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Report

Stabilization of Misoprostol with Hydroxypropyl Methylcellulose (HPMC) Against Degradation by Water

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The stability of misoprostol oil is significantly improved in a hydroxypropyl methylcellulose (HPMC) dispersion (1:100). In order to assess the effect of water on misoprostol stability, the rate of misoprostol degradation was investigated in the misoprostol/HPMC dispersion at 55°C, along with the water sorption isotherm, under seven different relative humidity (RH) conditions ranging from 0 to 81%. The results indicated that the first-order rate constants of misoprostol degradation increased in a concave-up fashion as the water content of the dispersion increased. Below 30% relative humidity (~2% water), the first-order rate constants of misoprostol degradation were found to be minimum. The results of the stability study were interpreted in terms of the changing structure of HPMC as it related to the mobility of water and misoprostol within the HPMC dispersion.

KEY WORDS: misoprostol; solid-state stability; water sorption isotherm; hydroxypropyl methylcellulose (HPMC).

INTRODUCTION

Studies described in a previous paper showed that misoprostol and HPMC are miscible at the proportions used in the study. From these results it was suggested that the increased stability of misoprostol in the HPMC dispersion could be due to decreased mobility of reactants in the glassy misoprostol/HPMC dispersion, rather than a specific interaction between misoprostol and the HPMC (1).

Several gas sorption studies in the literature suggested that at low gas pressures, penetrant molecules occupy microvoids in the glassy material (2–4). As the gas pressure increases, the dissolved water content increases and the material is gradually plasticized. During this structural change from the glassy to the rubbery state of the polymer, the diffusion coefficient of the penetrant increases significantly (5–7). In the case of water sorption in polymers, the increase in the dissolved water content, the structural change in the polymer, and the different mobility for water and misoprostol as a function of water content should influence the stability of a water-sensitive compound solubilized in the polymer. Dehydration of misoprostol, which is the first step in the degradation of the compound, is catalyzed by water (Scheme I) (unpublished results).

In this study, the correlation between misoprostol stability and HPMC–water interaction was examined in a 1:100 misoprostol/HPMC dispersion. The stability of misoprostol and the amount of water uptake were investigated at seven different relative humidity environments from 0 to 81% at 55°C.

MATERIALS AND METHODS

Chemicals

Misoprostol and misoprostol/HPMC (1:100) dispersion were prepared at Searle. To prepare the misoprostol/HPMC dispersion, HPMC was dispersed in ethanol by stirring the mixture for about an hour. Later misoprostol was dissolved in the mixture. Ethanol was evaporated with a rotary evaporator and the resultant residue was ground and then dried in a vacuum oven at 40°C, to less then 1% water content. The final product was passed through a 40-mesh sieve. All the reagents used in this study were HPLC grade.

Sample Preparation

Stability Samples. Two hundred fifty-milligram samples of misoprostol/HPMC dispersion in 50-ml plastic screw-cap tubes were placed into seven different desiccators and stored in a 55°C oven (see Table I for the list of the saturated salt solutions that were used in the study). P_2O_5 was used to achieve 0% relative humidity.

Samples for Water Content Measurements. The accurately weighed dispersion samples with a 2% initial water content in 50-ml plastic screw-cap tubes were placed into the same desiccators mentioned above. A 500-mg dispersion sample was used in the studies below 30% relative humidity and a 250-mg dispersion sample was used in the studies above 30% relative humidity. The water contents of the dispersions were measured in duplicate after 2 and 6 weeks of storage at 55°C. In addition to the 2- and 6-week samples, the water content of the samples stored at 30% relative humidity was measured on the 11th week and that of the samples stored below 30% relative humidity was measured on the 23rd week.

