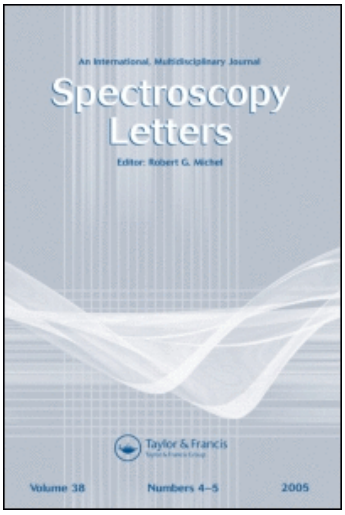

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Noninvasive Method for Determination of Propylene Carbonate in Pharmaceutical Formulations Using Fourier Transform-Infrared Spectrometry

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NONINVASIVE METHOD FOR DETERMINATION OF PROPYLENE CARBONATE IN PHARMACEUTICAL FORMULATIONS USING FOURIER TRANSFORM-INFRARED SPECTROMETRY

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ABSTRACT:

A noninvasive stability-indicating assay method utilizing Fourier Transform-Infrared/Attenuated Total Reflectance (FT-IR/ATR) Spectrometry for the determination of propylene carbonate in pharmaceutical formulations is described. The linearity of propylene carbonate response was studied by use of its carbonyl stretching frequency after spectral subtractions were performed to remove interfering bands. Analyses were performed on aqueous solutions of propylene carbonate, an aqueous cream formulation, and an anhydrous ointment spiked with propylene carbonate.

INTRODUCTION:

Propylene carbonate, a cyclic ester, functions as a polar additive in cosmetic formulations and as a vehicle in pharmaceutical ointments and creams. Al-

though stable under normal storage conditions, it undergoes degradation at elevated temperature and in the presence of acids, bases or salts (1).

Previous assay procedures reported in the literature include GC (2,3) and HPLC (4). GC methods suffer from problems related to thermal degradation of propylene carbonate in the injection port and on the column. The HPLC assay requires several steps in sample preparation prior to HPLC analysis.

An alternative to these methods, the FT-IR/ATR technique which utilizes the principles of internal reflection spectroscopy (5,6), has been made practical by the development of liquid cells designed specifically for FT-IR spectroscopy.

EXPERIMENTAL:

Apparatus: A cylindrical ATR cell with a zinc selenide crystal as the internal reflection element (CIRCLE CELL, Spectra Tech, Inc.) was used for all measurements. Spectra obtained were the result of 300 co-added scans obtained at 4 cm^{-1} resolution with Happ-Genzel apodization. The FT-IR instrument used was a Nicolet 5DXB equipped with a DTGS detector and operated under a dry air purge.

The infrared beam is focused by the optics of the Circle Cell at a 45 degree angle onto the zinc selenide crystal, where the beam then undergoes internal reflec-

tions as it travels along the length of the crystal. On each reflection the beam penetrates into the sample approximately 1.5 microns. With 10 reflections, the effective pathlength is 15 microns which results in absorbances in the correct range for aqueous solution measurements.

Reagents:

Propylene carbonate, propylene oxide and propylene glycol were used as purchased from Fisher (Fair Lawn, NJ). Allyl alcohol and propionaldehyde were used as purchased from Kodak (Rochester, NY).

Samples:

The method was developed utilizing samples of aqueous solutions of propylene carbonate prepared on a W/V basis (Sartorius Electronic Balance, Model 1712MP8), a 0.01% Fluocinolone Acetonide Cream (Goldine Labs, Ft. Lauderdale FL) and Polyethylene Glycol Ointment USP, the latter two being spiked with known amounts of propylene carbonate on a W/W basis. Spectra of the neat degradation products of propylene carbonate were collected, as well as spectra of mixtures of propylene carbonate and its degradation products. Samples were filled into the Circle Cell to a height sufficient to completely cover the zinc selenide crystal.

