Drug Development and Industrial Pharmacy, 32:377–387, 2006

ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040500519367

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Effect of Excipient and Processing Variables on Adhesive Properties and Release Profile of Pentoxifylline From Mucoadhesive Tablets

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ABSTRACT The bioavailability and onset of action of drugs with high first-pass metabolism can be significantly improved by administration via the sublingual route. The objective of this study was to evaluate the effect of polymer type and tablet compaction parameters on the adhesive properties and drug release profile from mucoadhesive sublingual tablet formulations. Pentoxifylline was selected as the model drug because it has poor oral bioavailability due to extensive first-pass metabolism. Two polymers known to possess mucoadhesive properties, carbomer and hydroxypropyl methyl cellulose (HPMC), were used to prepare the formulations. Tablets were prepared by using direct compression technique and evaluated for in vitro dissolution, drug-excipient interactions, and adhesive properties. In general, there was a decrease in the rate of drug release with an increase in the concentration of polymers. No drug-excipient interactions were evident from differential scanning calorimetry or high-performance liquid chromatography analysis. For the formulations containing HPMC, the force of mucoadhesion increased with an increase in the concentration of polymer; however, for carbomer formulations, no such correlation was observed. Force of mucoadhesion decreased as a function of hydration time in both of the polymers.

KEYWORDS Mucoadhesion, Sublingual, Adhesive force, Drug release, Carbomer, HPMC, Pentoxifylline

INTRODUCTION

The oral route is the most popular and convenient route of drug administration available. However, for a number of drugs, a high bioavailability of the drug cannot be achieved via oral administration due to rapid hepatic/extrahepatic first-pass metabolism, which might lead to the formation of therapeutically inactive entities. Moreover, exposure to acidic pH in the gastric environment could lead to degradation of the drug (Rathbone et al., 1996; Miyazaki et al., 2000). As a result, the overall bioavailability of the drug might be significantly reduced. For drugs prone to presystemic losses, one of the approaches to improve drug bioavailability could be

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the use of buccal, sublingual, or gingival routes of administration, which could effectively minimize losses due to first-pass metabolism, enzymatic degradation, and/or degradation attributable to low pH environments. In addition, these routes of administration could offer the advantage of rapid onset of drug action as the rich supply of blood vessels in the oral cavity immediately transports the drug substance to the systemic circulation.

A number of review articles (Gupta et al., 1990; Kruth et al., 1993; Smart, 2004; Birudaraj et al., 2005) have addressed the opportunities and challenges of drug delivery via the buccal, sublingual, and gingival routes. It has been reported that the sublingual route is more permeable than buccal or gingival routes and also provides superior bioavailability with faster and less erratic absorption for many drugs (Harria & Robinson, 1992). In addition, it has been described that keratinization, which could act as a substantial physiological barrier to drug absorption, is significantly less in the sublingual area (devries et al., 1991). However, disadvantages of sublingual/buccal administration include difficulties with masking the taste and smell for drugs that possess an unpleasant taste and/or smell, respectively, and potential drug losses caused by salivary washout or loss of the dosage form due to involuntary swallowing. To minimize drug losses attributable to the latter causes, the use of bioadhesive polymers has been proposed (Knuth, et al., 1993). A few mucoadhesive formulations, including isosorbide dinitrate (Risordan®, Rhone-Poulenc Rorer), prochlorperazine (Buccastem M®, Reckitt Benckiser Healthcare), and the recently FDA-approved testosterone buccal system (Striant®, Columbia Laboratories, Inc.) have been successfully commercialized.

Reviews by Lee et al. (2000) and Smart (2004) describe the various polymers currently being used in the development of bioadhesive or mucoadhesive dosage forms, most of which belong to the category of polyacrylic acid or cellulose derivatives. In addition, a number of natural polymers, such as chitosan, and natural gums, such as xanthan and alginates, have been used. For our studies, we selected a high molecular weight carbomer resin, which is a cross-linked polyacrylic acid polymer that swells to form a hydrogel in aqueous solution, along with hydroxypropyl methyl cellulose, a cellulose derivative that also forms a hydrogel in aqueous solution.

Polymer properties and their interactions with mucus membranes have been reviewed by Peppas and Buri (1985). In general, in the presence of water molecules, hydrogels produce a network-like structure that depends on the chemical nature of the polymers- and release entrapped drugs depending on their unique swelling characteristics (Peppas et al., 2000). Because the pKa of carbomers is 6.0 ± 0.5, the carboxylate groups on the polymer backbone ionize, resulting in repulsion between the negative charges, which adds to the swelling properties of the polymer (Noveon Product Info, 2005). Although carbomers produce an insoluble swollen network in aqueous medium, hydroxypropyl methyl cellulose produces a soluble gel structure. In terms of viscosity in aqueous solution, carbomers produce a very high level of viscosity compared with hydroxypropyl methyl cellulose at similar concentrations (Ahuja et al., 1997).

