C—O—C stretching of the ester. The presence of strong bands at 1158, 1135, 1091 as well as 1032 cm^{-1} were clear indications of C—O stretching due to phenolic —OH group. While a frequency at 667 cm^{-1} established the presence of OH out-of-plane bending of bonded —OH group, the absorption peaks at 849 and 702 cm^{-1} were retained indicating the presence of out-of-plane aromatic ring bend. There were also strong absorptions at 1464, 1485, 1584, 1614, 1679, and 1685 cm^{-1} indicating the presence of C═O due to ester and C═C due to aromatic ring, the last two were absent when spectrum was taken in $CHCl_3$.

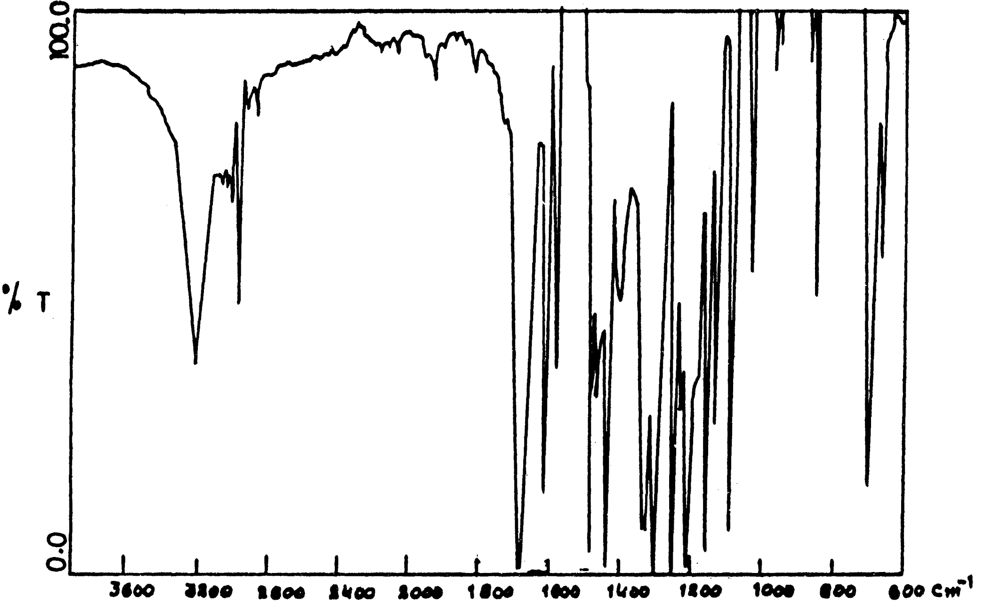

Fig. 2 IR spectrum for methyl salicylate in 5% carbon tetra chloride.

(b) MENTHOL

Absorption between 4000–600 cm^{-1}: The spectrum of menthol taken in different concentrations of $CHCl_3$ showed strong absorptions at 3612 and 3458 cm^{-1} indicating the presence of free —OH as well as bonded —OH group freqencies respectively (Fig. 3). The aliphatic —CH stretching vibrations were clearly seen at 2954, 2924 and 2870 cm^{-1}. The absorption at 1454 cm^{-1} was due to asymmetrical bend of CH_3 group while a geminal dimethyl doublet was present at 1385 and 1369 cm^{-1}. The in-plane bend due to —OH group was located at 1346 and 1214 cm^{-1}.