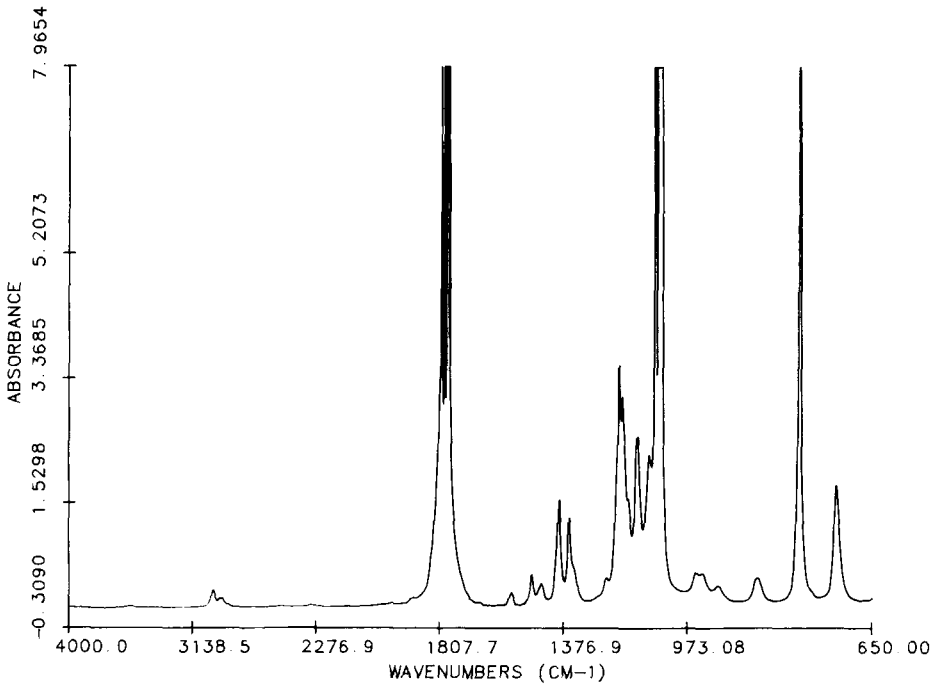

FIG. 1 - Spectrum of neat propylene carbonate. Note strong carbonyl absorption at 1779.5 cm^{-1}.

All spectral subtractions, calculations of peak areas and peak absorbances were performed with software obtained with the 1280 Nicolet computer.

RESULTS AND DISCUSSION:

The spectrum of neat propylene carbonate is shown in Figure 1. The strongest band is the carbonyl absorption occuring at 1779.5 cm^{-1}. The relatively high frequency absorption for this carbonyl is due to the

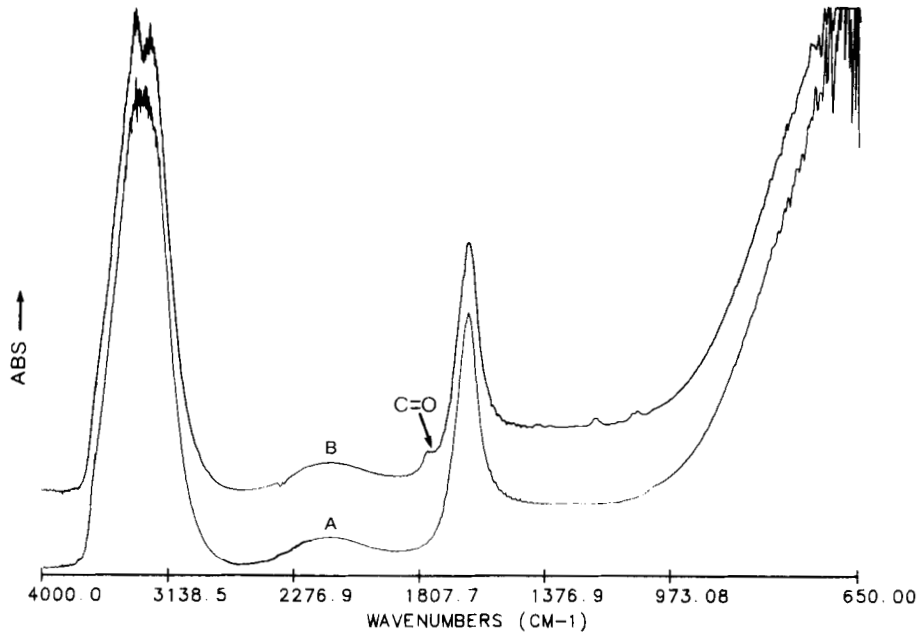

FIG. 2 - Spectrum of distilled water (A) and of a 1.25% (W/V) aqueous solution of propylene carbonate (B).