It is believed that the predominant mucoadhesive forces involved in the functioning of carbomers and hydroxypropyl methyl cellulose are hydrogen bonding and/or polymer chain interpenetration with the exact mucoadhesion mechanism unknown. In a comparison of the mucoadhesive force of various polymers subjected to the same conditions, carbomers were found to possess significantly higher mucoadhesive force than hydroxypropyl methyl cellulose (Smart, 1992). Previous studies have reported the use of carbomers and hydroxypropyl methyl cellulose in combination in mucoadhesive formulations (Ishida et al., 1981; Ikinci et al., 2000; Chun et al., 2003); however, we chose to study these polymers separately in the formulations of the same drug to evaluate their individual performance that is unaffected by the presence of the second polymer.

The model drug used in this study was pentoxifylline, which is available in the US market as a 400-mg extended-release tablet dosage form (Trental®, Aventis; generics). Chemically, pentoxifylline is a xanthine derivative with a pKa of 0.28 and is highly soluble in water. Pentoxifylline is well absorbed from the gastrointestinal tract (>95%), yet the actual amount of drug bioavailable to the body is only about 20% because of extensive hepatic first-pass metabolism that accounts for the loss of 60–70% of the administered dose (Raz et al., 1988) with enzymatic degradation in the blood accounting for the remaining loss. Oral extended-release formulations are designed to reduce the dose frequency to once or twice daily for enhanced patient compliance, but in pentoxifylline, this approach has not proved to be very successful because the drug continues to be prescribed three to four times a day to achieve and maintain therapeutic concentrations in the blood.

The goal of this study was to develop mucoadhesive sublingual tablet formulations of pentoxifylline and evaluate their physicochemical properties in vitro.

When used in vivo, the proposed delivery system is expected to bypass first-pass metabolism, thus improving bioavailability of the drug in animal/human models.

MATERIALS AND METHODS

Materials

Pentoxifylline was obtained from Sigma Chemical Co., St. Louis, MO. The polyacrylic acid polymer Carbopol® 974P (high molecular weight acrylic acid network polymer cross-linked with small amounts of polyalkenyl ether; glass transition temperature 100–105°C; pKa 6.0 ± 0.5; viscosity of 0.5% dispersion 29,400–39, 400 cP), henceforth referred to as "carbomer," was a gift from Noveon, Inc., Cleveland, OH. Hydroxypropyl methylcellulose (Methocel® K100M; pH of 1% solution in water 5.5–8.0; viscosity of 2% dispersion 80,000–120, 000 cP), henceforth referred to as "HPMC," was a gift from The Dow Chemical Co., Midland, MI. α-Lactose monohydrate, referred to as "lactose" was obtained from Sigma Chemical Co. Citric acid monohydrate and sodium phosphate dibasic dihydrate were obtained from Fisher Scientific, Pittsburgh, PA. Distilled filtered water, used throughout the studies, was obtained from a Nanopure® water system (0.2-μm filter; Barnstead Intl, Dubuque, IA). All the formulations were prepared and stored in the dark at room temperature in sealed and foil-covered borosilicate glass containers.

Methods

Preparation of Tablets

Flat-faced core tablets containing 200 mg of pentoxifylline were prepared by direct compression. The diameter of the die used was 13 mm, providing a potential contact area of 1.33 cm^2 for the tablets. The total tablet weight was kept constant at 300 mg. Six different concentrations of the mucoadhesive polymers, carbomer and HPMC (5%, 10%, 15%, 20%, 25%, and 50% of the inactive part, corresponding to 1.66%, 3.33%, 5%, 6.66%, 8.33%, and 16.66% w/w of the total tablet weight, respectively), were used in the preparation of tablets for a total of 12 different formulations (Table 1). Lactose was used as the bulk-forming agent, with no other excipients being used. To study the effect of compaction pressure, tablets of a selected formulation were prepared by using 500, 1000, 1500, or 2000 kg of pressure. To study the effect of the duration of compaction, tablets of a selected formulation were compacted by using 1000 kg of pressure and left in the die punch under pressure for 20, 40, 60, and 80 seconds. The thickness of the tablets was measured with a micrometer placed perpendicular to the diameter. All the tablets were stored for 48 h or more to allow for adequate stress relaxation before any tests were conducted on them. Tablet hardness was measured by using a Pfizer hardness tester, and six determinations were averaged.

Characterization of Tablets

In Vitro Dissolution

In vitro dissolution studies were conducted in paddle-type USP dissolution apparatus Type II (VK 7010, Varian, Cary, NC) to study the effect of polymer type and concentration and compaction parameters on drug release. The medium used for these dissolution tests was 900 mL of double-distilled, degassed water

TABLE 1 **Composition of Pentoxifylline Formulations Studied**

Formulation ID	Pentoxifylline (mg)	Carbomer (mg)	HPMC (mg)	Lactose (mg)
CARB5	200	5		95
CARB10	200	10		90
CARB15	200	15		85
CARB20	200	20		80
CARB25	200	25		75
CARB50	200	50		50
HPMC5	200		5	95
HPMC10	200		10	90
HPMC15	200		15	85
HPMC20	200		20	80
HPMC25	200		25	75
HPMC50	200		50	50

per vessel, maintained at 37 ± 0.5°C. The paddle rotation speed was set at 100 rpm. Samples were collected at predetermined time intervals (5, 10, 20, 40, 60, 120, 240, 360, 420, and 480 min) with an auto sampler fraction collector, and the aliquots were analyzed for drug content with use of an UV spectrophotometer (Lambda Bio, Perkin Elmer, Shelton, CT) set at 273 nm (The Merck Index, 1996). All dissolution studies were conducted in six replicates to ensure a high sample power and confidence in the results. A 400-mg commercial generic extended-release matrix-type tablet of pentoxifylline was cut in half to obtain the 200-mg commercial counterpart to our formulation, and dissolution tests, in six replicates, were conducted on the halved tablets. The dissolution results from the commercial formulation were used as the control for statistical analysis.

