Drug Development and Industrial Pharmacy, 33:855–864, 2007

ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040701377516

informa
healthcare

Mucoadhesive Dosage form of Lidocaine Hydrochloride: I. Mucoadhesive and Physicochemical Characterization

Rana Abu-Huwaij
Department of Pharmaceutics, College of Pharmacy and Medical Sciences, Al-Ahliyya Amman University, Amman, Jordan

Shereen Assaf and Mutaz Salem
Department of Pharmaceutical Technology, College of Pharmacy, Jordan University of Science and Technology, Irbid, Jordan

Alsayed Sallam
Specialized Pharm Research Company (STD), Amman, Jordan

The aim of this study was to characterize a buccal mucoadhesive film using lidocaine and its hydrochloride salt (LDHCL) as a model drug. Buccal films were developed using carbopol 971P as a mucoadhesive polymer, and glycerol as a plasticizer. Scanning Electron Microscope, Differential Scanning Calorimetry, X-ray powder diffraction, and Fourier Transform Infra Red techniques were used to characterize the mucoadhesive films. Bioadhesive properties were evaluated using the Universal Instron Instrument with chicken pouch as a model tissue.

LDHCL and its base were present in carbopol 971P films in a molecular dispersion state without exerting any effect on the glass transition of these films. The mucoadhesive force between the chicken pouches and the film containing glycerol did not change by time during the tested period (1–20 min), while increased with increasing the amount of glycerol (10–40% w/w of polymer content). Furthermore, a linear increase in the mucoadhesive force was accompanied by the increase in the film thickness, while a linear decrease followed by plateau was obtained when loading the patch with LDHCL at concentration above 1 mg/cm^2.

Loading carbopol film with lidocaine base, in a concentration up to 6 mg/cm^2 decreased linearly the mucoadhesive properties, which could be attributed to salt formation between the acidic carboxylic moiety of carbopol and basic lidocaine.

Keywords lidocaine hydrochloride; buccal film; mucoadhesion; physicochemical characterization

INTRODUCTION

Drug delivery by non-parenteral routes has gained significant attention over the last decade, particularly for the delivery of therapeutically important proteins and peptides. While each non-parenteral route of drug administration has its associated advantages and disadvantages, the buccal route has some unique compelling benefits making it worth trying; such benefits include avoiding first pass effect, easy accessibility and better patient compliance. The buccal mucosa was investigated as a potential site for local drug delivery several decades ago (Khanna et al., 1997), but the interest on systemic transmucosal drug administration is growing fast nowadays (Artusi et al., 2003; Minghetti et al, 1998). The major challenge for such delivery is the retention of the delivery system in the oral cavity for the desired duration. The use of excellent mucoadhesive polymers such as carbopol gives a great opportunity to meet this challenge. Various bioadhesive mucosal dosage forms have been developed as tablets (Liabot et al., 2002), gels (Jones et al., 1997), disks (Tiwari et al., 1999), patches (Wong et al., 1999), and more recently films (Cui & Mumper, 2002). A variety of drug substances have been administered by the buccal route. Examples include peptides like calcitonin (Torres-lugo), steroids such as testosterone (Jay et al., 2002), anti-hypertensive agents such as metoprolol tartarate (Wong et al., 1999) and diltiazem (Singh et al., 2002), and analgesic such as burenorphine (Guo, 1994) and oxycodone (Parodi et al., 1996). An ideal buccal film should be flexible, elastic, soft, with accepted size and thickness, yet adequately strong to withstand breakage due to stress from mouth activities. It must also possess good bioadhesive strength so that it can retain in the mouth for a desired duration (Singla et al., 2000). It should be non-irritant, do not cause teeth discoloration, resist metabolic barrier, and be capable of releasing a drug at appropriate rate.

Carbopol 971P NF polymer is a carboxyvinyl hydrophilic polymer. This type of polymer is an excellent candidate for bioadhesion. It was found to be the strongest mucoadhesive polymer among the tested polymers in Eouani et al. (2001) and

Address correspondence to Rana Abu-Huwaij, College of Pharmacy, Amman University, Amman 19328, Jordan. E-mail: rhuwaij@yahoo.com

Wong et al., (1999) studies. It is a high purity grade of Carbopol 941 polymerized in ethyl acetate versus benzene. The carboxyl groups provided by the acrylic acid backbone of the polymer are responsible for many of the product benefits.

Lidocaine hydrochloride [2-Diethylamineoacetate-2′,6′-xylidide] is a white odorless crystalline powder, with a slightly bitter taste. Lidocaine (lignocaine) is the most important amide local anesthetic (Perry et al., 2005). It is also used as an antiarrhythmic agent given only by intravenous route. Lidocaine provides a rapid onset of action (15–30 min). However, it undergoes extensive first-pass hepatic metabolism, where only 3% of orally administered lidocaine appear in plasma (Katzung, 1998).

