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Incompatibility of polyvinyl acetate phthalate with benzocaine: Isolation and characterization of 4-phthalimidobenzoic acid ethyl ester

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Summary

The interaction of benzocaine with polyvinyl acetate phthalate in propylene glycol or a mixture of propylene glycol and ethyl alcohol was studied. The 4-phthalimidobenzoic acid ethyl ester, a major product that formed during storage, was isolated and characterized.

Introduction

The study of chemical interactions between active drugs and pharmaceutical adjuvants, during product preparation and storage, constitutes an important phase in drug product design. Such interactions can influence product stability, modify drug release kinetics, reduce bioavailability, and may produce compound(s) that can cause adverse effects. In this paper, the results of a study on the interaction of benzocaine with polyvinyl acetate phthalate (PVAP), a polymer widely used as an enteric coating agent, in propylene glycol or a mixture of propylene glycol and ethyl alcohol, are reported. The development objective of the study that identified this interaction involved a liquid dosage form for both oral and topical applications.

Benzocaine (4-aminobenzoic acid ethyl ester) is a potent local anesthetic. It is commonly used to relieve pain due to hemorrhoids, contact dermatoses such as poison ivy, poison oak, burns including sun burn, and oral conditions such as toothaches, cold sores, and canker sores. Numerous dosage forms including lozenges, suppositories, creams, lotions, ointments, sprays, and aerosols, are currently available as over-the-counter drug products. According to the Federal Drug Administration (F.D.A.), products containing 5–20% benzocaine are safe for such use.

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Because of the presence of a primary amine group, benzocaine is highly susceptible to chemical interactions with pharmaceutical adjuvants that contain a carbonyl functionality. Simmons et al. (1970) reported the presence of *N*-glucoside, a product formed as a result of interaction between the amine group (of benzocaine) and a glucose moiety, in several commercial throat lozenge products. The incompatibility of benzocaine with citric acid, corn syrup, and natural cherry flavor, the excipients commonly used in the making of lozenges, has been reported by Kabasakallan et al. (1969). Corn syrup contains glucose, whereas both reducing sugars (glucose, etc.) and aldehydes are present in natural cherry flavor. The reaction between aldehydes and benzocaine has been reported to give Schiff-base complexes. With citric acid, the formation of a citric monoamide has been proposed. Higuchi and Miki (1961) studied the kinetics of interaction between citric acid and benzocaine in water (pH 4.0) at 95 °C, and found that the reaction proceeds to completion relatively rapidly. The monoamide, however, readily reverts to the free acid and benzocaine on continued heating at 95 °C. Kinstlers and Pormale (1977) reported the preparation of carboxymethylcellulose amide from the reaction between carboxymethylcellulose and benzocaine in dimethylformamide at 40–110°C.

Experimental

Materials

The U.S.P. grade benzocaine was purchased from Ruger Chemical Co., Inc. (Hillside, NJ, U.S.A.). The PVAP samples, four different lots that varied in phthalyl content from 56.6 to 61.2%, were received from Colorcon Inc. (West Point, PA, U.S.A.).

All other solvents were either analytical reagent, spectroscopic, or chromatographic grade quality.

Instruments

The pulse Fourier-transform ^{1}H- and ^{13}C-NMR spectra were recorded at 30°C on a 200 MHz Varian VXR or Bruker spectrometer, using chloroform-d_1 as a solvent which also provided the deuterium lock signal. The ultraviolet-visible and Fourier-transform infrared spectra were measured (in acetonitrile and as a KBr pellet, respectively) using a Beckman DU-70 and a Nicolet 5DXC spectrophotometer, respectively. The electron-impact mass spectrum was obtained by a direct probe method on an AEIMS-30 spectrometer utilizing an ionization energy of 30 eV and a probe temperature of 160°C.

Preparation of PVAP-benzocaine samples and isolation of the in-situ produced product

The test PVAP-benzocaine formulations were prepared by dissolving PVAP and benzocaine, separately, in different weight ratios, in propylene glycol or a mixture of propylene glycol and ethyl alcohol, followed by mixing the respective solutions. The resulting viscous solution was stored at room temperature in a glass bottle with a screw cap.