Differential Scanning Calorimetry

The stability and compatibility of the matrix materials (polymers and lactose) with the drug were studied by using a differential scanning calorimeter (MDSC 2920, TA Instruments, New Castle, DE). The tablets were gently crushed using a mortar and pestle, and approximately 10-mg sample was crimped in flat aluminum pans with an empty pan serving as the reference. The pans were ramp heated from 25 to 300°C at the rate of 10°C/min. Similar studies were done on each individual component of the formulations, and their thermograms were compared with those obtained from the compacted tablet formulations.

Adhesive Force

The adhesive properties of the formulations were studied by using a texture analyzer (TAXT2i, Texture Technologies Corporation, Scarsdale, NY). The calibration and analytical methods used were similar to methods described by Tobyn et al. (1995). Specifically, tablets were immobilized in a custom-designed Perspex ring with double-sided adhesive tape and hydrated by using 200 µL of Mcllvaine buffer (17.65 mL of 0.1 M citric acid, added to 32.94 mL of 0.5 M dibasic sodium phosphate and 40.41 mL water, adjusted to pH 6.8 and stored at 4°C), which was spread quickly and evenly on the exposed surface. The measurement probe was brought in contact with the hydrated tablet surface at a speed of 0.5 mm/sec and a force of 5 g was applied for 20 sec. The force of detachment of the probe from the tablet surface was measured at 1, 3, 5, 10, 20, and 25 min following hydration.

High-Performance Liquid Chromatography

A modified high-performance liquid chromatographic (HPLC) analysis was developed for pentoxifylline based on a method described by Srinivasu et al. (1999). The mobile phase consisted of an 18:81.9:0.1 mixture of acetonitrile, water, and acetic acid, set at a flow rate of 1 mL/min. A Symmetry® C_{18}, 3.5 µm, 4.6 × 150 mm column (Waters, Milford, MA) was used with a high-performance liquid chromatograph (Waters 2487 Dual Absorbance UV Detector, Waters 1525 Binary HPLC pump, Waters 717 plus Autosampler, Millennium® 32 data acquisition software), with the detector set at a wavelength of 274 nm. Samples were diluted with an equal part of mobile phase, and a 20-µL sample mixture was injected into the pump by using the autosampler. The dilution with the mobile phase was done to make the sample more polar and to ensure better retention and separation. Samples from dissolution studies were analyzed, and the data were studied for possible drug-excipient interactions.

Data Analysis

Statistical analysis was performed with SAS® software (SAS Institute, Cary, NC). Tukey-Kramer's adjustment, which controls the experimentwise error rate at the $\alpha = 0.05$ level, was used to determine significance among all possible pairs of formulations and interactions. At $P \leq 0.05$, data were considered to be significant. For the in vitro dissolution analyses, the time points of measurement up to 240 min were compared for statistical purposes as the in vitro release profile after the 4 h time point assumes limited importance from a clinical standpoint. Formulations that required longer durations to release the total drug content were rejected during the formulation selection process which was aimed at future in vivo studies, owing to practical considerations for reasonable residence time in the sublingual region, with or without mucoadhesion.

RESULTS AND DISCUSSION

Preparation of Tablets

The tablets were easy to remove from the die cavity regardless of the compression conditions, indicating that within this experimental setup there was no need to add a lubricant to the formulations. The compacts had smooth, shiny surfaces and experienced no capping or chipping, particularly around the edges. The thickness

of the tablets averaged 2 mm and was considered appropriate for sublingual application. As anticipated, the hardness of the tablets increased with an increase in the concentration of the polymers. The hardness of the carbomer containing tablets ranged from 7.3 to 9.7 kg and that for the HPMC containing tablets ranged from 6 to 8.6 kg, indicating that carbomers may offer slightly superior binding properties compared with HPMC.

In vitro Dissolution

Effect of Polymer Concentration on Drug Release

In general, regardless of the polymer type, the rate and extent of drug release decreased with an increase in the concentration of the polymer. Figure 1A shows the percentage of drug released from the formulations containing various concentrations of carbomer. As seen in Fig. 1A, the experimental tablets containing carbomers exhibit a faster rate of drug release than the control. The control formulation required an average of 8 h to release the total amount of drug, which could be considered a desirable release profile for a sustained release preparation. However, in pentoxifylline, any amount of orally absorbed drug is expected to undergo rapid metabolism, and it is plausible that formulations that gradually release small amounts of drug over a long duration may actually lead to subtherapeutic plasma concentrations and require frequent dosing to sustain adequate plasma levels of the drug. Formulations CARB5 and CARB10 released approximately 98% and 82% of the drug, respectively, within the first 20 min. For formulations CARB20, CARB25, CARB50, the amount of drug released was not significantly different from the control up to 1 h. However, at 2 h or longer, the drug release from all carbomer formulations, with the exception of CARB50, became significantly different from the control. Statistically compared, up to 1 h the cumulative percent drug release from formulation CARB15 significantly differed from the experimental formulations containing smaller amounts of carbomer; at the subsequent time points, no difference was observed. As is further evident from Figure 1A, formulations CARB20, CARB25, and CARB50 released 26%, 18%, and 14% drug, respectively, within the first 20 min and required approximately 4 h to release 100% of the drug. From a patient convenience perspective, having the tablet positioned under the tongue for 4 h or longer to ensure complete drug release may not be a practical option (or necessary), regardless of the mucoadhesive properties of the formulation. Therefore, for future in vivo studies, we only selected formulations that were capable of releasing 100% of the drug within approximately 2 h.