carbon of the carbonyl being part of the 5-membered ring structure of propylene carbonate. The restricted freedom results in a higher force constant for the bond and a higher frequency absorption. The carbonyl band at 1779.5 cm^{-1} was used for all quantitation.

Figure 2 shows the spectrum of distilled water and of a 1.25% (W/V) aqueous solution of propylene carbonate. The carbonyl absorption of propylene carbonate can be seen as a small shoulder on the left side of the OH bending vibration of water which occurs at 1630 cm^{-}

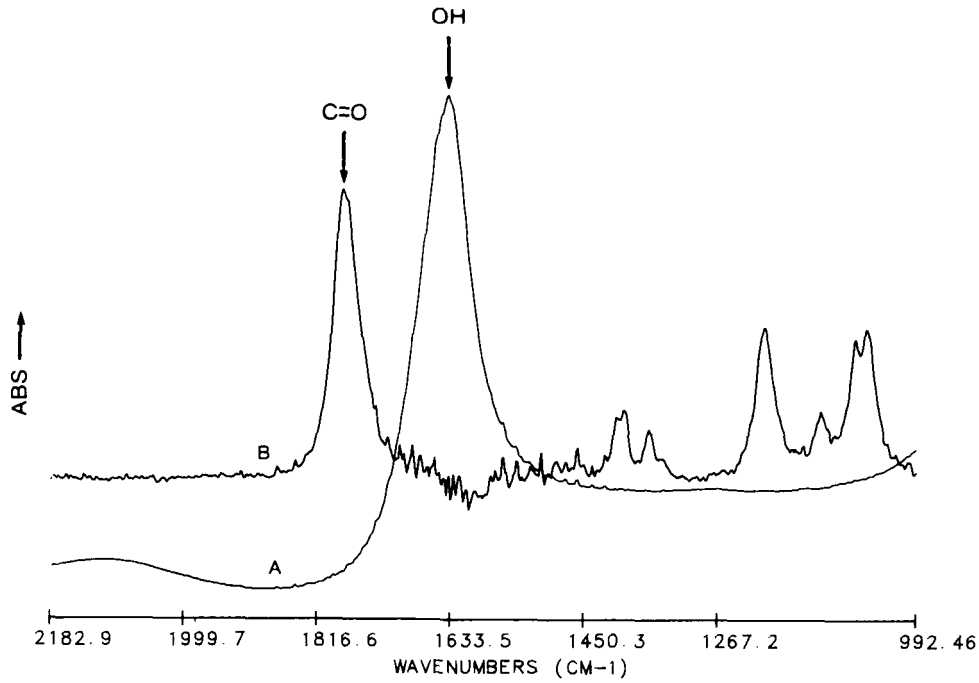

FIG. 3 - Spectrum of distilled water (A) and subtraction result of 1.25% solution of propylene carbonate minus water (B).

[1]. The contribution of water to the spectrum can be removed by an interactive subtraction technique using software provided with the Nicolet computer. The amount of water absorption subtracted is varied to achieve optimum subtraction as evidenced by nulling of the OH bending vibration of water. The subtraction result of 1.25% aqueous solution of propylene carbonate minus water is shown in Figure 3, along with the spectrum of distilled and deionized water to show where the contribution of water has been removed.