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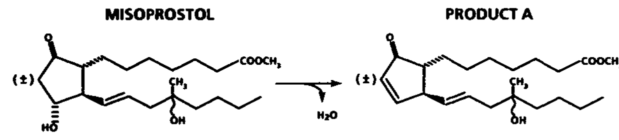

Scheme I

Analytical Method for Misoprostol

Into a 100-mg dispersion, 10 ml acetonitrile was added to extract misoprostol. After 2 hr of shaking, the mixture was centrifuged at 2000 rpm for 30 min. A 2-ml aliquot from the supernatant was dried under a gentle N_2 stream. The residue was reconstituted with 2 ml of mobile phase. The liquid chromatographic analysis was performed with a Waters 590 HPLC instrument equipped with a Waters 710B (WISP) auto sampler and a Waters 481 UV detector (Waters/Millipore, Millford, MA). A Zorbex-C8, 15 × 0.46-cm column (Dupont, Wilmington, DE), was used. The mobile phase consisted of a mixture of acetonitrile, methanol, and water (25/30/35, v/v). The flow rate was 1.5 ml/min and the injection volume was 50 μl. The detection of column effluent was performed by UV absorption at 210 nm, and peak area measurements were used for quantitation. At each time point, duplicate samples were analyzed to determine the percentage of misoprostol remaining. Intra- and interday and total relative standard deviations for the misoprostol analysis in the dispersion are 1.1, 1.5, and 1.9%, respectively.

Analytical Method for Water Content Analysis

A gas chromatographic method was developed to determine the water level in the misoprostol/HPMC dispersion. The samples were immediately capped following removal from the desiccators. The water analysis began with addition of 25 ml of dry methanol into the dispersion in the container. The mixture was sonicated for 1 min and centrifuged for 30 min at 1700 rpm. An aliquot of supernatant was removed and placed into a crimped-top auto sampler vial and analyzed using a HP 5890 gas chromatograph equipped with an 7673A Auto sampler and a thermal conductivity detector (Hewlett Packard, Rolling Medows, IL). The sample injection volume was 5 μl. A Porpak Q Glass 6-ft × 2-mm-i.d. (80–100) column was used (Waters/Millipore, Millford, MA). The oven, injector, and detector temperatures were 90, 110, and 225°C, respectively. The flow rate of helium was 35 ml/min. The water standard curves were obtained with 0.25 to 10% water levels. Peak area measurements were used for quantitation.

Table I. Saturated Salt Solutions Used in the Study

Type of salt solution	% relative humidity at 55°C[a]
NaOH	4.27 ± 0.73
LiCl	11.03 ± 0.23
$MgCl_2$	29.93 ± 0.16
$CoCl_2$	48.02 ± 1.40
$NaNO_3$	68.15 ± 0.49
KCl	80.70 ± 0.35

[a] From Ref. 8.

Data Analysis

Models were fit to both the stability and the water sorption isotherm data using the Procnonlin procedure of the statistical analysis system (SAS) (9). This procedure estimates parameters by nonolinear least squares and also calculates asymptotic standard errors of these estimates, based on the linearization of the nonlinear model.

Stability Data. Misoprostol stability data were analyzed using the following first-order model:

$$[\text{misoprostol}] = (A_{o,i}) \exp{(-k_i)t} \qquad (1)$$

where $(A_{o,i})$ is the initial misoprostol concentration and (k_i) is the first-order degradation rate constant at a given percentage relative humidity. Since the dispersion samples in each desiccator had different physical conditions, such as water content and polymer structure, a different A_o was assumed for the data at each percentage relative humidity.

Water Sorption Isotherm Data. The water sorption isotherm data were analyzed using Eq. (2), which was derived based on the concept of dual-mode sorption theory (10,11).

$$C = C_{h'}\, b\,\text{RH}/(1 + b\,\text{RH}) + K_d\,\text{RH}/(Y - \text{RH}) \qquad (2)$$

where C is the gram weight of water per 100-g weight of the dry dispersion. $C_{h'}$ is a "hole saturation" constant, RH is the relative humidity, b is a "hole affinity" constant representing the ratio of water absorption and desorption in microcavities, K_d is Henry's law constant, and Y is the activity coefficient which defines the deviation of the water solubility from ideality. The first part of Eq. (2) describes sorption according to Langmuir theory (3,10) and the second part describes sorption according to Henry's law (3,11).

RESULTS

In Fig. 1, the percentage remaining of misoprostol at 55°C is shown as a function of time at relative humidities from 30 to 81%. The stability results at relative humidities less than 30% are presented in Table II.