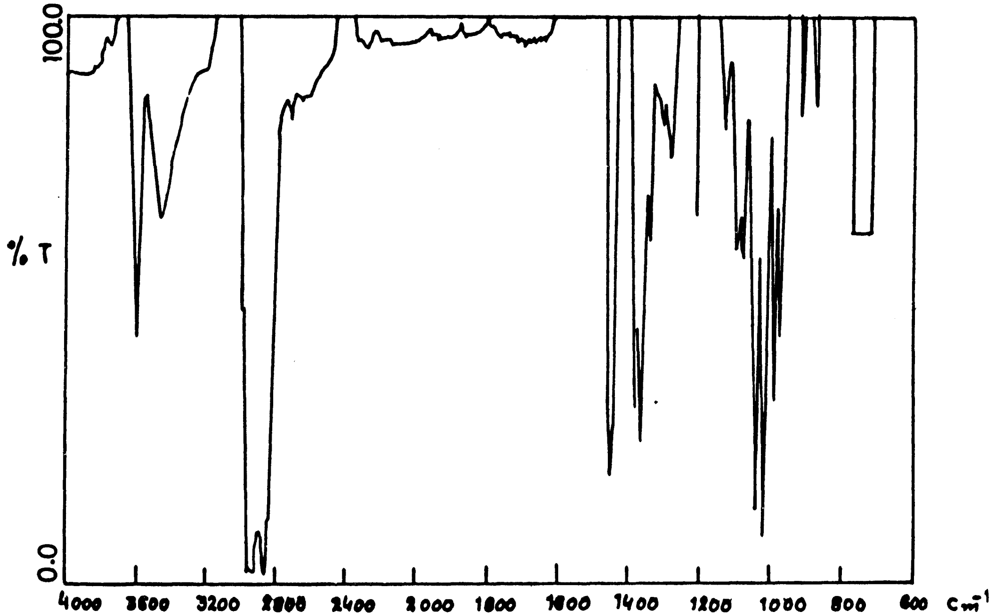

Fig. 3 IR spectrum for menthol in 11% chloroforrn.

The absorption at 1094, 1079, 1043 and 1021 cm^{-1} was assigned to —CO stretching due to the presence of aliphatic —OH group.

There were also absorptions at 991, 976 and 716 cm^{-1} which could be assigned to CH_2 rocking vibrations.

When the infrared spectrum of menthol was determined in different concentrations of CCl_4 intense bands were noted at 3622 and 3358 cm^{-1} indicating the presence of both free —OH and bonded —OH stretching vibrations in the meloecule (Fig. 4).

The aliphatic —CH stretching frequencies due to methylene and methyl groups were observed at 2954, 2924 and 2870 cm^{-1}, An absorption band at 1454 cm^{-1} was due to CH_3 deformation while a doublet at 1384 and 1368 cm^{-1} showed the presence of isopropyl group in menthol. A number of absorption bands were seen at 1345, 1308, 1289 and 1177 cm^{-1} which could be associated to wagging and twisting of CH_2 group. The absorptions bands at 1101, 1079, 1044 and 1024 cm^{-1} are due to —CO bending vibrations of the secondary hydroxyl group in menthol. The frequencies at 992 and 919 cm^{-1} may be associated due to rocking of the isopropyl group.

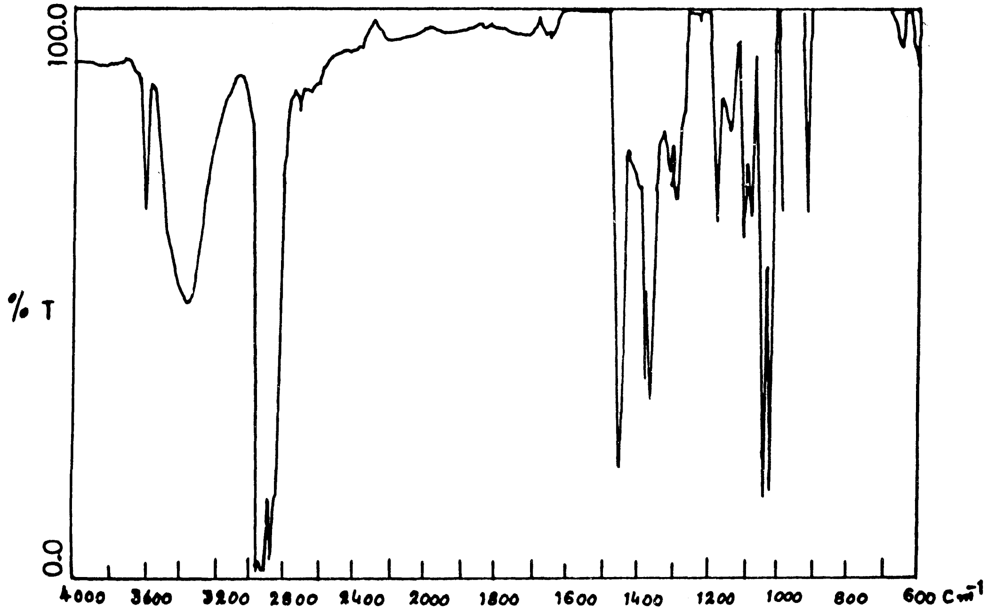

Fig. 4 IR spectrum for menthol in 9% carbon tetra chloride.