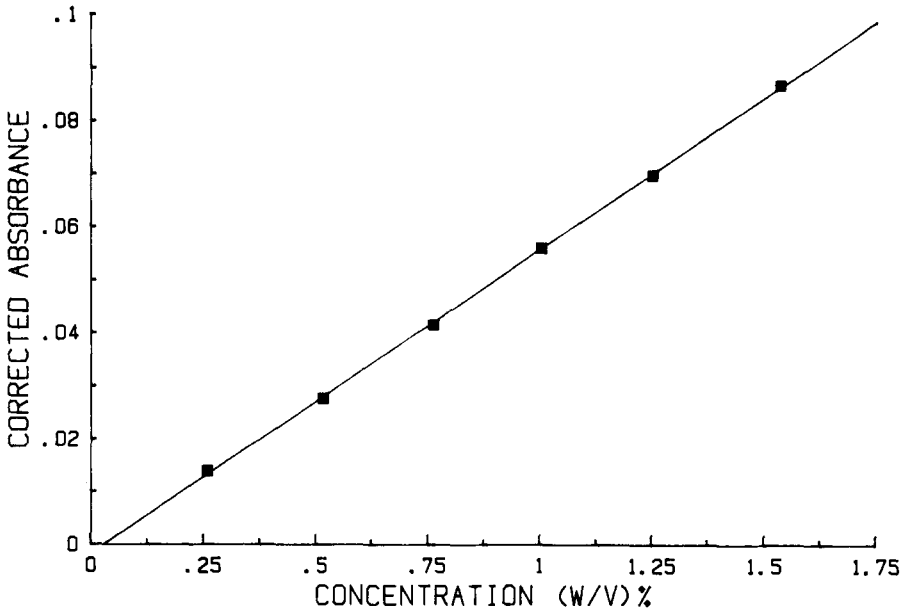

FIG. 4 - Calibration plot for solutions of propylene carbonate.

Linearity of propylene carbonate's carbonyl peak absorbance was studied in the concentration range, 2.5 - 15 mg/mL. A linear regression analysis of these results yields a correlation coefficient of 0.9998 and a y-intercept of -0.0015 (Figure 4).

Similar results were obtained on spiking 0.01% Fluocinolone Acetonide Cream (FAC) and Polyethylene Glycol Ointment USP, with propylene carbonate. Figure 5 shows the spectrum of FAC and FAC spiked with 3.15% propylene carbonate. The subtraction result with the contribution of FAC removed is shown in Figure 6.

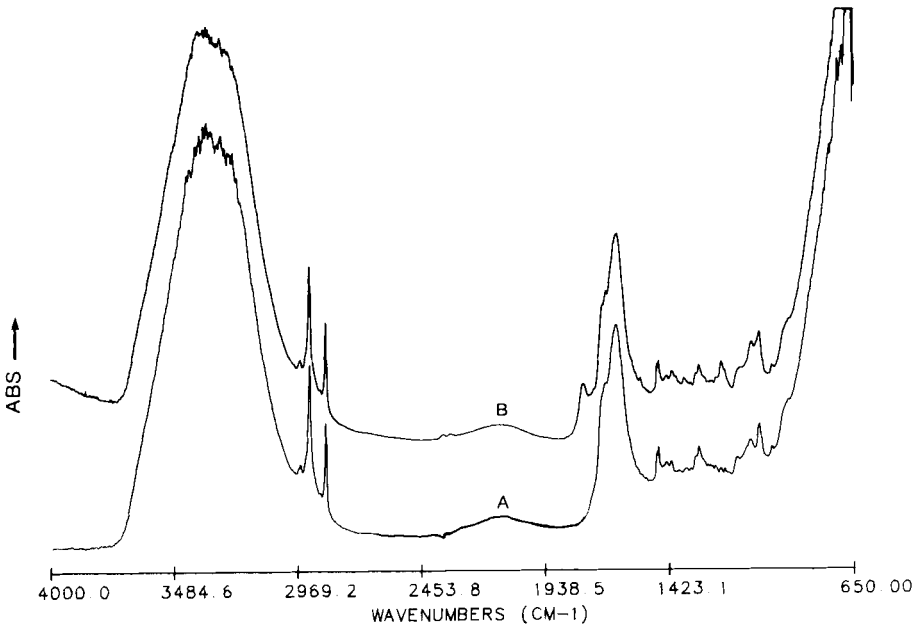

FIG. 5 - Spectrum of 0.01% Fluocinolone Acetonide Cream (A) and FAC spiked with 3.15% propylene carbonate (B).