The overall objective of the present study was to develop a buccal mucoadhesive film releasing lidocaine hydrochloride and to physically characterize and evaluate its mucoadhesion strength.

MATERIALS AND METHODS

Materials

Lidocaine base, lidocaine hydrochloride, carbopol 971P, was kindly donated by APM, (Salt-Jordan). Glycerol 99.5% reagent grade was supplied by Sharlau, (Barcelona-Spain). Polyethylene glycol 400 was supplied by Montplet & Estebansa (Barcelona-Spain). All chemicals were used as supplied and water used in all experiments was HPLC grade supplied by Acros (New Jersey).

Preparation of Mucoadhesive Films

Films containing different proportions of lidocaine hydrochloride or lidocaine base and carbopol 971P were prepared by casting/solvent evaporation technique from plasticizer-containing polymer solutions. Standard plasticized carbopol 971P solution (1.5% w/v) was prepared by soaking the required amount of the polymer in water for 24 h. Polymer solution was prepared by dispersing the polymer in water using paddle stirrer mixer with three blades for half an hour, then adding glycerin (30% w/w of polymer content) to plasticize the polymer and mixing for 2 min. Different plasticizers (propylene glycol, polyethylene glycol 400, and glycerol) were tried with different concentrations (10, 20, 30, 40 w/w of polymer content). The optimum concentration that provided the best practical films for handling, flexibility, and peeling out of the plastic petri dishes was glycerol with 30% w/w of polymer content.

The plasticized polymer aqueous solution was centrifuged for 15 min, and left to stand for 24 h to assure hydration and allow trapped air bubbles to be removed. An accurately weighed amount from the plasticized polymer solution was cast into plastic petri dish with a diameter of 8.9 cm (area of casting = 62.2 cm^2), and dried in the oven at 40°C for 2 days for complete dryness.

Medicated films were prepared by adding lidocaine hydrochloride directly to the carbopol solution, while lidocaine base was first dissolved in ethanol before adding to polymer solution.

The dried films were peeled from the plastic dishes after drying, cut into circular shape of smaller size for mucoadhesion studies (diameter = 2 cm; surface area = 3.14 cm^2). Then, the films were stored at 20 ± 1°C in a desiccator containing saturated solution of sodium dichromate ($Na_2Cr_2O_7$) which provided an environmental condition of 55% relative humidity, for at least 2 days before testing. The thickness of each film was measured using a micrometer at five locations (center and four corners), and the mean thickness was calculated. Samples with air bubbles, nicks or tears, or having mean thickness variations of greater than ± 5% were excluded from analysis.

Thermal Analysis

Differential Scanning Calorimetric Analysis (DSC) thermograms were recorded for lidocaine, lidocaine hydrochloride, carbopol 971 powder, as well as for their physical mixture and film, using DSC (TA-50WSI, KYOTO, SHIMADZU, JAPAN). The DSC thermograms were recorded on a calibrated differential scanning calorimeter. Samples of 3 mg each predried overnight in a vacuum oven were placed in crimped aluminium pans. Thermal analysis was performed, using empty crimped pan as a reference, at a scan rate of 10°C per min from 20 to 300°C under nitrogen purge at a constant flow rate of 20 mL/min.

The glass transition temperature (T_g) of the films and the effect of moisture content, drug content and plasticizers on the glass transition temperature (T_g) were determined using the cooling system of the DSC. Thermal analysis was performed at a scan rate of 10°C per min from –30 to 200°C.

Thermogravimetric analysis (TGA) of lidocaine, lidocaine hydrochloride, carbopol 971P powders, and films were measured using a thermogravimetric analyser (TGA-50, Shimadzu, Japan). A sample size of 3 mg was weighed into an aluminium pan. The measurements were obtained at 30–300°C at a heating rate of 10°C/min, under nitrogen purge at a constant flow rate of 20 mL/min.

Fourier Transform Infrared (FTIR) Analysis

The Fourier transform infrared spectra of lidocaine, lidocaine hydrochloride, carbopol 971P, as well as their physical mixture and film (2:1 polymer: drug), were measured using Nicolet Avatar 5.1 ESP 360 spectrometer (Nicolet instrument corporation).

X-ray Powder Diffractometer Analysis

X-ray diffraction patterns of lidocaine, lidocaine hydrochloride, carbopol 971P powder as well as their physical mixture and film, were measured using X-ray powder diffractometer PW 1729 equipped with X-ray generator, Philips, Netherlands-Holand.