Figure 1B shows the release profiles of HPMC containing formulations of pentoxifylline. With the exception of formulation HPMC50, an initial burst release was observed for all HPMC formulations, and the differences in cumulative percent release, compared with the control, were statistically significant for every time point up to 4 h. Formulations HPMC5 and HPMC10 released more than 90% of the drug within the first 20 min, and there was no statistically significant difference in the release

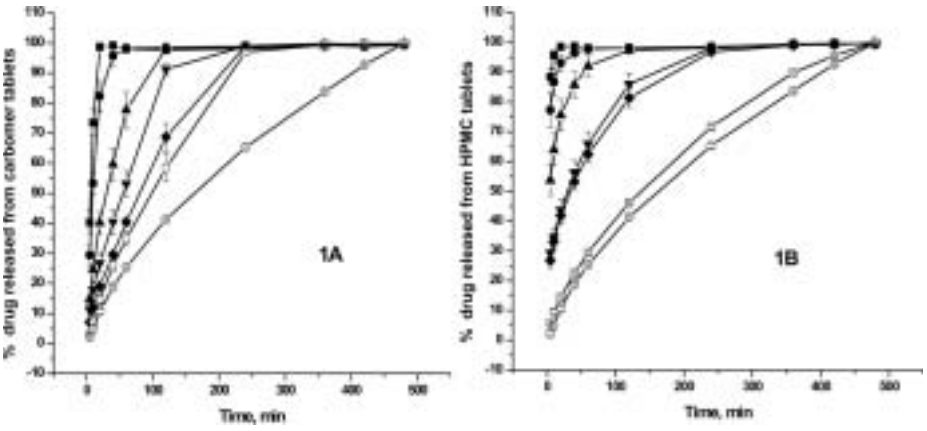

FIGURE 1 Cumulative percentage drug release (average ± SEM, n = 6) from formulations containing various concentrations of carbomer (A) and HPMC (B); ■ 5%, ● 10%, ▲ 15%, ▼ 20%, ◆ 25%, and □ 50% polymer in the inactive component of the formulation; ❍ represents the control (commercial formulation).

profiles for these two formulations. For formulation HPMC15, although the burst release was less pronounced than tablets containing smaller amounts of HPMC, the drug release profile did not significantly differ from them. Formulation HPMC15 released the entire drug content within 2 h, whereas HPMC20 and HPMC25 required up to 4 h for 100% drug release. The cumulative percent release from formulation HPMC15 significantly differed from HPMC20 and HPMC25 up to 1 h; however, at 2 h and beyond, there was no statistically significant difference in drug release pattern among the three formulations. Nevertheless, the release pattern from each of these formulations differed significantly from formulation HPMC50, as well as the control. Formulation HPMC50 required approximately 8 h to release 100% of the drug content. It is of interest that the release profile of this formulation was observed to be very similar to that of the control with no statistically significant differences, indicating that the commercial generic tablet of pentoxifylline, which is known to contain HPMC, perhaps contains comparable levels of the polymer in formulation.

Effect of Polymer Type on Drug Release

When different polymers are used for essentially the same purpose, such as mucoadhesion in the current study, it is interesting to observe how the polymers compare with each other. With the exception of formulation HPMC50, the drug release profiles from the carbomer formulations (Fig. 1A), compared with those from HPMC formulations (Fig. 1B), indicate a trend for rapid drug release from HPMC formulations. When formulations with different polymers but the same polymer content were compared with each other (i.e., CARB5 vs. HPMC5), the only formulations whose overall release profile significantly differed from each other were CARB50 and HPMC50. However, although the overall release profiles did not vary significantly between the carbomer and HPMC formulations containing low concentrations of polymer, an initial fast-release effect was observed with the HPMC formulations compared with a gradual-release profile for the carbomer formulations. This might be due to the fact that the conversion of the carbomer from the glassy to rubbery state, caused by inward flux of water, was much slower than HPMC. Nevertheless, within the experimental framework used in this study, the two polymers appeared to be interchangeable in formulation to achieve similar drug release profiles.

Our overall results indicate that at higher concentrations, HPMC functioned as a better retardant of drug release than carbomer; however, the carbomer is a better retardant of drug release than HPMC at lower concentrations (≤25% of the inactive component of the formulation). This is perhaps due to the swelling controlled relaxation of the hydrated carbomer molecules that may have reached a threshold level and could not retard the drug release any further once a certain concentration of polymer had been achieved in formulation (in this specific case, >25% of the inactive component of the formulation). This was similar to the observation by Ponchel et al. (1987) and may be attributable to the phenomenon of diffusion of the drug through a three-dimensional network of gel structure formed by water influx into the tablet. Thus, any differences in drug release profiles between carbomer and HPMC tablets could also be attributable to the differences in the nature of the formation of their gel networks.