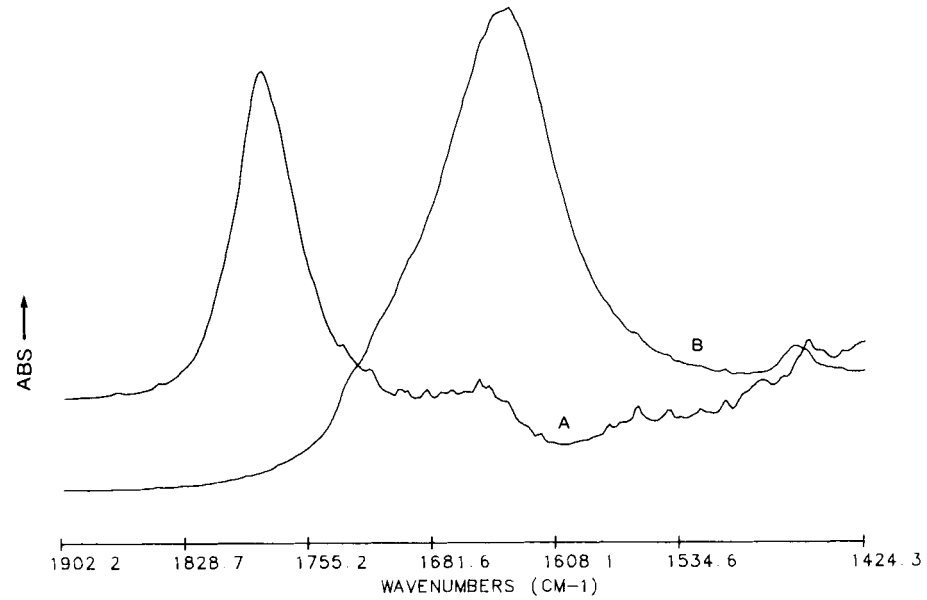

FIG. 6 - Subtraction result of FAC spiked with propylene carbonate minus FAC (A) and spectrum of unspiked FAC (B).

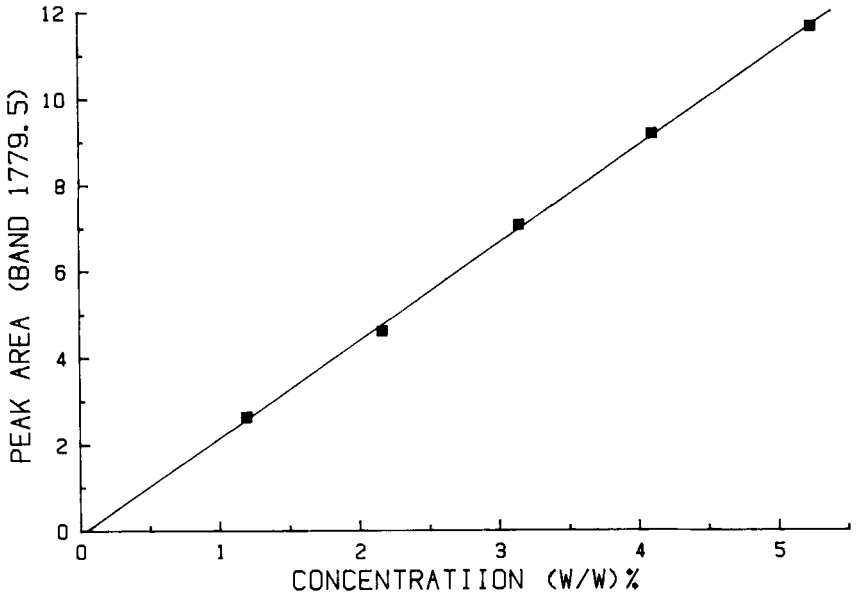

FIG. 7 - Calibration plot for FAC spiked with propylene carbonate.

