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COMMUNICATION

Physical Structure Characterization of Theophylline in Some Acidic Film-Forming Polymers

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ABSTRACT

The physical structure and drug-polymer interactions of theophylline in Eudragit L100, shellac, polyvinyl acetate phthalate (PVAP), cellulose acetate phthalate (CAP), hydroxypropylmethylcellulose acetate phthalate (HPMCP), and hydroxypropylmethylcellulose (HPMC) were studied. The drug-polymer films were prepared by casting and were characterized using powder X-ray diffractometry (PXRD), nuclear magnetic resonance (NMR) spectroscopy, and thin-layer chromatography (TLC). Theophylline was found to recrystallize in the modification II form in all kinds of polymers, which was the same as that recrystallized solely from the solvent system and the original powder. The PXRD and NMR results indicated a superficial drug-polymer interaction between theophylline and Eudragit L100, while there was no evidence of interaction for the others. No drug decomposition was observed by TLC for all drug-polymer mixtures.

Key Words: *Acidic film polymers; Drug-polymer interactions; Physical structure characterization; Theophylline.*

INTRODUCTION

Various film polymers have been used widely in film coating formulations and in the development of sustained-release or site-specific-release dosage forms. Such polymers have been reported to interact with numerous drugs in drug-polymer mixtures (1–5), which may create problems in stability, release characteristics, bioavailability, and pharmacological activity of the drug. The objective of this study was to examine the possibility of any

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molecular interaction between the basic drug theophylline and some acidic polymers commonly used in film coating and sustained-release formulations. Powder X-ray diffractometry (PXRD), nuclear magnetic resonance (NMR), and thin-layer chromatography (TLC) were used for the examination.

MATERIALS

Theophylline was obtained from Knoll AG, Ludwigshafen, Germany. Eudragit L100, shellac, and hydroxypropylmethylcellulose acetate phthalate (HPMCP) were from Rohm GmbH Chemische Fabrik, Darmstadt, Stroever Schellack ''SSB,'' Bremen, and Syntapharm, Mülheim-Ruhr, Germany, respectively. Polyvinyl acetate phthalate (PVAP) and HPMC (Methocel E5 Premium EP) were from Colorcon Limited, Königstein, Germany. Cellulose acetate phthalate (CAP) was from Eastman Chemical Products, Kingsport, TN. Isopropanol and acetone were from E. Merck, Darmstadt, Germany.

METHODS

Preparation of the Drug-Polymer Mixtures

The 30-ml portions of drug-polymer mixtures at 0%, 10%, 30%, 50%, 70%, and 100% w/w of theophylline in 2% w/v polymeric solutions (Eudragit L100, shellac, PVAP, CAP, or HPMCP in 1:1-isopropanol:acetone (by volume) and HPMC in 1:1:2-isopropanol:acetone:water [by volume]) were cast onto a petri dish covered with a polytetrafluoroethylene (PTFE) film tape (Scotch type 5480, 3M, USA). The petri dish was placed in a vacuum oven at room temperature set at 200 mbar until the solvent was completely removed. Dried films were kept in glass containers protected from light and were stored in a desiccator at room temperature until use.

Physical Structure Characterization of the Drug-Polymer Mixtures

A PXRD (Stoe and CIE GmbH, Darmstadt, Germany) was utilized. The measuring unit worked with a rotating anode in the transmission technique with the following specifications: $CuK_{\alpha 1}$ radiation, carbon monochromator, 40 kV voltage, 200 mA current, position scanning detector (PSD), scanning rate 10 sec/°2θ over a range of 5°–50° 2θ. The ^{1}H-NMR spectra were determined using a NMR spectrometer (300 ARX, Bruker-Franzen Analytik GmbH, Bremer, Germany) at 300 K employing dimethylsulfoxide as a solvent. TLC was carried out using a 0.25-mm silica gel TLC plate with fluorescent indicator (Polygram SIL G/UV_{254}, Macherey-Nagel GmbH and Co., Düren, Germany). The mobile phase was 9:1-methylene chloride:methanol (by volume), and the spots developed were visualized under ultraviolet light.

RESULTS AND DISCUSSION

Effect of Solvent Systems on Recrystallization of Theophylline

Basically, theophylline was found to exhibit four different polymorphs, defined as modification I, modification II, hydrate form, and unknown modification (6). The PXRD results revealed that theophylline powders recrystallized in 1:1-isopropanol:acetone (solvent system for Eudragit L100, shellac, PVAP, CAP, and HPMCP) possessed modification II, while those recrystallized in 1:1:2-isopropanol:acetone:water (solvent system for HPMC) possessed the hydrate form (Fig. 1).