Effect of Compaction Pressure and Compaction Time on Drug Release

We selected the 15% concentration level of either polymer in the inactive component of the formulation to evaluate the effect of compaction pressure and compaction time on drug release. As observed from Fig. 2 and 3, compaction pressure and compaction time did not have any significant effect on the rate of drug release from formulations containing either polymer.

Study of Drug-Excipient Interactions

Any interaction between the drug and the polymer or lactose could cause potential degradations or affect the subsequent therapeutic efficacy of the drug. Differential scanning calorimetry studies were done to monitor for any interactions between the drug and the excipients in terms of thermal parameters. Figure 4 shows the collective thermograms for all the carbomer formulations that were compared with the thermograms of the individual formulation components. Significant shifts in the endotherms and/or appearance of new endo- or exotherms would be indicative of possible interactions between the drug and the excipients; however, none were observed. The melting point of

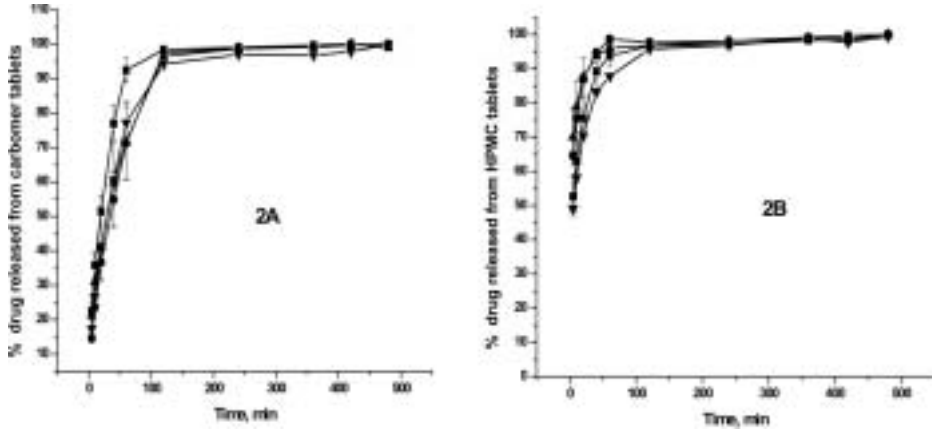

FIGURE 2 Effect of compaction pressure on cumulative percentage drug release (average ± SEM, n = 3) from formulations containing 15% carbomer (A) and 15% HPMC (B) in the inactive component of the formulation; ■ 1/2 ton, ● 1 ton, ▲ 1.5 ton, and ▼ 2 ton pressure.

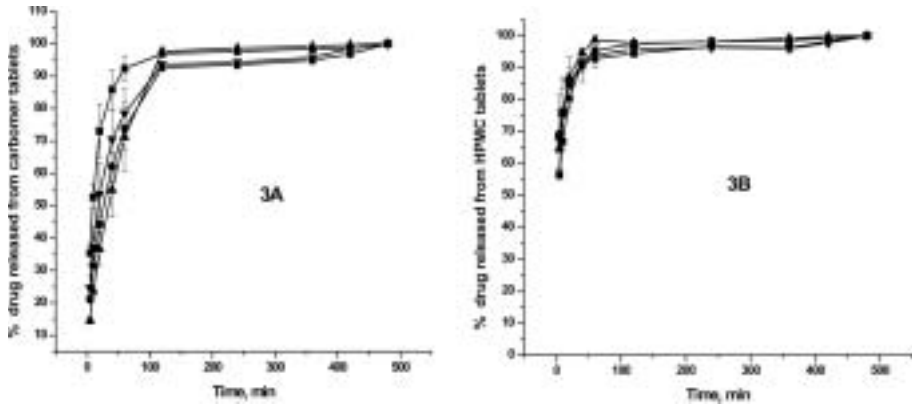

FIGURE 3 Effect of compaction time on the cumulative percentage drug release (average ± SEM, n = 3) from formulations containing 15% carbomer (A) and 15% HPMC (B) in the inactive component of the formulation; ■ 20, ● 40, ▲ 60, and ▼ 80 seconds.

pentoxifylline is reported to be 103–107°C (Raz et al., 1988). Examination of the thermogram in Fig. 4 reveals that the melt endotherm of pentoxifylline occurred at 104°C. Lactose depicted two endotherms, one of which was at its melting point around 150°C and the second at 215°C, which was likely due to decomposition that resulted in charring of the samples in and around the crimped edges of the pans. The carbomer showed an endotherm with an onset at 237°C, which is likely to be its melt, followed by decomposition.

The results of similar differential scanning experiments for all HPMC formulations are presented in Fig. 5. HPMC revealed a broad endotherm with onset around 100°C and peaking at about 150°C. The broad and blunt pattern of this endotherm could be indicative of higher mobility or chain flexibility for HPMC molecules, when compared with carbomer, for the nonhydrated state of the two polymers. No significant shift in the endotherms or the appearance of new peaks or disappearance of anticipated peaks were observed for any of these studies, which indicates that there is no likely interaction of the drug with either of the polymers, carbomer or HPMC, or with lactose.