All samples turned intense yellow in color and produced a long, needle-shaped crystalline product on storage. The white to off-white crystalline product was separated by decantation, followed by washing with an aqueous-alcoholic (30:70) solution. Further purification of the product was achieved by treating the solid with an aqueous solution of sodium bicarbonate in acetone, followed by removal of the acetone and subsequent extraction with chloroform. The product was finally recrystallized from acetonitrile.

Results and Discussion

The air-dried crystalline solid melts at 158–59°C. The molecular weight of the compound, as determined by mass spectrometry, is 295.

The ^{1}H-NMR spectrum (Fig. 1) of the product shows chemical shifts due to aryl protons centered at δ 7.60, 7.81, 7.97, and 8.18 ppm, and at δ 4.41 and 1.41 ppm due to methylene and methyl groups, respectively. Integration of the peaks gave proton ratios of 2:2:2:2:2:3, respectively. An analysis of the splitting pattern of the signals at 7.60 (doublet, $J = 8.5$ Hz) and 8.18 ppm (doublet, $J = 8.6$ Hz) clearly indicated the presence of a

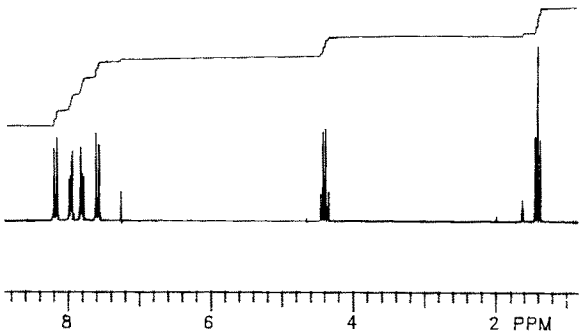


Fig. 1. ^{1}H-NMR spectrum of the compound isolated.

para-disubstituted benzene ring, whereas the signals centered at 7.81 (two doublets, $J = 5.5$ Hz) and 7.97 ppm (two doublets, $J = 5.5$ Hz) were attributed to protons of an *ortho*-disubstituted benzene ring.

The infrared spectrum (Fig. 2) of the compound exhibits a very strong absorption band at 1708 cm^{-1} and a medium band at 1785 cm^{-1}, due to C=O stretching vibrations. A survey of suggested infrared frequencies for C=O groups in the literature (Williams and Fleming, 1966) indicated that these absorption bands are due to the carbonyl groups of a cyclic five-membered imide (–CO–N–CO–) ring. The band due to the C=O (ester) stretching mode, which appears at 1680 cm^{-1} in the spectrum of benzocaine, could not be identified. It is likely that a large shift to a higher frequency, due to the *para*-phthalimide ring substitution, might have occurred, causing it to appear along with the imide carbonyl absorption bands. There are no bands in the region 3500–3300 cm^{-1}, suggesting the absence of a $-NH_2$ or $>NH$ group in the compound. In the spectrum of benzocaine, absorptions due to unsymmetrical and symmetrical $-NH_2$ stretching modes appear at 3416 and 3339 cm^{-1}, respectively. Also absent in the spectrum of the compound is a band due to the NH_2 bending vibra-