Linear regression of the peak integral of the carbonyl band for the concentration range 1.15 - 5.25% (W/W) gives the calibration plot in Figure 7.

To demonstrate that the assay is stability indicating, spectra of all of the degradation products of propylene carbonate were collected, including propylene glycol, allyl alcohol, propionaldehyde and propylene oxide. Propionaldehyde is the only degradation product which has an infrared absorption near the 1779.5 cm^{-1} carbonyl absorption of propylene carbonate. Propionaldehyde has a carbonyl absorption at 1728 cm^{-1} (Figure

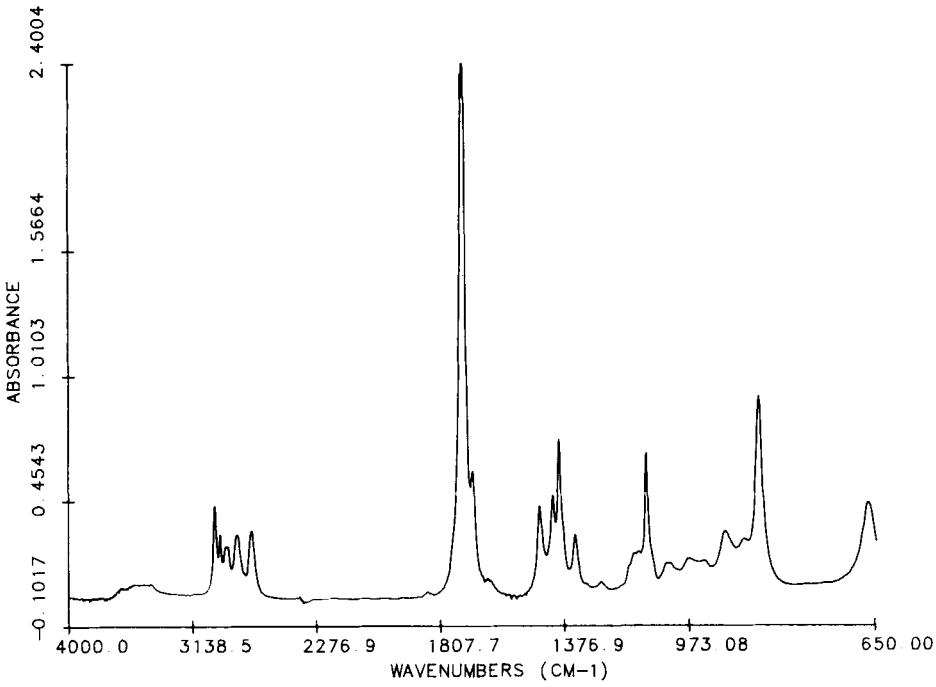

FIG. 8 - Spectrum of neat propionaldehyde showing carbonyl absorption at 1728 cm^{-1}.

8). This carbonyl is shifted far enough from that of propylene carbonate, so that its contribution can be removed by subtraction techniques. Figure 9 shows the spectrum of an aqueous solution of propylene carbonate and its degradation products. Also in Figure 9 is the spectrum of an aqueous solution of propionaldehyde, which contains the interfering peaks from the carbonyl of propionaldehdye and the OH bending vibration of