Morphology Analysis

Morphology of mucoadhesive film was observed under a scanning electron microscope using Everhart Thornly detector (ETD). Film samples were mounted on aluminium stubs with adhesive carbon disk substrate. Then gold coated to about 30 nm thickness using an gold sputtering method with Argon gas medium under a high vacuum (1200 V) and 20 mA.

Evaluation of Mucoadhesion

The mucoadhesive strength of the medicated and non-medicated buccal films was determined at room temperature, using an Instron universal testing instrument. Chicken pouch taken from a freshly slaughtered chicken, removed of its contents and surface fats, was being used as the model tissue to study the bioadhesion. The pouch was immediately frozen at –20°C in a phosphate saline buffer solution (2.38 g Na_2HPO_4, 0.19 g KH_2PO_4 and 8.0 g NaCl per 1000 mL HPLC water adjusted with phosphoric acid to pH of 7.0), and only thawed to room temperature before use.

The chicken pouch was mounted onto a cylindrical crosshead support of 2.0 cm diameter and 4 cm length and secured with a rubber band. The whole crosshead support was positioned at the bottom of the measuring system. The circular film of 2.0 cm diameter was affixed to the other crosshead support, secured with a rubber band, and aligned to the other crosshead to ensure that the film come into direct contact with the exposed surface of the chicken pouch. The chicken pouch was wetted with 0.1 mL saline phosphate buffer. It was introduced by micropipette onto the centre of the mucosa and instantly spread over the whole surface.

Upon contact of the film and substrate (contact area 3.14 cm^2), the probe was compressed at predetermined force (1.0 N), and applied for 5 min (time of contact between mucoadhesive device and substrate). This was proceded by an extension stage into each sample at pre-defined rate of 2.0 mm/s until total separation of the components was achieved. The mucoadhesive performance of the samples was determined by measuring the resistance to the withdrawal of the crosshead (maximum detachment force F_{max} in newton 'N') at suitable magnification (20 times) reflecting the mucoadhesion characterisation of the polymeric films with mucus. The force was displayed in kilograms on the Instron and was converted into force units as follows:

$$\text{Force of adhesion (N)} = \text{Corrected reading (kg)} \times \text{Gravity acceleration (m/s}^2\text{)}$$

$$\text{Corrected reading} = \text{Instron reading (kg)} \times (20/100)$$

Runs were performed in 3–5 replicates analyses for each formulation at room temperature using a fresh sample in each case. The mean and standard deviations were calculated.

RESULTS AND DISCUSSION

Thermal Analysis

DSC thermograms of lidocaine and lidocaine hydrochloride powder revealed that there was a sharp endothermic peak at around 68 and 79°C due to melting of the crystalline form of lidocaine and lidocaine hydrochloride.

Vacuum dried carbopol 971P powder and nonplasticized film casting exhibited two endothermic peaks attributed to transition temperature at approximately 26 and 98°C, and a broad endothermic one at a higher temperature exhibited melting followed by decomposition of the polymer. It was noted that thermal melting and decomposition of the polymer film took place at lower temperature than the polymer powder, as shown in Figure 1. The onset of decomposition for the film was at 240°C, while for the polymer powder the onset was at 290°C. These changes corresponded to changes at TGA. There were two steps in weight loss; the change in weight loss at lower temperature was attributed to moisture loss, and the higher to the polymer decomposition. These values have a good agreement with the results obtained in the Singla et al. (2000) study.

Figure 2a shows the effect of drying condition of carbopol 971P on the glass transition temperature (T_g). Polymer dried in overnight at vacuum oven with a temperature of 20°C had moisture content of 3.25%, and T_g of 20°C. While polymer dried overnight at vacuum oven with a temperature of 100°C had a lower moisture content of 2.64% and higher T_g value of 26.93°C. Water is a good plasticizer, where the transition temperature is decreased upon the presence of moisture.

Figure 2b shows the effect of adding 30% w/w of polymer content glycerol as a plasticizer to the film, where the two transition temperatures (T_g) were decreased to about 15 and 75°C. However, adding lidocaine or lidocaine hydrochloride to the plasticized film showed no effect on the transition temperature. Figure 3 shows the presence of the sharp endothermic peak of the melting point of the base and the salt, in the DSC thermograms of the physical mixtures of carbopol 971P and drug (1:2,

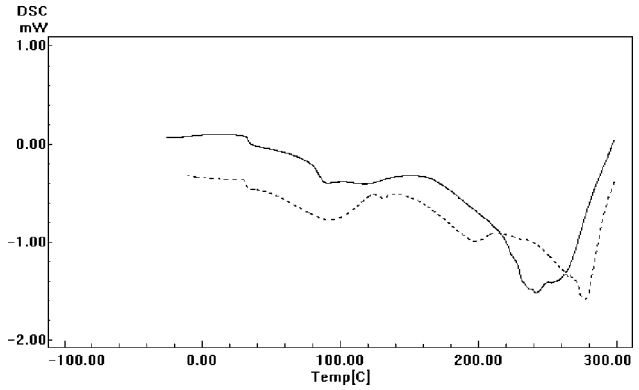

FIGURE 1. DSC thermograms at 10°C/min of carbopol 971P powder and film dried in vacuum oven. (Solid line: non-plasticized carbopol film, dashed line: carbopol powder).