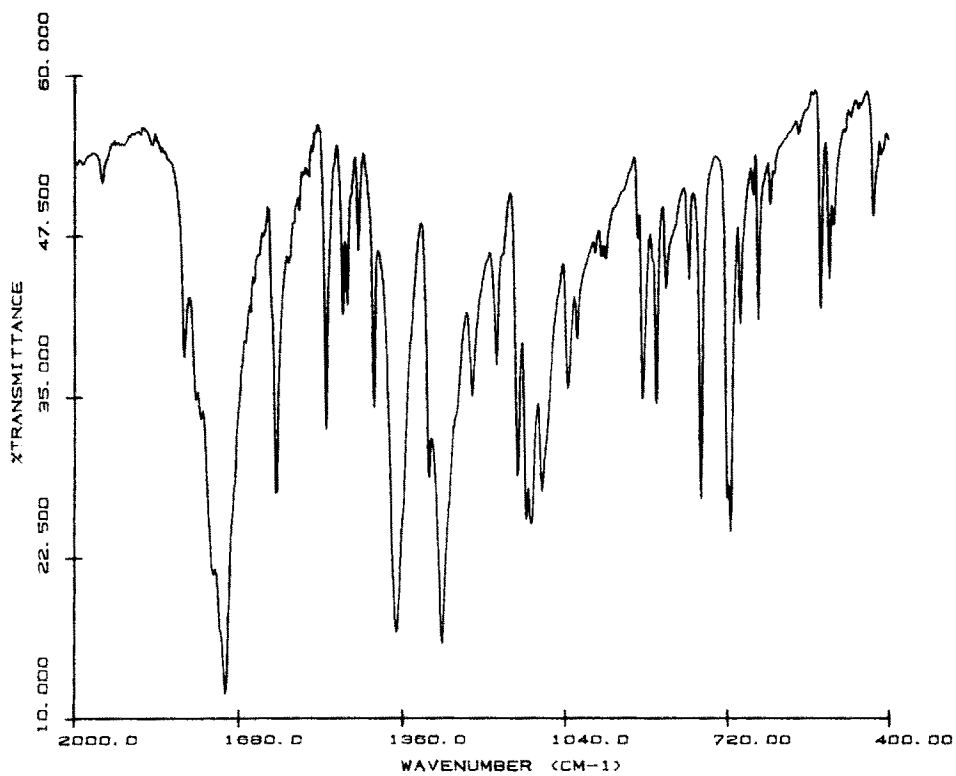
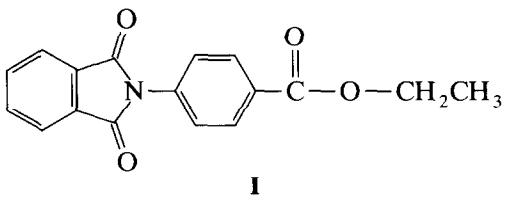


Fig. 2. Infrared spectrum of the compound isolated.

tion, which in the case of benzocaine appears at 1637 cm^{-1}.

The ^{1}H-NMR, infrared and mass spectral data, plus the fact that the PVAP used contained some residual phthalic acid, all indicated that the compound is a condensation product formed in situ as a result of the interaction between benzocaine and the free phthalic acid. The following structure (**I**) was assigned to the compound:



I

Further evidence for the structure **I** was produced by the ^{13}C- and two-dimensional (2-D) heteronuclear NMR spectra. The ^{13}C-NMR spectrum of the compound was obtained using the APT (Attached Proton Test) pulse sequence, which afforded the methine and methyl carbon signals having phase opposite to that of methylene and quaternary carbons (Fig. 3). The 2-D NMR spectrum of the compound (Fig. 4) indicated that signals at 125.92 and 130.39 ppm in the ^{13}C-NMR spectrum are due to methine carbons attached to protons of the *para*-disubstituted benzene ring, and resonances at 123.93 and 134.65 ppm are from carbons that are bound to protons of the *ortho*-disubstituted ring. Further assignment of these and of quaternary carbons was made based on estimates of substituent effects. The resonance at 61.18 ppm, being opposite in phase, is assigned to methylene carbon, whereas the signal at 14.33 ppm is attributed to the methyl carbon.

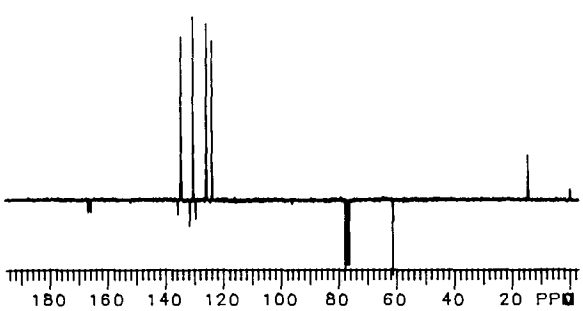


Fig. 3. ^{13}C-NMR nuclear magnetic resonance of the compound isolated.

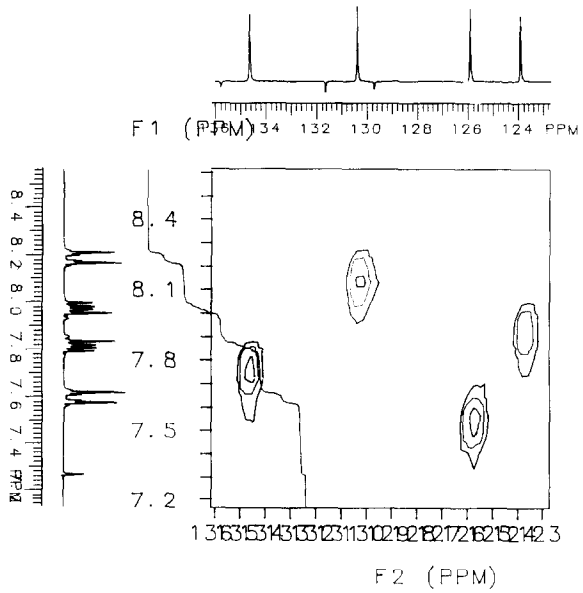


Fig. 4. 2-D NMR spectrum of the compound isolated.