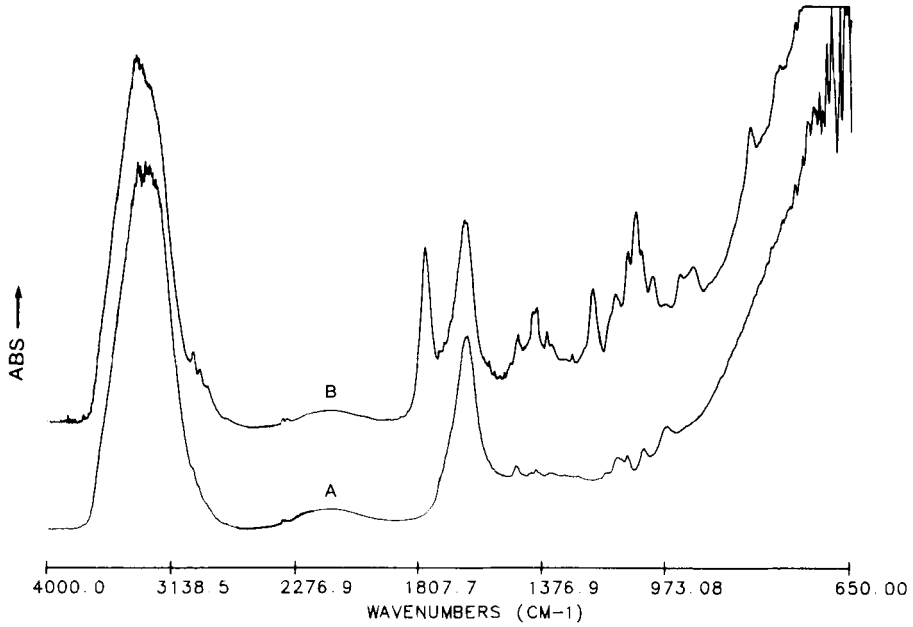

FIG. 9 - Spectrum of 10% propionaldehyde solution (A) and an aqueous solution of 10% propylene carbonate, 10% allyl alcohol, 10% propylene oxide, 10% propionaldehyde and 10% propylene glycol (B).

water. Figure 10 shows the subtraction result of the mixture of propylene carbonate and its degradation products minus the solution of propionaldehyde. The difference spectrum shows the interference-free carbonyl of propylene carbonate.

In conclusion, the FT-IR/ATR technique presented has been shown to be useful as a noninvasive and stability-indicating assay method for the determination of propylene carbonate in pharmaceutical formulations. The precision of the technique is comparable to that of

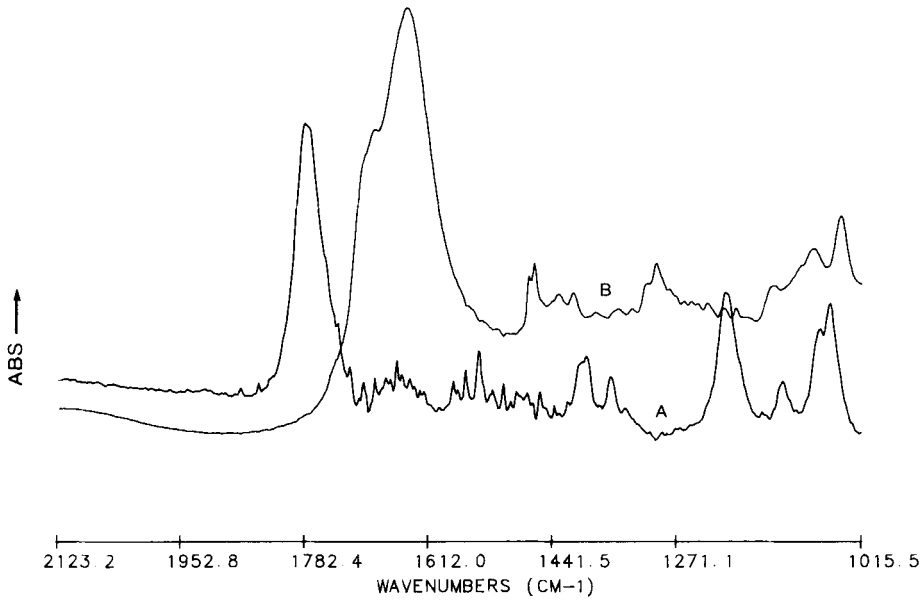

FIG. 10 - Subtraction result of aqueous solution of propylene carbonate and degradation products minus 10% propionaldehyde (A), and spectrum of 10% aqueous solution of propionaldehyde (B).

other methods (4) with a coefficient of variation of 1.24%, yet no sample preparation is required.

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