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Report

Physical State of Misoprostol in Hydroxypropyl Methylcellulose Films

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Scanning electron (SEM) and light microscopy (LM), differential scanning calorimetry (DSC), and dynamic mechanical analysis (DMA) techniques were utilized to determine the miscibility of misoprostol and HPMC in the films with a misoprostol content from 0 to 29%, prepared using ethanol and methylene chloride/methanol ($MeCl_2$/methanol, 50:50). Transmission infrared (TIR) analysis was used to look for evidence of any interaction between misoprostol and HPMC. The LM and SEM analysis of the ethanol cast films indicated no oil droplets. The DSC thermograms of the films showed no evidence of a −33°C transition, which is characteristic of pure misoprostol. The DMA showed that the glass–rubber transition temperature (T_g) of the pure HPMC was lowered from 163 to 125–130 and 85–87°C in the presence of 10 and 27–28% misoprostol. Based on these results it is suggested that misoprostol is solubilized in HPMC at concentrations up to 29%. The TIR analysis of the films showed no evidence of interaction between misoprostol and HPMC.

KEY WORDS: scanning electron microscopy (SEM); transmission infrared (TIR); differential scanning calorimetry (DSC); dynamic mechanic analysis (DMA); misoprostol; hydroxypropyl methylcellulose (HPMC); film.

INTRODUCTION

Misoprostol, a synthetic prostaglandin, is indicated for the prevention of NSAID-induced gastric ulcers. The compound is an oil at room temperature. While misoprostol is highly unstable in the pure oil state, its stability is significantly enhanced in a hydroxypropyl methylcellulose (HPMC) (1:100) dispersion (the first-order rate constant of misoprostol degradation for oil at 55°C is about 84 times greater than that of the dispersion) (1). It is important that the physical state of misoprostol in HPMC be determined to understand the mechanism of enhanced misoprostol stability in HPMC (1).

If misoprostol and HPMC are not miscible, then the resultant dispersion should contain two phases. In such a dispersion, only the oil droplets buried within the polymer should be protected from degradation, as long as the polymer is in the glassy state (2,3). If misoprostol oil is miscible with the polymer, then a solid solution results. In such a solid matrix, the stability of misoprostol is expected to be at a maximum due to low mobility of the reactants in the glassy medium (4). Further, if any specific interactions, such as complexation, exist between misoprostol and HPMC, these may enhance the stability of misoprostol in the dispersion.

Thermal analytical methods, such as differential scanning calorimetry and dynamic mechanical analysis, are routinely employed to determine the effect of solutes, solvents, and other additives on polymer thermomechanical properties (T_g, melting point, etc.) (5–8). In a solid dispersion with miscible components, the T_g and melting temperatures corresponding to the pure exicipients are shifted or lost (5–7). However, if the components are immiscible, such measurements show transitions corresponding to pure components (5,9). Further, in a mixture with an immiscible oil component, droplets of the oil should be detectable using light and scanning electron microscopic techniques (2,3). The infrared technique is powerful in detecting interactions, such as complexation and hydrogen bonding, in both the solid and the solution state (10,11).

In this study, HPMC films containing 0 to 29% misoprostol were prepared using either ethanol or $MeCl_2$/methanol (50/50) as the solvents. The physical properties of the above films were examined by light and scanning electron microscopy, differential scanning calorimetry, dynamic mechanical analysis, and transmission IR techniques to determine the physical state of misoprostol in HPMC. Misoprostol has the structure shown in Scheme I.

MATERIALS AND METHODS

Materials

Misoprostol was synthesized by Searle. HPMC (3cps)

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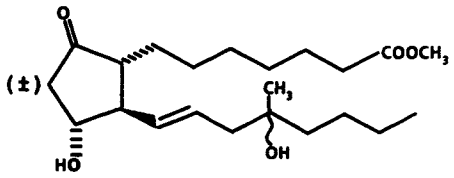
MISOPROSTOL



Scheme I

(Pharmacoat 603) was obtained from Shin Etsu Chemicals (Tokyo). The solvents used in the studies were all HPLC grade.

Film Preparations

Ethanol was employed as one of the solvents because the misoprostol/HPMC (1:100) dispersion used in the commercial tablets is prepared using ethanol. Misoprostol is soluble, whereas HPMC swells but does not dissolve in ethanol. Both HPMC and misoprostol are soluble in a 50:50 (w/w) mixture of methylene chloride ($MeCl_2$) and methanol. From the results of previous stability studies, it was predicted that misoprostol should be stable in both $MeCl_2$ and ethanol during the time period employed in this study. To prepare the films, misoprostol was first dissolved in the solvent, and then HPMC was added. The HPMC–ethanol suspensions were stirred for about 4 hr. The $MeCl_2$/methanol solutions were clear after several minutes of stirring. To produce films, the solvents were slowly evaporated under ambient conditions in plastic (when ethanol was used) and in glass petri dishes (when $MeCl_2$/methanol was used) with the lids on. The relatively dry films were further dried in a 55°C oven for 24 hr. The thickness of the films varied from 0.13 to 0.29 mm.