We also conducted HPLC experiments to confirm the lack of drug-excipient interactions. Although the simpler technique of UV spectroscopy was used to analyze all the dissolution study samples, the HPLC analysis was simultaneously developed with the aim of analyzing plasma samples in future in vivo studies. In the current study, we used the same analytical method to investigate for potential drug-excipient interactions that may have occurred in the solid state during the mixing and direct compression processes, anticipating

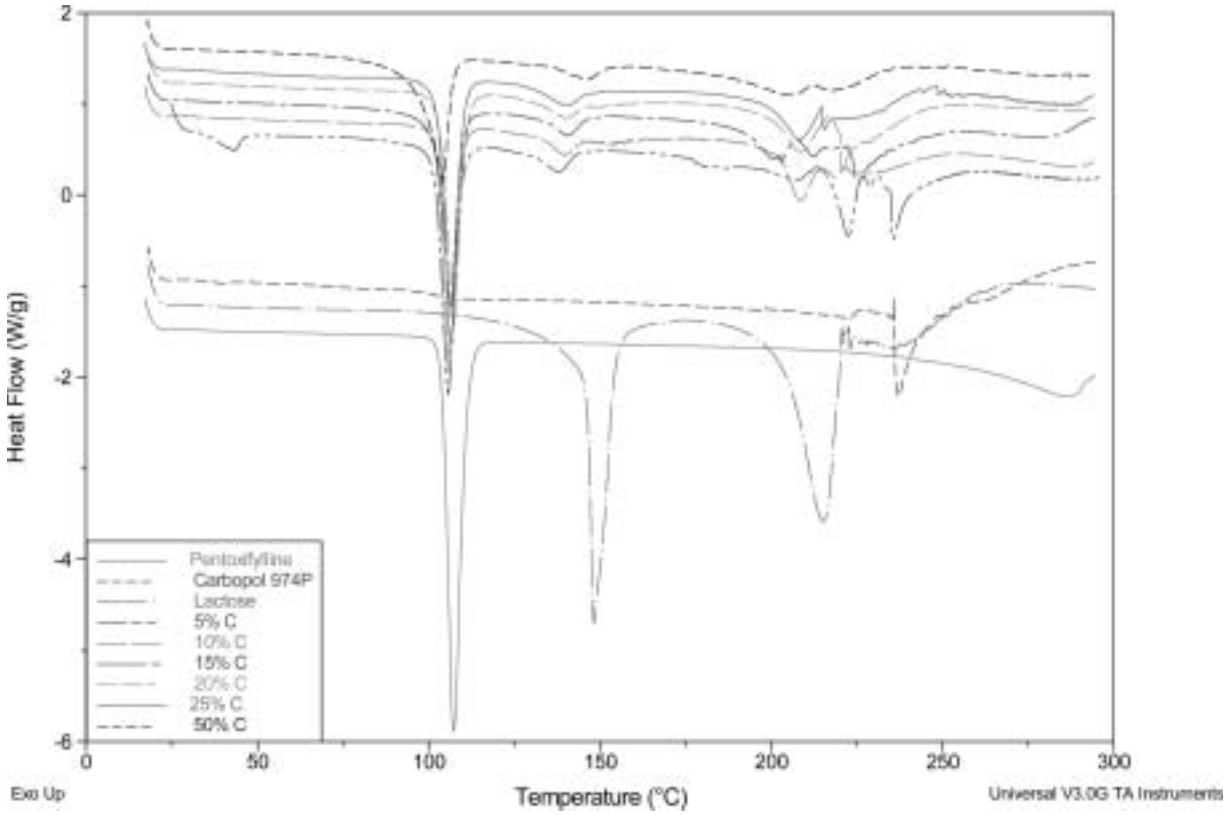

FIGURE 4 **Thermograms of formulations containing carbomer, compared with thermograms of the individual components of the formulations.**