Interaction Studies of Theophylline-Polymer Mixtures

The PXRD patterns of theophylline-polymer mixtures at various drug concentrations for shellac, PVAP, CAP, HPMCP, and HPMC revealed that both peak heights and sharpnesses (degree of crystallinity) were directly proportional to drug concentrations in the films, with their positions remaining unchanged. The diffractograms of drug-polymer mixtures at 50% drug for all polymers above are illustrated in Fig. 1 and show the characteristic main peaks of modification II at 3°, 13°, 23°, 25°, and 27° 2θ. It is interesting to note that theophylline recrystallized with HPMC was in the form of modification II although the solvent system used was 1:1:2-isopropanol:acetone:water, from which the drug alone recrystallized in the hydrate form, as mentioned above. Neither splitting nor shifting of the peak was observed for all of these theophylline-polymer mixtures, indicating no formation of a new chemical bond between the drug and polymers.

Figure 2 illustrates the diffractograms of theophylline–Eudragit L100 mixtures at various drug concentrations, which also exhibit the same behavior as those of the above polymers in that the peak intensities are pro-

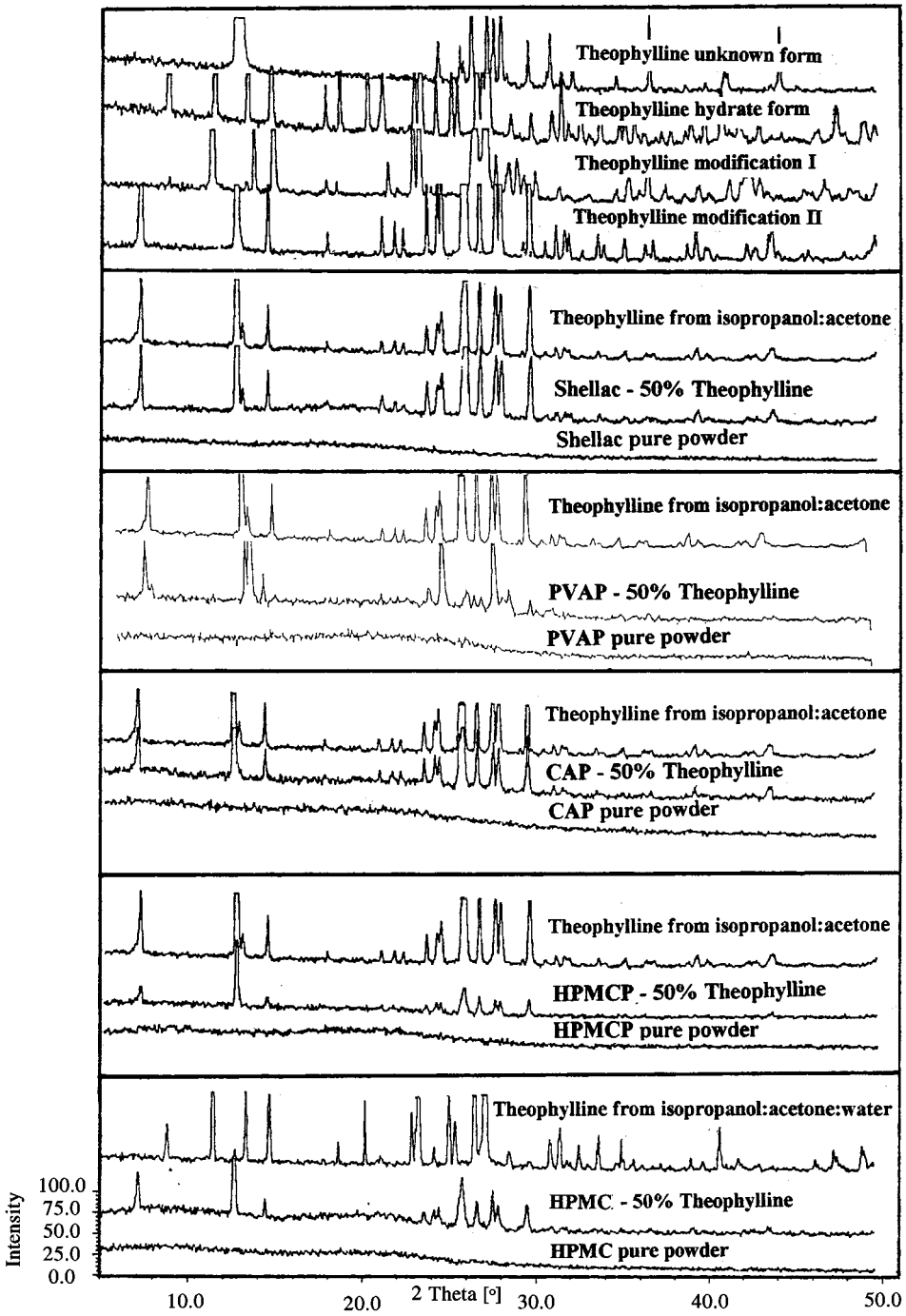

Figure 1. PXRD diffractograms of theophylline-polymer mixtures for shellac, PVAP, CAP, HPMCP, and HPMC at 50% theophylline concentration.