Differential Scanning Calorimetry (DSC) Analysis

DSC thermograms were obtained using a DuPont 9900 thermal analysis system (DuPont, Wilmington, DE). The scanning rate was 20°C/min. The weights of the film samples were 8–18 mg. All DSC measurements were performed with open pans. The samples were scanned first from −70 to 125°C. After cooling to −70°C they were rescanned up to 250°C. All the DSC runs were performed in duplicate.

Light Microscopic (LM) Determinations

The determinations were performed using a Standard Zeiss microscope equipped with cross polarizers. Flakes were prepared by scraping the films.

Scanning Electron Microscopic (SEM) Determinations

Samples were attached to the aluminum SEM specimen holders with double-sided adhesive tape. The samples were then coated with a thin layer of gold–palladium, (approximately 400 Å) with an EMSCOPE sputter coater (Model SC500) (EMSCOPE Ltd, Ashford, England). The Zeiss digital scanning electron microscope (Model DSM 950) (Carl Zeiss Inc., Thornwood, NY) was operated at 4 kV. Secondary electrons were detected and used for image formations.

Dynamic Mechanical Measurements (DMA)

The dynamic mechanical properties, storage modulus, loss modulus, and tan δ of the films (~3.0 × 0.35 cm) were measured as a function of temperature, using a Rheometrics Solid Analyzer (Model RSA II) (Rheometrics Inc., Piscataway, NJ). The testing was conducted at a constant frequency of 11 Hz from −120 to 250°C and a heating rate of 2°C/min. The environmental chamber was purged with dry N_2 during the runs. The films were kept in 0% relative humidity at room temperature for 2 days before the DMA measurements. The measurements were performed in duplicate.

Transmission IR Analysis (TIR)

The TIR measurements were conducted using an IBM FTIR-32 instrument (IBM, Danbury, CT) equipped with a Bruker infrared microscope. The neat samples were placed on top of a NaCl plate (1 mm) to obtain the spectrum.

RESULTS

Appearance of the Films

All ethanol-cast films, including the control, were opaque. However the $MeCl_2$/methanol-cast films were transparent. Plasticization was evident from the texture of both the ethanol- and the $MeCl_2$/methanol-cast films.

LM and SEM Examinations

The LM and SEM examination of the flakes of 0, 9, and 29% misoprostol-containing films cast from ethanol indicated similar structures, with no indication of a misoprostol oil phase in any of the films (see Figs. 1a and b for the SEM results).

DSC Results

Pure Misoprostol and HPMC. Figures 2a and b give the DSC thermograms of misoprostol and HPMC. In Fig. 2a, the second-order phase transition at −33°C is characteristic of misoprostol.

Ethanol- and $MeCl_2$/Methanol-Cast Films. The DSC thermograms of 0 to 29% misoprostol-containing films prepared using both ethanol and $MeCl_2$/methanol were measured. The DSC result for the 29% misoprostol containing film cast from ethanol is given in Fig. 2c as an example (the results for the $MeCl_2$/methanol films were similar to the ethanol cast films). In the DSC thermograms, the −33°C transition of misoprostol was shifted in the misoprostol containing films. The broad transition between −18 and 25°C in Fig. 2c was less apparent in the DSCs of the films containing less than 17% misoprostol.

DMA Results

The DMA scans of the 10 and 27–28% misoprostol-containing films cast from both solvents are given in Figs. 3a and b, along with the DMA scan of the control film cast from ethanol. The DMA of the control film cast from $MeCl_2$/methanol was not attempted since the film was very brittle. The primary T_g of HPMC, which has a value of 163°C, was lowered to ~125–130 and 85–87°C when 10 and 27–28% mi-