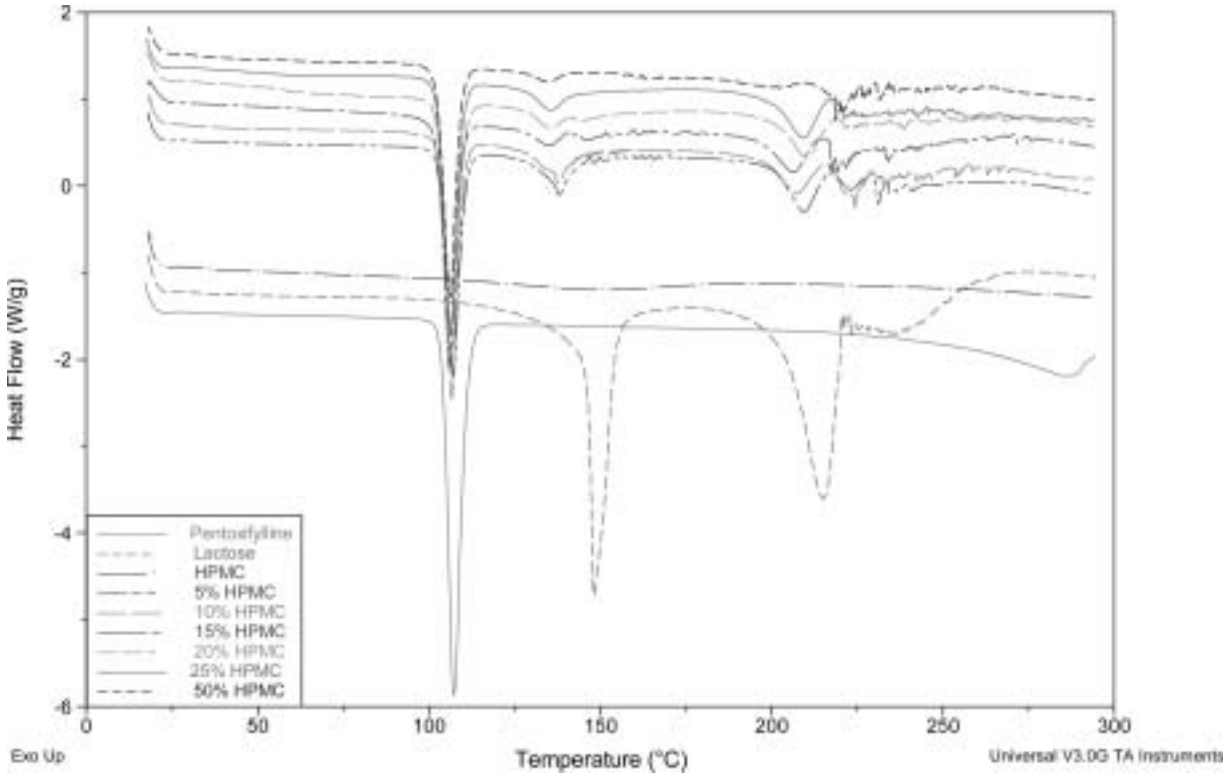

FIGURE 5 **Thermograms of formulations containing HPMC, compared with thermograms of the individual components of the formulations.**

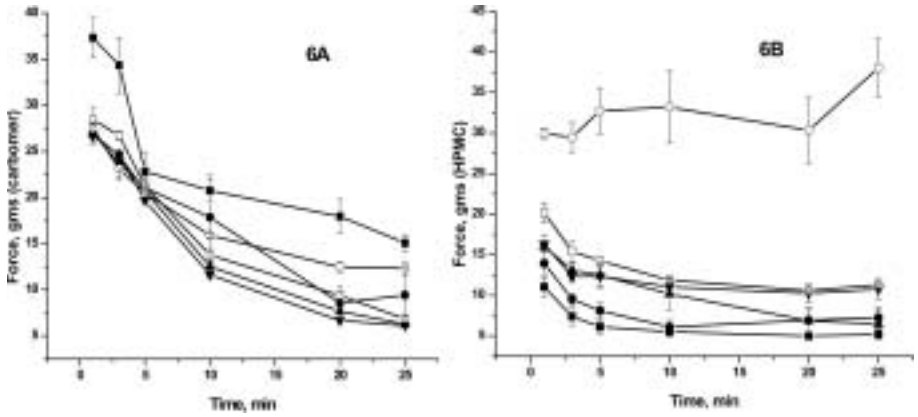

FIGURE 6 **Relationship of mucoadhesive force (average ± SEM, n = 3) with time of hydration for formulations containing various concentrations of carbomer (A) and HPMC (B); ■ 5%, ● 10%; ▲ 15%, ▼ 20%, □ 25%, and ❍ 50% polymer in the inactive component of formulation.**

that a structural change would reflect on the retention time and/or peak shape of pentoxifylline. The retention time was noted to be 6.8 min; samples from dissolution studies neither exhibited any change in retention time of pentoxifylline nor changes in peak shape, confirming the results from the DSC studies, which indicated the lack of any drug-excipient interactions.

Mucoadhesion Studies

The mucoadhesive behavior of the two polymers was expected to be dependent on the distribution of the polymer on the surface, as well as on their unique hydration properties. Figure 6 compares the mucoadhesive force as a function of time of hydration for the carbomer (Fig. 6A) and HPMC formulations (Fig. 6B), respectively. The range of maximum force of detachment (i.e., mucoadhesive force or force of adhesion) for carbomer formulations was 27.5–37.5 g, whereas for the HPMC formulations the force was 12–21 g (with the exception of formulation HPMC50), indicating that compared with HPMC, the carbomer produces stronger forces of adhesion following hydration. It was observed that the average mucoadhesive force of formulation CARB50, which was 27.47 g following 1 min of hydration, decreased to 12.33 g subsequent to 25 min of hydration. This behavior was in agreement with the studies reported by Tamburic and Craig (1997) and Tobyn et al. (1995), who observed that the mucoadhesive strength decreases with increasing duration of hydration time. As observed from Fig. 6A, for the tablets containing 10–50% carbomer in the inactive component of the formulation, the decrease in force of adhesion appears to correlate with increased duration of hydration; however, this trend was not found to be statistically significant.