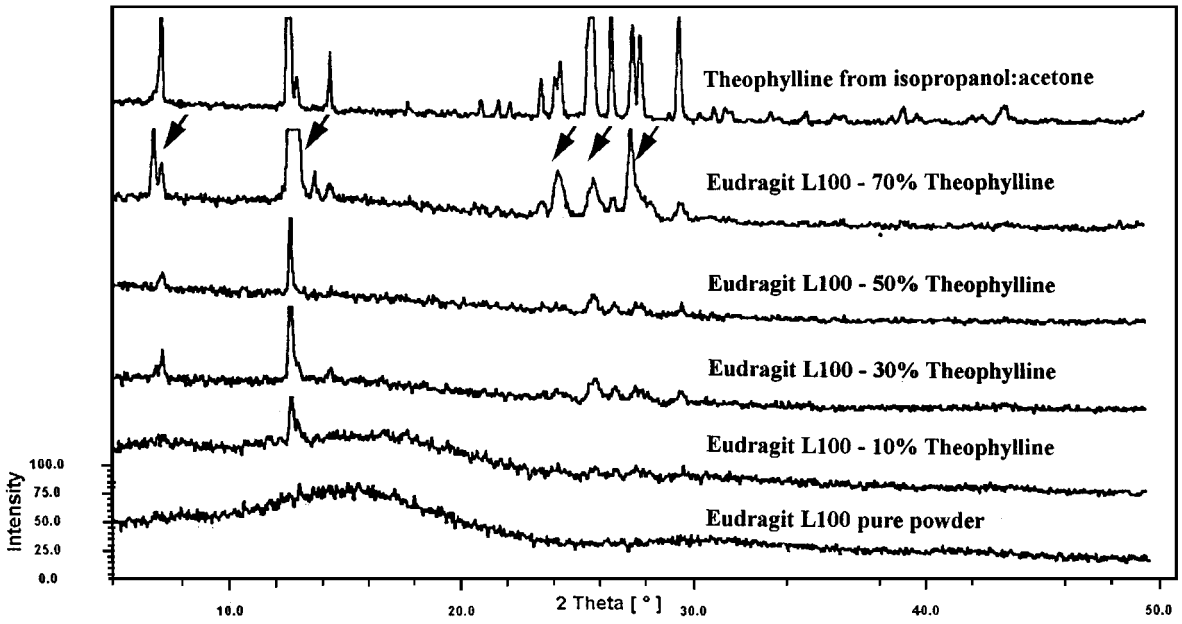

Figure 2. PXRD diffractograms of theophylline–Eudragit L100 mixtures at various drug concentrations.

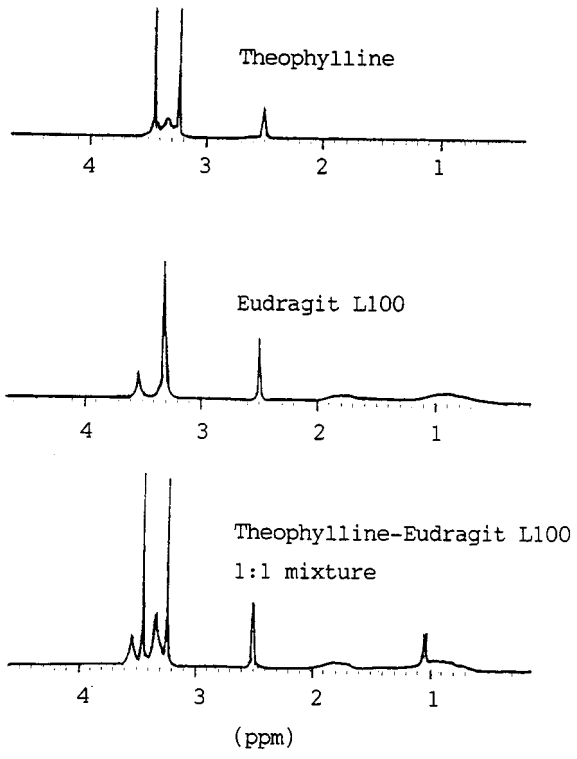

Figure 3. ^{1}H-NMR spectra of 1:1 theophylline:Eudragit L100 mixtures.

portional to drug concentrations in the film. The crystalline form of theophylline dispersed in Eudragit L100 film was also similar to that recrystallized solely from the solvent mixture, that is, it was the modification II type. The splitting of the peak at about 3° 2θ and the differences in peak intensities (marked by arrows) suggest that a drug-polymer interaction may occur at the surface of dispersed crystalline theophylline with low binding tendency, which may somehow lead to drug decomposition.

Further investigation of any possibly superficial interaction between theophylline and Eudragit L100 in the mixture was conducted using ^{1}H-NMR; the spectrum of their 1:1 mixture is compared with those of pure drug and polymer in Fig. 3. Although the NMR spectrum of the mixture generally seems to be the combination of the spectra of both theophylline and Eudragit L100, it can clearly be seen that the peak intensity of Eudragit L100 at about 3.30 ppm is greatly reduced along with an emergence of a new small peak at about 1.05 ppm. These δ values of chemical shift suggest a mild secondary valence binding between theophylline and Eudragit L100. The most probable mild interaction taking place would be between the –NH proton of theophylline and –CO–O– group of Eudragit L100. However, no significant decomposition of theophylline due to such weakly mutual bonding was found using TLC.

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