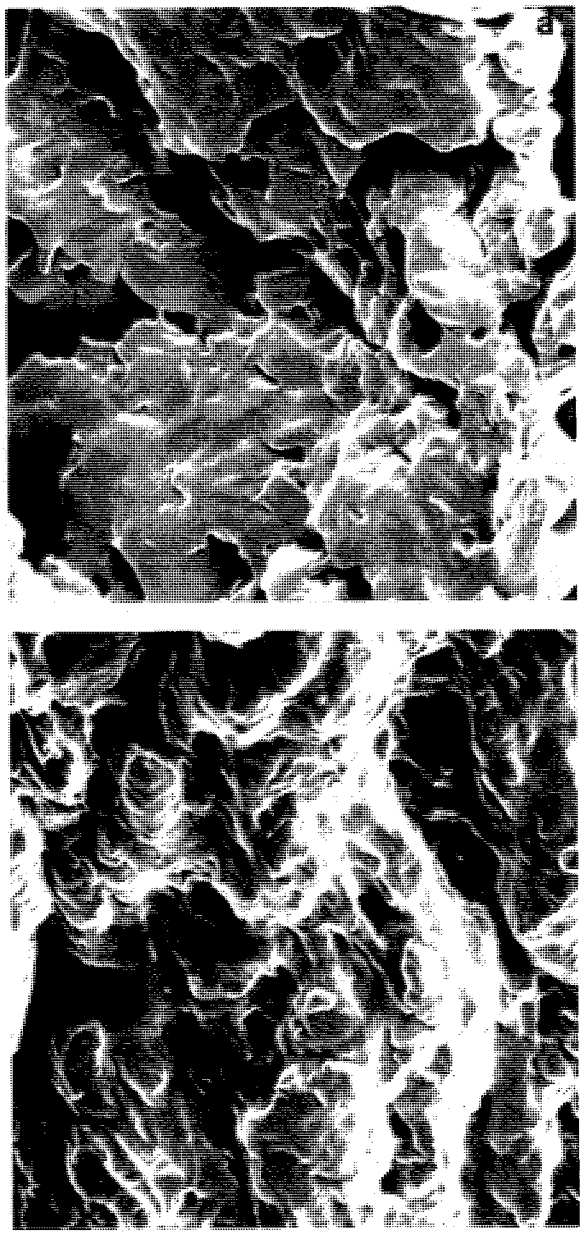


Fig. 1. (a) The SEM of flakes of HPMC film. (b) The SEM of flakes of 30% misoprostol-containing HPMC film cast from ethanol. ×2000; reduced 30% for reproduction.

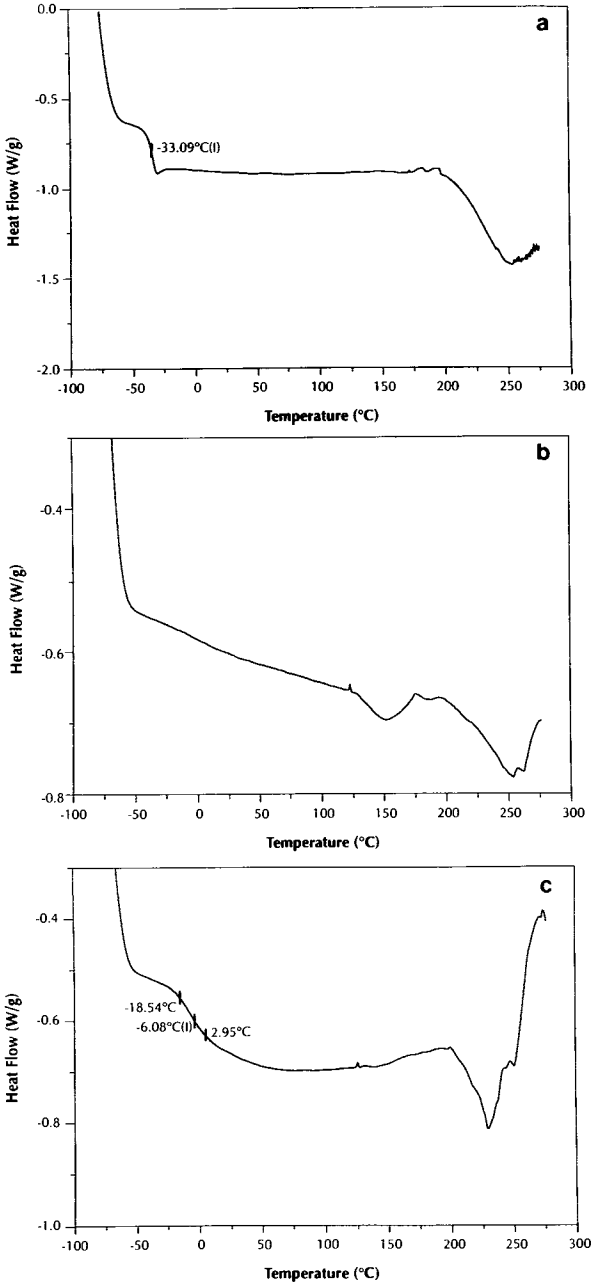


Fig. 2. (a) The DSC thermogram of pure misoprostol oil. (b) The DSC thermogram of the HPMC film cast from ethanol. (c) The DSC thermogram of the 29% misoprostol-containing HPMC film cast from ethanol.

soprostol was present in the films. In the 27–28% films, there was an additional transition at 18°C which may correspond to the broad transition seen in the DSC thermograms around the same temperature (Fig. 2c).