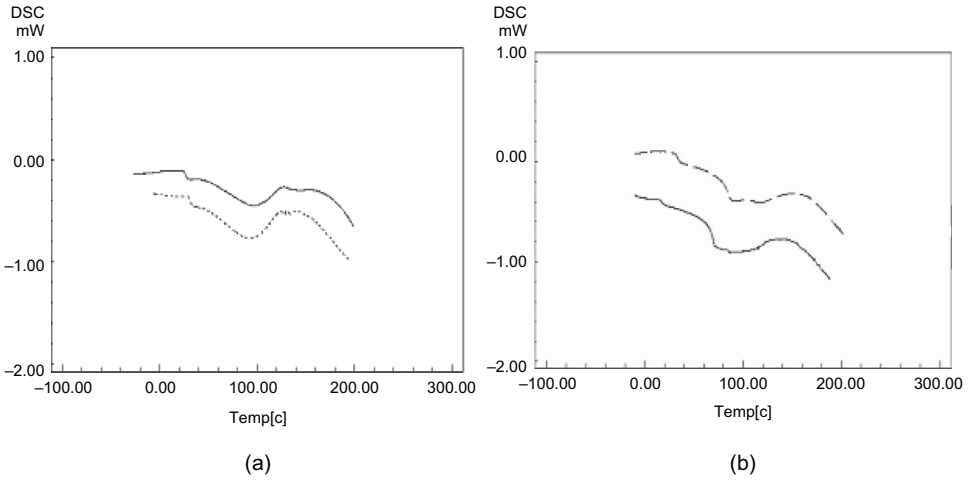

FIGURE 2. DSC thermograms at 10°C/min showing (a) Effect of moisture content on the transition temperature of carbopol. (Solid line: carbopol powder dried overnight in vacuum oven, dotted line: carbopol powder dried in overnight in vacuum oven with 100°C). (b) Effect of 30% w/w of the dry polymer content glycerol on the transition temperature of carbopol. (Solid line: glycerol plasticized carbopol film, dotted line: non-plasticized carbopol film).

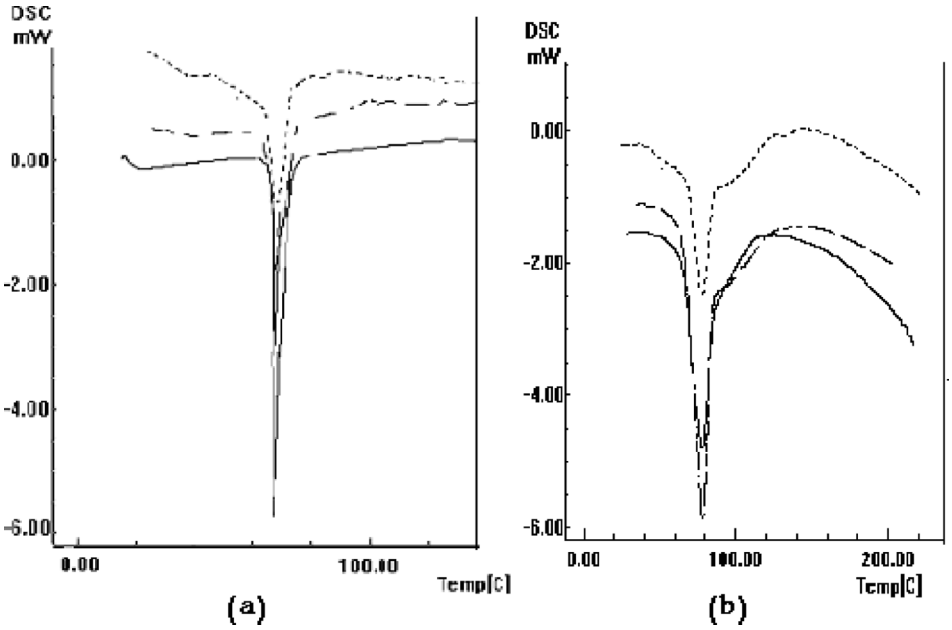

FIGURE 3. DSC thermograms at 10°C/min of different ratios of physical mixture from (a) carbopol and lidocaine base. (b) carbopol and lidocaine hydrochloride (Dotted line: 1:2 lidocaine:carbopol, solid line: 1:1 lidocaine:carbopol, dashed line: 2:1 lidocaine:carbopol).