The carbonyl carbon resonances, belonging to an imide ring and an ester group, generally absorb between 150 and 180 ppm (Moore and Dalrymple, 1976). The two signals appearing at 166.81 and 165.84 ppm in the ^{13}C-NMR spectrum of the compound are clearly due to the imide and ester carbonyl carbons. When protons appearing at 7.97 ppm in the ^{1}H-NMR spectrum of the compound were selectively irradiated, the signal at 166.81 ppm collapsed, confirming that the lowest-field resonance (166.81 ppm) is due to the imide carbonyl carbons.

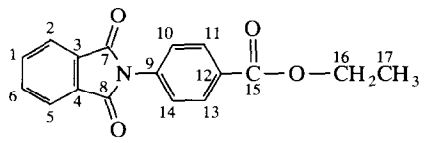
A complete listing of ^{1}H- and ^{13}C-NMR chemical shift values and their assignment is presented in Table 1.

The ultraviolet/visible spectrum of the compound, in acetonitrile, shows two absorption bands with maxima at ~ 213 nm (ϵ = 31 920 M^{-1} cm^{-1}) and ~ 248 nm (ϵ = 26 320 M^{-1} cm^{-1}), and a shoulder at ~ 303 nm.

The preparation of 4-phthalimidobenzoic acid ethyl ester, **I**, was first reported by Limpricht (1898) from the reaction between phthalyl chloride and benzocaine in the presence of aluminum

TABLE 1

^{1}H- and ^{13}C-NMR chemical shifts of 4-phthalimidobenzoic acid ethyl ester



^{1}H-NMR		^{13}C-NMR	
Chemical shift [a] (δ, ppm)	Multiplicity [b], no. of H, assignment, coupling constant (J)	Chemical shift [a] (δ, ppm)	Assignment
8.18	d, 2H, $H_{11,13}$, J = 8.6 Hz	166.81	$^{Q}C_{7,8}$
7.97	two d, 2H, $H_{2,5}$, J = 5.5 Hz	165.84	$^{Q}C_{15}$
7.81	two d, 2H, $H_{1,6}$, J = 5.5 Hz	135.82	$^{Q}C_{9}$
7.60	d, 2H, $H_{10,14}$, J = 8.5 Hz	134.66	$C_{1,6}$
4.41	q, 2H, H_{16}, J = 7.2 Hz	131.65	$^{Q}C_{3,4}$
1.41	t, 3H, H_{17}, J = 7.1 Hz	130.92	$C_{11,13}$
		129.73	$^{Q}C_{12}$
		125.92	$C_{10,14}$
		123.93	$C_{2,5}$
		61.18	C_{16}
		14.33	C_{17}

[a] ppm from tetramethylsilane (TMS). [b] d, doublet; q, quartet; t, triplet. Q, quaternary carbon in the APT spectrum.

chloride. Gori (1926) and Vanag and Veinbergs (1942) prepared the compound by reacting benzocaine with phthalic anhydride at 150 °C and in acetic acid, respectively. The melting point of the compound, as reported by these workers, is 150–153 °C, about 5–8°C less than that exhibited by the compound isolated in the present study. In the present investigation, the formation of 4-phthalimidobenzoic acid ethyl ester, **I**, probably occurred from a reaction between benzocaine and free phthalic acid. However, the base-catalyzed in situ interaction between PVAP-phthalate and benzocaine, producing 4-phthalimidobenzoic acid ethyl ester as an insoluble product, cannot be excluded.

The formation of 4-isophthalimidobenzoic acid ethyl ester instead of 4-phthalimidobenzoic acid ethyl ester, **I**, in the present study is ruled out because the former has a much lower melting point (112–113 °C; Ganin et al., 1987).

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