TIR Results

The TIR spectra of the misoprostol oil and pure HPMC film that was cast from $MeCl_2$/methanol are given in Figs. 4a and 4b (the TIR spectra of the pure HPMC film cast from ethanol was similar to that cast from $MeCl_2$/methanol). The strong band at 1740 cm^{-1} in the spectrum of misoprostol is due to carbonyl stretching of both the five-membered-ring ketone and the ester carbonyl. The difference TIR spectrum resulting from subtraction of the 0% misoprostol-containing HPMC film from the 28% misoprostol-containing HPMC film, cast from $MeCl_2$/methanol, is presented in Fig. 4c. The difference TIR spectra for the ethanol cast films were similar to that shown for the $MeCl_2$/methanol films. Also, the difference TIR spectra of the 1, 5, and 10% misoprostol-containing films were similar to those shown in Fig. 4c, except the relative intensity of the 1740 cm^{-1} peak decreased as the misoprostol content of the film decreased.

DISCUSSION

The shift in the characteristic −33°C transition of miso-

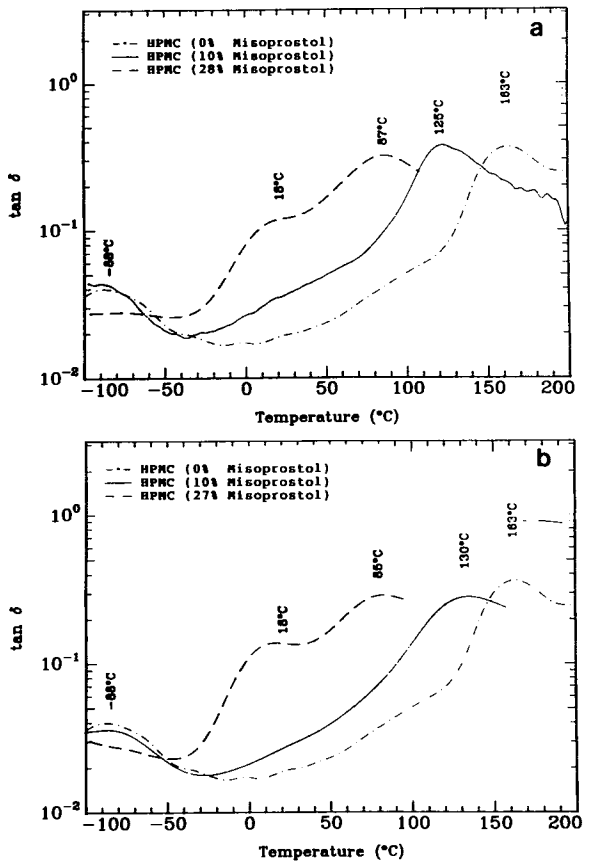


Fig. 3. (a) The DMA of 0 to 28% misoprostol-containing HPMC films. The 10 and 28% films were cast from $MeCl_2$/methanol and the 0% film was cast from ethanol. (b) The DMA of 0 to 27% misoprostol-containing HPMC films cast from ethanol.