1:1, 2:1 carbopol 971P:drug). However, this endothermic peak was absent in the DSC thermogram for the film preparations having the same ratios of the polymer and drug. This result may indicate the amorphous state of the drug or the interaction of the drug with carbopol 971P during film formation but not when physically mixed. However, the latter possibility is more reasonable and supported by the other characterization techniques shown later. The result was similar to the result of Khoda et al. (1997) which reported the disappearance of the endothermic peak due to melting of lidocaine hydrochloride from the thermogram of hydroxypropyl cellulose film, but not from that of the physical mixture of lidocaine hydrochloride and hydroxypropyl cellulose.

Fourier Transform Infra Red (FTIR)

The FTIR spectrum of the same materials supports the DSC results. Carbopol 971P showed a strong peak at 1710 cm^{-1} due to carbonyl group of carboxylic group stretching, and this stretching did not change in the film samples of carbopol. Similarly LD and LDHCL showed strong peak at 1650 cm^{-1} representing the carbonyl group stretching of the amide group. The

FTIR spectrum of the lidocaine hydrochloride showed two sharp bands appeared at the range 1450–1550 cm^{-1} due to C-N stretching where the one with higher energy was due to the bond with higher inductive effect (O-C-N). However, there was only one broad peak at the same range revealing the equivalency of the two C-N bonds in lidocaine base. Figure 4 shows the spectrum of the physical mixtures of carbopol and either lidocaine base or lidocaine hydrochloride in a ratio of 2:1 respectively, where a broad peak appeared at the range 1650–1715 cm^{-1} due to summation of the two carbonyl groups stretching of the polymer and the drug. This indicated that there was no interaction between the drugs and the polymer when physically mixed. However, in the case of the films having the same ratio of LDHCL and the polymer, there was an upper field shift in the summation peak indicating an interaction took place between the drug and the polymer. Nurkeeva et al. (2002) in the article of polymeric complexes of lidocaine hydrochloride with carbopol by using potentiometric titration and FTIR analyses, showed that the binding of lidocaine hydrochloride to carbopol occurred due to electrostatic forces like hydrogen bonding and hydrophobic interaction. In the FTIR the 1539 cm^{-1} band, corresponding to amide vibration of LDHCL, broadened in the spectrum of the poly-complex and shifted to the higher wavenumber area (1545 cm^{-1}) as the result of a combination of carbopol carboxylate anion and LDHCl amide group vibrations. The spectral data explained in this study along with the data of Nurkeeva et al. demonstrate the electrostatic nature of complexation between LDHCL and