PURE MIXTURE OF METHYL SALICYLATE AND MENTHOL

When the infrared spectum of a pure mixture of methyl salicylate and menthol was examined in different croncentrations of $CHCl_3$, strong absorption bands were located at 3614, 3448 and 3198 cm^{-1} indicating the presence of the free —OH stretching vibration due to —OH group present in menthol as well as bonded —OH present in methyl salicylate and menthol respectively. The stretching vibration at 3198 cm^{-1} was due to aromatic C—H group while absorptions at 2956, 2924 and 2870 cm^{-1} were due to aliphatic C—H stretching of CH_3 and CH_2 groups present in menthol. An absorption band located at 1677 cm^{-1} was an indication of C═O group of methyl salicylate. The frequencies at 1386 and 1369 cm^{-1} could be assigned to *gem*-dimethyl group present in menthol. A large number of absorption bands between 1250–1022 cm^{-1} can be assigned to C—O—C and C—C—O symmetrical and asymmetrical vibrations due to ester function. The absorption bands at 991, 965 and 848 cm^{-1} are due to C—H out-of-plane bendings of the aromatic ring (Fig. 5).

The infrared spectrum of a pure mixture of methyl salicylate and menthol taken in different concentrations of CCl_4 showed absorption bands at 3622, 3194, 3070, 3052 and 3000 cm^{-1}. These frequencies can be associated to free —OH group in menthol, bonded —OH group in menthol and methyl salicylate and to the aromatic C—H stretching vibrations respectively. The absorption frequencies at 2954, 2922, 2870 cm^{-1} can be associated to the C—H stretching vibrations of CH_3 and CH_2 groups of menthol. An absorption band at 1678 cm^{-1} was due to C═O of the ester group. The aromatic C═C stretching vibrations of methyl salicylate were located at 1614, 1584, 1485 and 1464 cm^{-1}. The absorption at 1440 cm^{-1} and 1397 cm^{-1} could be associated to CH_3 in menthol respectively. A

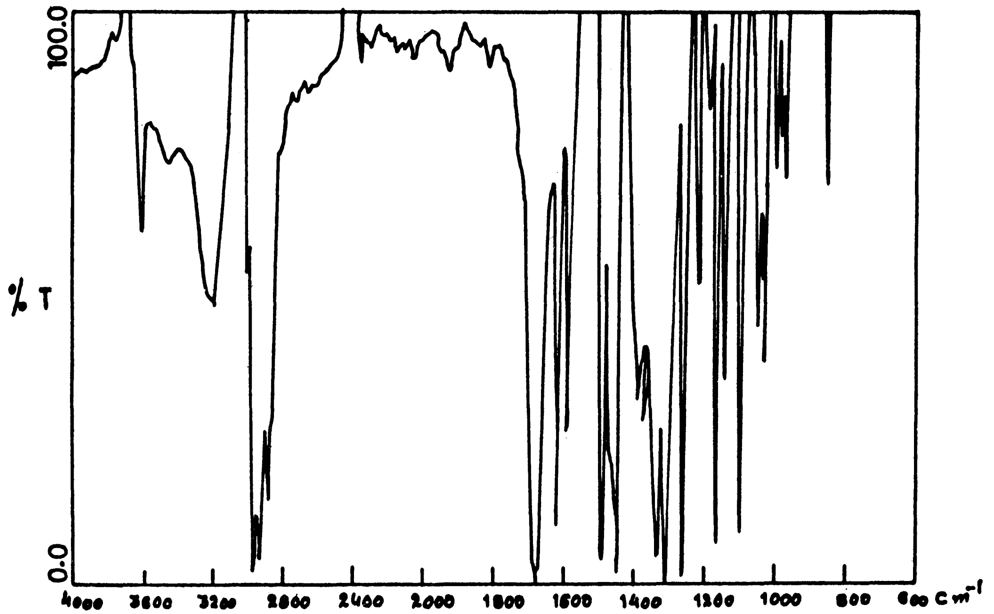

Fig. 5 IR spectrum for pure mixture of menthol and methyl salicylate in 5% chloroform.

doublet due to isopropyl group was clearly seen at 1385–1368 cm^{-1}. A large number of frequencies between 1337 and 1044 cm^{-1} were due to C—O—C symmetrical and asymmetrical vibrations of the methyl ester group. The out-of-plane C—H ring bending vibrations in methyl salicylate were observed at 848, 801, 702 and 667 cm^{-1} (Fig. 6).