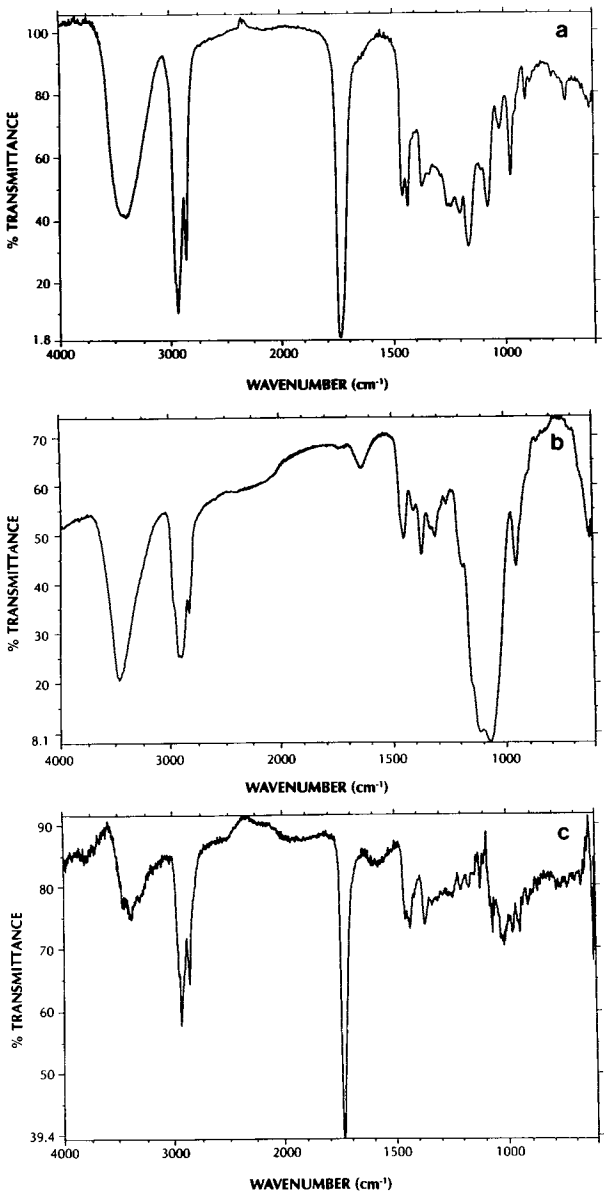


Fig. 4. (a) The TIR spectrum of pure misoprostol oil. (b) The TIR spectrum of the pure HPMC film cast from $MeCl_2$/methanol. (c) The difference TIR spectrum of misoprostol obtained by subtracting the TIR spectrum of the pure HPMC film from the 28% misoprostol-containing film cast from $MeCl_2$/methanol.

prostol to higher temperatures in the DSC of the $MeCl_2$/methanol-cast films suggests that misoprostol is molecularly dispersed in the HPMC films. In the DMA measurements, plasticization of HPMC by misoprostol in a concentration-dependent manner is further evidence for the miscibility of misoprostol and HPMC, at the concentrations used in the study.

Examination of the ethanol-cast films by LM and SEM did not indicate the presence of any oil droplets. Further, the DSC and DMA data for the ethanol-cast films were remarkably similar to the data for the $MeCl_2$/methanol-cast films. Thus it is proposed that misoprostol and HPMC are also miscible when ethanol is used as the casting solvent.

The misoprostol/HPMC dispersion (1:100) used in commercial tablet formulations is prepared using a procedure that is very similar to that employed in this study, except that ethanol is evaporated using a rotary vacuum evaporator in the commercial process. Therefore it is expected that in the 1:100 misoprostol/HPMC dispersion, misoprostol and HPMC are miscible.

The TIR data indicated that the position of the band as a result of both the ketone and the ester carbonyl stretching at 1740 cm^{-1} of pure misoprostol is unchanged in the spectra of the ethanol- and $MeCl_2$/methanol-cast films. However, the OH region of the misoprostol and difference spectra (below 1500 cm^{-1}) show some minor differences in terms of peak intensities and locations, which could be due to plasticization of HPMC by water and subtraction artifacts. Overall the TIR data suggest that there is no evidence for hydrogen bonding or complexation between the HPMC and the misoprostol carbonyl moieties, in the cast films. Similar to the findings described in this study in the solid state, the binding studies by Velasquez *et al.* found no interaction between misoprostol and HPMC in solution (12).

The observed miscibility of misoprostol with HPMC could be derived from the similarity in the polarity of the compounds. In general, the miscibility of different systems can be predicted by comparing the solubility parameter values for the components. Usually, solid materials and solvents which have similar solubility parameter values in close

ranges are likely to be miscible with each other, provided there is not a wide difference in their polarity, extent of hydrogen bonding, and other properties (14,15). Using the method described by Fedhors (14), the solubility parameters of misoprostol and HPMC were calculated as 10.8 and 11.8, respectively (based on 2 mol of methyl and 0.25 mol of hydroxypropyl substitution per mol of anhydroglucose in HPMC). This is consistent with the experimental data provided in this paper.

The plasticization of HPMC by misoprostol could be explained by the free volume theory. In this theory, the free volume is inversely proportional to the molecular weight (13). Addition of small molecules with high free volume creates excess free volume in the polymer–additive mixture. This causes increased mobility for the polymer chains and decreased T_g (13).

In conclusion, the results indicate that misoprostol and HPMC are miscible at concentrations from 0 to 29%. No evidence for specific interaction between misoprostol and HPMC which could contribute to stabilization of the misoprostol was found. It is suggested that misoprostol is stabilized by being dissolved in the glassy matrix of HPMC. The glassy matrix of HPMC should provide an efficient barrier against penetrants, such as water, which has been shown to be a catalyst in the dehydration of misoprostol.

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