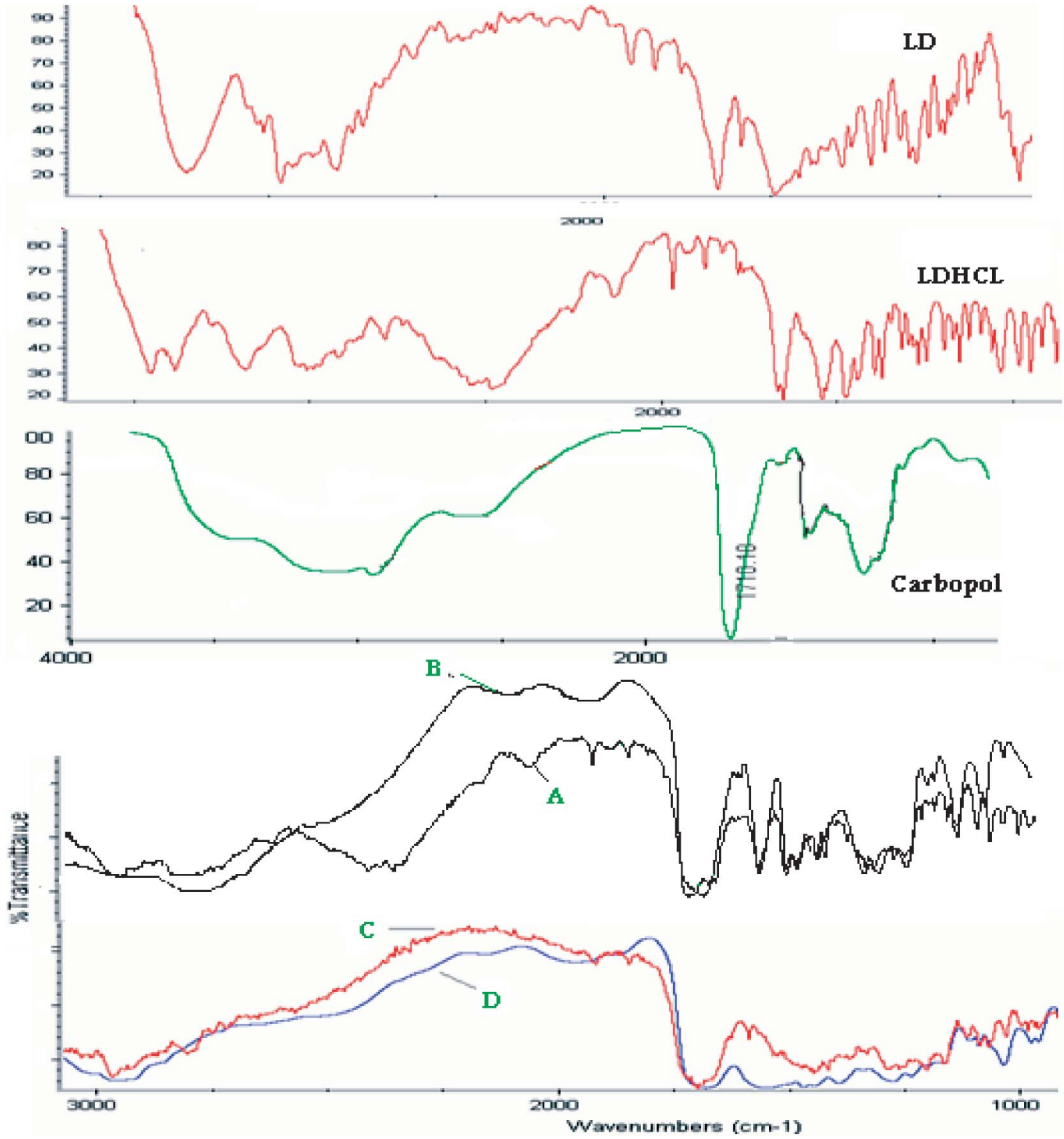

FIGURE 4. FTIR spectra for Lidocaine (LD), Lidocaine hydrochloride (LDHCL), carbopol film, physical mixture of carbopol and lidocaine hydrochloride (A), film of lidocaine hydrochloride (B), physical mixture of carbopol and lidocaine (C), and film of lidocaine (D).

carbopol. Furthermore, similar result was observed for the FTIR analysis of lidocaine hydrochloride films composed of ethyl cellulose and hydroxypropyl cellulose (Kang et al., 1999), where hydrogen bond formation was assumed.

However, the shift of peaks of carbonyl stretching moved to the lower field in case of using lidocaine, which could be due to salt formation between the quaternary nitrogen and the carboxyl group of carbopol. Furthermore, the appearance of a weak band instead of strong band for amino group at about 2850 cm^{-1} suggested the formation of Lidocaine carbopol salt. Lidocaine, is a weak basic compound with a pKa value of 7.9. The decrease in solution pH < 7.9 increases its apparent solubility. Carbopol in water (1% w/v) has a pH of 2.5–3.0, (Pharmaceutical Excipients, 2006) which are much lower than the pKa of LD. Upon addition of LD to carbopol dispersion in water, LD neutralizes the acidic polymer and a hydrogel is formed. We simply referred to it as an acid base reaction forming a salt. It was reported that carbopol-lidocaine aqueous gel behaves as a reservoir of lidocaine in which a high proportion of drug is under the form of ion pairs (Jimenez-Kairuz et al., 2002). Another publication considered the interaction between carbopol and lidocaine as a salt formation (Burgalassi et al., 1996; Elkheshen, 2001). Recently, Ganesh S. Bommareddy et al. (2006) showed that ionic interactions between the protonated amines of the salts (chlorpheniramine maleate and diphenhydramine hydrochloride) and the carboxylates of the carbopol resin are suggested to be the reason for the slower release of the salts of weakly basic drugs from a dissolution medium of 0.05 M phosphate buffer (pH 7.4).

X-Ray Diffraction

The X-ray diffractograms of lidocaine and lidocaine hydrochloride showed that the drug is highly crystalline in nature, as indicated by the numerous distinctive sharp peaks in the spectra. While the diffractogram of carbopol 971P shows diffraction with no sharp peaks revealing its amorphous nature. Figure 5 shows X-ray diffraction of the physical mixture from carbopol 971P and lidocaine or lidocaine hydrochloride and their film preparations, a sharp peak due to presence of crystalline lidocaine and lidocaine hydrochloride appeared in the physical mixture samples, while the films show the absence of any crystallinity. This presumably suggested that there was no interaction between the polymer and the drug in the physical mixture; meanwhile the drug molecule was present in a dissolved state in the film, as amorphous state or molecular dispersion. Previous studies showed that that lidocaine existed in the amorphous condition in a film produced by hot-melt extrusion technology (Repka et al., 2005).