In Fig. 2, the measured water content of the misoprostol/HPMC dispersion is plotted as a function of the percent-

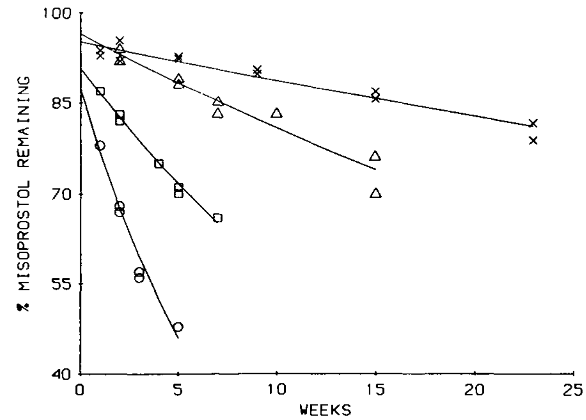

Fig. 1. The percentage remaining of misoprostol in 1:100 dispersion is plotted as a function of time at the relative humidities: (x) 30% RH, (△) 48% RH, (□) 68% RH, and (○) 80% RH. The temperature of the study was 55°C. The line that goes through the data points were obtained using Eq. (1).

Table II. Percentage Misoprostol Remaining at 55°C as a Function of Time and Percentage Relative Humidity (% RH)

	Time (weeks)				
% RH	6	10	17	23	31
0	98.0	88.7	95.0	92.2	91.0
	100.0	87.6	94.2	92.5	91.4
4.3	98.0	92.1	94.1	92.0	91.1
	92.0	92.6	93.8	93.2	91.7
11	96.0	91.3	91.9	91.0	88.7
	96.0	90.8	92.3	90.5	89.1

Table III. The Values of Constants Estimated from the Dual-Mode Sorption Model

Constant	Value (±SE)
K_d	4.68 ± 3.10
$C_{h'}$	0.50 ± 0.74
b	53.36 ± 290
Y	1.24 ± 0.32

age relative humidity (water sorption isotherm). The estimates of the parameters which were obtained from the analysis of data based on the dual-mode sorption model are given in Table III.

In Fig. 3, the estimated first-order rate constants of misoprostol degradation are plotted as a function of the water content of the dispersion.

DISCUSSION

In Fig. 1, it was shown that the rate of misoprostol degradation increases as the percentage relative humidity of the environment increases. In this study, a first-order model was selected to represent the stability data since it was previously established that misoprostol degradation follows first-order kinetics in the solid formulation (unpublished results). In Fig. 3, the estimated first-order rate constants for misoprostol degradation were found to increase in a concave-up manner as the water content of the dispersion increased. Overall, the stability of misoprostol was found to be at a maximum below 2% water levels.

In order to explain the stability results in Fig. 3, it is important to review the interaction of water with polymers as a function of increasing water content. The modified dual-mode sorption model [Eq. (2)] used for the water sorption isotherm data in Fig. 2 postulates that water is absorbed in an initially glassy polymer by two concurrent processes: (1) filling of a limited number of microcavities or holes in the glassy polymer, Langmuir mode (2,3,10); and (2) ordinary dissolution, Henry's law mode (2–4,10,11). For an initially dry polymer in the glassy state, the very first water molecules occupy the microcavities (4,12,13) and may also interact with specific sites (OH groups in the case of cellulosic polymers) (4,14). As the percentage relative humidity increases, the polymer becomes plasticized because of the increasing number of dissolved water molecules (3,4). The mobility of the sorbed molecules increases significantly upon going from the glassy to the rubbery state as a result of this relaxation (5–7). In starch, the mobility of water at 25°C was shown to increase from 10^{-10} to 10^{-7} cm^2 sec^{-1} as the water content increased from 0.8 to 100% (5).

In Fig. 3, the rate of misoprostol degradation is minimum in the region of the water sorption isotherm where the dual-mode sorption model postulates that water occupies the microcavities and interacts specifically with OH groups in HPMC ($C_{h'}$ region). Further, in the $C_{h'}$ region the mobility of water and misoprostol is expected to be relatively low in the unplasticized glassy polymer. At higher relative humidities, as the dissolved water content increases and the polymer becomes plasticized, the mobility of both water and misoprostol should increase, leading to higher rates of misoprostol degradation as seen in Fig. 3. In preformulation studies, water was found to be one of the catalysts in the dehydration of the compound. Therefore the role of water in the degradation of misoprostol is twofold, that of a plasticizer and a catalyst.