Although Smart et al. (1984), Park and Robinson (1985), and Ahuja et al. (1997) have reported on the dependency of mucoadhesive properties on the polymer concentration, in our studies the formulations containing the lowest percentage of carbomer, CARB5, showed the highest force of adhesion following brief periods of hydration. It is plausible that for formulations containing this level of carbomer, the polymer molecules at the surface are spaced sufficiently apart from each other by the lactose molecules, allowing for rapid and complete hydration of the polymer structure, which consequently produces high forces of adhesion following brief periods of hydration. Further hydration loosens the matrix at the surface and leads to diffusion of water into the core of the tablet, thus diminishing the force of adhesion. In formulations in which the percentage of carbomer is higher, it is plausible that the polymer molecules have incomplete access to moisture and fail to be completely hydrated immediately on exposure to the aqueous media. This partial hydration of carbomer molecules may lead to the lower force of adhesion observed immediately following exposure to aqueous media. With increasing swelling and erosion of the polymer following hydration, it is evident that the force of adhesion decreases for every formulation of carbomer, and the overall trend remained the same.

In contrast to carbomer formulations, the mucoadhesive force exhibited by HPMC formulations appeared to correlate with the concentration of polymer

in formulation. Lower HPMC concentrations in formulation produced significantly lesser forces of adhesion than the corresponding carbomer formulations (12–21 g for HPMC compared to 27.5–37.5 g for carbomer, respectively, for the tablets containing 5–25% polymer in the inactive component of the formulation). Similar to the carbomer formulations, the force of adhesion decreased with increased hydration for formulations HPMC5 through HPMC25 (Fig. 6B), although the downslide levels off rapidly and the magnitude of decrease in the force of adhesion was smaller than the carbomer formulations. Although statistical differences in force of adhesion values were not found to be significant at any time point compared with the carbomer formulations, a variation in trend was observed in the HPMC formulations; the force of adhesion appeared to increase slightly with an increase in concentration of HPMC in formulation, whereas no such correlation was observed for the carbomer formulations. As seen in Fig. 6B, the adhesion behavior of formulation HPMC50 was strikingly different from the remaining group. Following 1 min of hydration time, the mucoadhesive force produced by this formulation was 29.97 g, which appeared to increase to 38.03 g following 25 min of hydration (as opposed to a decrease in mucoadhesion following hydration for all the carbomer formulations, as well as the remaining HPMC formulations). This increase was found to be statistically significant. Ponchel et al. (1987) observed a similar increase of adhesive force with 50% HPMC following 10 min of hydration and postulated that the mucoadhesive force is not only dependent on the interaction forces but also on the rheological properties at the interface, which in turn depends on the concentration of the polymer (Ponchel et al., 1991; Tamburic & craig, 1997).

The nature of difference in mucoadhesive force between carbomer and HPMC formulations could plausibly be attributed to formation of hydrogen bonds between the carbomer and proton accepting groups, which does not happen in case of HPMC because it does not contain proton-donating carboxyl groups (Tsuchida, & Abe, 1982; Mortazavi & Smart, 1994). Glass transition temperature (T_g) and polymer mobility have been considered to be important criteria for mucoadhesion by de Vries et al. (1988), indicating the lower the T_g, the higher would be the polymer mobility, which would produce higher levels of mucoadhesion. However, in our studies it was evident that carbomer, which exhibits low relaxation properties due to high T_g, demonstrated relatively higher adhesive forces in formulation than HPMC, which possesses lower T_g and, consequently, a higher polymer mobility. This suggests that polymer mobility might not be the predominant mechanism of mucoadhesion in this situation. This concept has also being supported by the results of a visualization study by Lehr et al. (1992), which demonstrated that there was an absence of interpenetration of poly (acrylic acid) chains into the mucus glycoproteins in the micrometer range.

CONCLUSIONS

This study comprises an in-depth investigation of the mucoadhesive nature and release properties of a model drug from a swellable or soluble hydrogel matrix. Mucoadhesive sublingual tablets of pentoxifylline were successfully developed, with the success parameters being defined as controlled release of drug, 100% drug release within a reasonable period of time, measurable mucoadhesive properties, and lack of drug-excipient interactions. The application of mucoadhesive polymers in buccal and sublingual drug delivery involves the consideration of two important aspects; 1) adequate adhesion of the polymer delivery systems to the targeted surface and 2) precise control of drug delivery from the hydrogel structure due to swelling and or formation of a soluble network structure of the polymer. In our experiments, there was a general decrease in the rate of drug release as the concentration of polymers was increased in the formulation. In general, the force of mucoadhesion of the formulations was found to decrease with increasing time of hydration. The mucoadhesive force appeared to correlate with polymer concentration for HPMC but not for the carbomer containing formulations. Incidentally, the pattern of higher mucoadhesive force exhibited by formulations containing low concentrations of carbomer and higher mucoadhesive force exhibited by formulations containing high concentrations of HPMC correlated well with the results of drug release studies from the same formulations. To reiterate the results from the dissolution studies, it was observed that at low concentrations, carbomer acts as a superior retardant of drug release compared with HPMC; however, at higher concentrations, HPMC was found to act as the superior retardant of drug release.

ACKNOWLEDGMENTS

The authors acknowledge research funding provided by National Institutes of Health grant 1R15DA015358-01 for study of the polymer properties and the general development of mucoadhesive sublingual drug delivery systems.

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