Films clarity assured by the scanning electron microscope, absence of drug indicating peaks in the DSC thermograms and X-ray diffraction of the films, in addition to the molecular shift in the stretching bands in the FTIR spectra, all together assured that the drug molecule was present with the polymer in a molecular dispersion level.

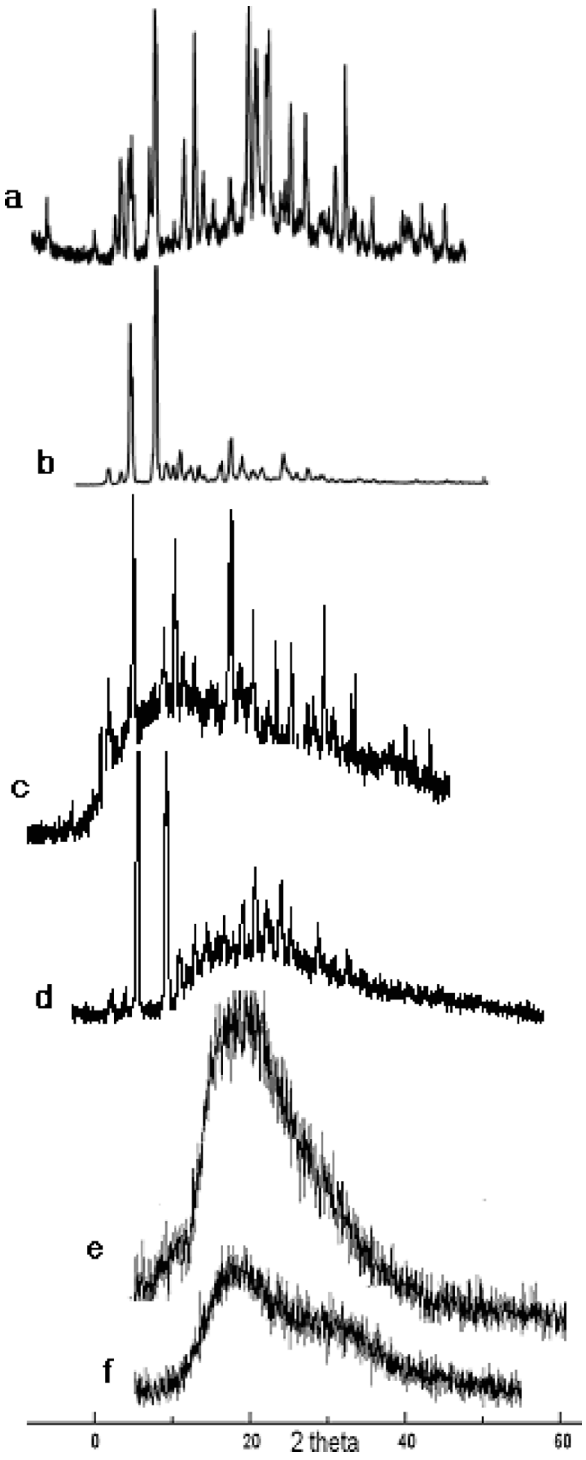

FIGURE 5. X-ray diffraction of (a) Lidocaine hydrochloride (b) Lidocaine (c) Physical mixture of carbopol 971P and lidocaine hydrochloride (d) Physical mixture of carbopol 971P and lidocaine; in a ratio of (2.5:1 carbopol:drug), (e) Carbopol 971P film loaded with lidocaine hydrochloride (f) Carbopol 971P film loaded with lidocaine; in a ratio of (2.5:1 carbopol:drug).

Adhesion Study

In the mucoadhesion process, several well-defined events have been identified (Liabot et al., 2002). Any factor affects the events whether polymer related factor or environmental factor would affect the force of mucoadhesion (Salamat-Miller et al., 2005).

The adhesive force was measured to represent the strength of the adhesive bond between the film and the biological tissue, which is considered to be a function of both the interaction energy between the adhesive and the mucosa, and the viscoelastic properties of the formulation (Tamburic & Craig, 1997).

For intraday precision, the coefficient of variation was 4.5%. Interday variation (day-to-day reproducibility of the measurement) was determined on four consecutive days, and the RSD was found to be 2.11–4.53% revealing the validity of the technique.