In food science, the effect of water activity on flavor entrapment (volatiles), fatty acid oxidation, enzymatic and

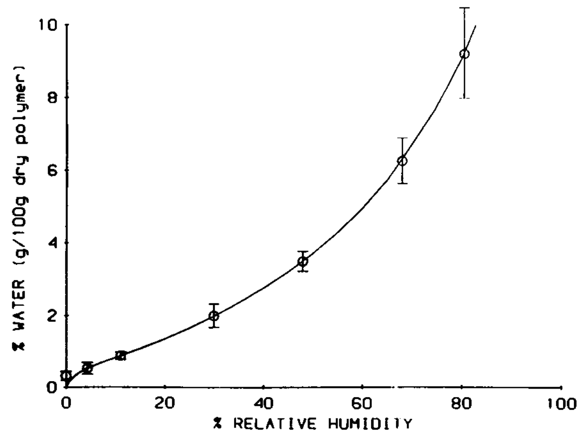

Fig. 2. The water sorption isotherm data for 1:100 misoprostol/HPMC dispersion at 55°C. The vertical bars represent the 95% confidence interval limits for the measured water levels. The line that goes through the data points was obtained using Eq. (2).

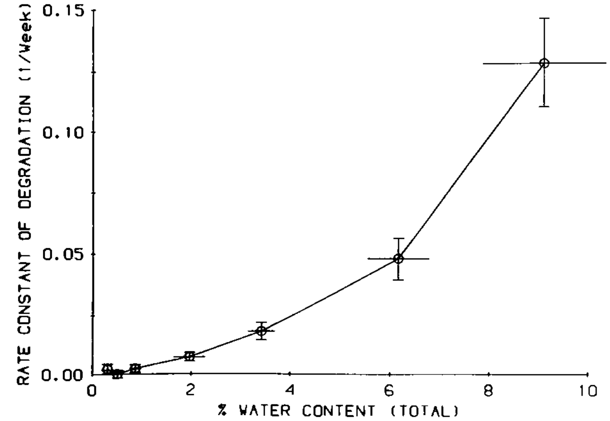

Fig. 3. The apparent first-order rate constants of degradation are plotted as a function of the water contents of the dispersion. The horizontal and vertical bars represent the 95% confidence interval limits for the water levels and estimates of the rate constants of degradation, respectively.

nonenzymatic reactions, and browning in polymeric dispersions has been widely recognized (15). It was shown that after the removal of the surface oil, no oxidation of linoleic acid could be detected if the lyophilized emulsion formulation of the oil and polymer was in the glassy state (16–18). Also, no loss of volatiles could be detected from the glassy polymers at temperatures below T_g (19–22). However, a rise in either the temperature or the moisture content, which produces a rubbery polymer, causes both fat oxidation and a loss of volatiles (16,18,19,22). Similarly, the enzymatic reaction of glucose oxidase with its substrate, glucose, could not be detected in a polymeric dispersion unless the temperature was raised above the characteristic T_g of the polymeric matrix (23).

The DMA and TMA measurements for relatively dry HPMC samples indicated a primary glass–rubber transition temperature around 160°C and a secondary transition temperature between 30 and 100°C (24,25). Using the Fox equation (26), it was estimated that the value of the primary glass–rubber transition temperature of HPMC would be lowered only to 90°C in the presence of 9% water (the highest water content measured in the isotherm data). Based on the above prediction, it does not appear that there is a direct correlation between the primary glass–rubber transition temperature in HPMC and the stability results. The secondary transitions occurring around 30 to 100°C may be playing a role here in initiating the mobility of the reactants (water and misoprostol) in the glassy HPMC. Further relaxation with increasing water content in the glassy HPMC would increase the mobility of the reactants, leading to an increased rate of misoprostol degradation. Future studies which will measure directly the mobility of the reactants as a function of water content are necessary to substantiate the validity of the hypothesis presented in this paper. Overall, our study and above studies reported in the literature point out the importance of the physical state of polymers in stabilizing food structure and drugs.

In summary, the results of the present study suggest that the stability of misoprostol in HPMC is affected by the polymer–water interactions. It is proposed that in the low-relative humidity region the stability of the compound is greatest due to low mobility for water and misoprostol in the glassy misoprostol/HPMC dispersion. In the higher-relative humidity region, the increased water content and plasticization of HPMC lead to an increased rate of misoprostol degradation.

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