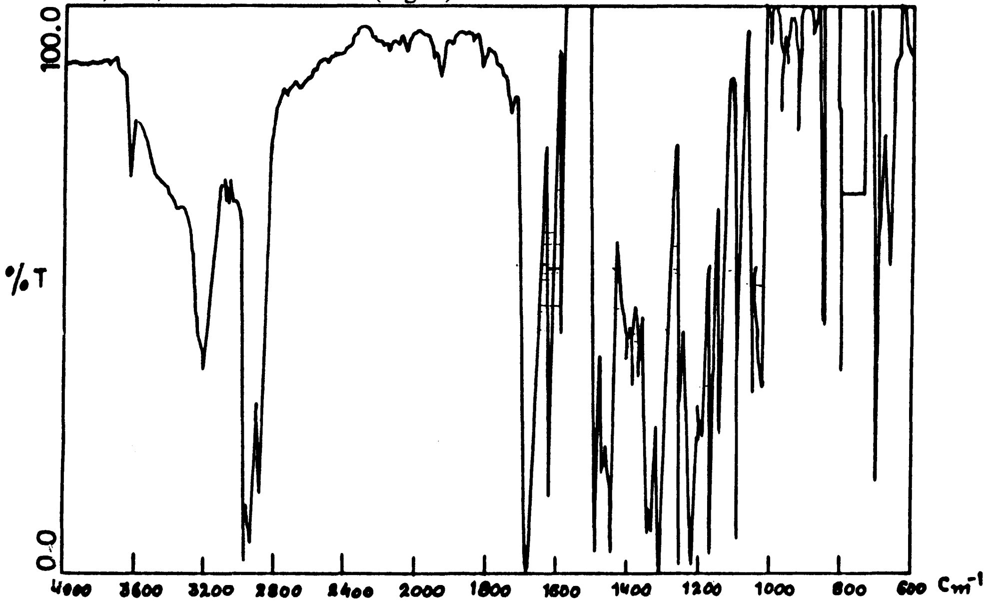

Fig. 6 IR spectrum for pure mixture of menthol and methyl salicylate in 5% carbon tetra chloride.

The infrared spectra of formulations containing menthol and methyl salicylate were examined in "neat form" as well as in different concentrations of carbon tetrachloride. In "neat form", the spectra showed some of the absorption peaks but all other peaks did not get resolved due to high concentration of the solution mixture. The absorption peaks at 3148 indicated the presence of bonded —OH and aromatic C—H which had coalesced together in the form of a band. The peak at 2830 cm^{-1} showed the presence of C—H stretching vibration of CH_3 and CH_2 groups. The frequencies at 993 and 876 cm^{-1} were due to methyl rocking of isopropyl group and out-of-plane C—H ring bending respectively.

An absorption peak at 666 cm^{-1} was indicative of out-of-plane bending of —OH group or bonded —OH group.

The infrared spectra of formulations containing menthol and methyl salicylate when examined in different concentrations of carbon tetrachloride showed spectra similar to those of the pure mixture except that the absorption peaks wre slightly shifted to lower frequencies.

RESULTS AND DISCUSSION

A detailed study of the infrared spectra was undertaken on pure drug samples of methyl salicylate, menthol, their pure mixtures and simultaneously on the two constituents obtained through the process of extraction from the commercial ointment preparations. The infrared data obtained from pure menthol using various concentrations of $CHCl_3$ and CCl_4 showed that free and bonded —OH stretching vibrations were always present in the molecules. However, in the case of methyl salicylate the presence of free —OH stretching vibrations was never seen indicating the presence of strong intramolecular hydrogen bond in the molecule. This hydrogen bond remained intact and could not be ordinarily broken by solvents, as there was no marked change in the absorption frquencies when studies were performed in various concentrations of either $CHCl_3$ or CCl_4.

The infrared spectrum obtained for the mixture of two constituents after its extraction from the formulation when taken in different concentrations of CCl_4 retained the —OH stretching band for methyl salicylate while that of the free —OH due to menthol at 3622 cm^{-1} was lost, that of the bonded —OH got shifted to 3424 cm^{-1} from 3358 cm^{-1}. However, when the spectrum of this mixture was determined in "neat form" the absorption bands could not be thoroughly resolved due to high concentration of the solution mixture. Further, the absorption band at 3358 cm^{-1} in different concentrations of CCl_4 observed in pure menthol was not seen for the pure mixture under the same conditions. The absorption frequency around 3196 cm^{-1} in pure methyl salicylate whether alone or in pure mixture was always present whether spectra were determined in $CHCl_3$ or CCl_4. However, the spectrum for the formulation in CCl_4 showed absorption peaks at 3424 and 3194 cm^{-1} indicating hydrogen bonded absorption bands contained in menthol and methyl salicylate. Thus the conclusion is made that there is presence of "intramolecular" hydrogen bond in methyl salicylate and presence of "intermolecular" hydrogen bond in menthol but there is no hydrogen bonding between the two drug molecules in the compound mixture.

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