Many authors have reported about chicken pouch (Khan et al., 2000; Peh & Wong, 1999; Wong et al., 1999) as a model biological tissue because it is highly available and easy to obtain. Wong et al. (1999) critically reviewed other model biological tissues and showed the advantages of the chicken pouch as a model membrane for testing bioadhesive performance. It has uniform surface, thus giving reproducible results with relatively small relative standard deviation values. In this study, chicken pouch was employed in the bioadhesive experiments in order to run comparative investigations of the influence of various film-forming agents and additive components on the adhesion in such systems, which would help in determining the optimum compositions of the bioadhesive patches.

Effect of Contact Time

Measuring force of adhesion after 1, 3, 5, 10, and 20 min of contact between the mucoadhesive film and chicken pouch, revealed that the force of adhesion was independent on contact time during the tested period (1–20 min). This is analogous to the observation of Shojaei et al. (2000), which showed that increasing the time of contact between the copolymer of polyacrylic acid-co-ethylhexyl acrylate and buccal tissue yeilded a linear increase in mucoadhesive forces for up to 60 seconds. While further increases in contact time 120–300 seconds led to plateau in mucoadhesive force.

Effect of Film Thickness

Figure 6 shows that the force of adhesion increased linearly (r^2 = 0.966) as the thickness of the mucoadhesive film increased. The bioadhesiveness increase with a corresponding increase in the hydrophilic polymer content (Wong et al., 1999). The driving potential for the free chain to be transported across the hydrogel mucus interface is its chemical potential gradient (Wise, 2000). As the concentration gradient of free polymer chains across the interface increased, the diffusion of free chains across the interface increased leading to stronger mucoadhesion.

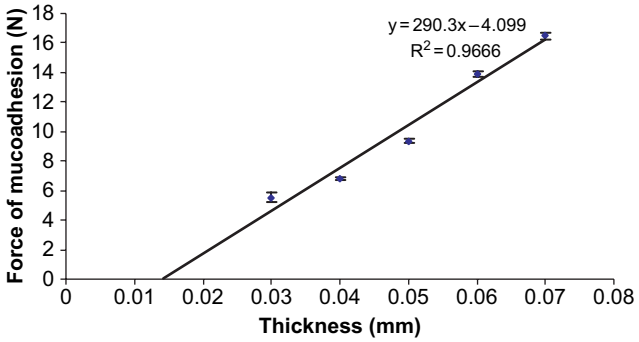

FIGURE 6. Effect of film thickness on the force of mucoadhesion between non-medicated glycerol plasticized carbopol 971P film and chicken pouch (each bar represents the standard deviations of 3–5 experiments).

The results obtained were in agreement with data provided by Parodi et al. (1996), where a thick gelatin disk showed higher in vitro detachment force than a thin one. In addition to Guo (1994) observations, where the average peeling strength of carbopol 934P/polyisobutylene/polyisoprene patches using the Instron increased with increasing patch thickness.

The intersection with the x-axis after extrapolating the line gave a non-zero value at zero time. It is well known that there is an optimum concentration of the polymer to show its bioadhesive effects, therefore a thickness of carbopol film less than 0.02 mm could be too small to exert a mucoadhesive effect that can be measured.

Effect of Drug Loadings

Figure 7 shows that loading the carbopol film of 0.05 mm thickness with lidocaine base led to a linear decrease in the in vitro mucoadhesion (r^2 = 0.9782). This decrease could be contributed to the interaction between lidocaine (basic drug) with

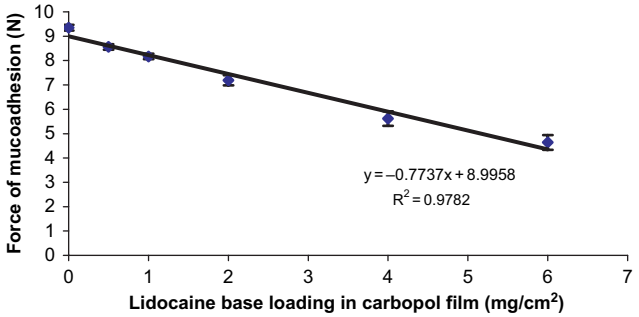

FIGURE 7. Effect of lidocaine base loading on the force of mucoadhesion between glycerol plasticized carbopol 971P film (0.05 mm thickness) and chicken pouch. The films were composed of 0.3 g carbopol, 0.9 g glycerol and 0, 1.57, 3.14, 6.28, 12.56, and 18.84mg lidocaine. (Each bar represents the standard deviations of 3–5 experiments).

the acidic carboxylic group of carbopol. This interaction shielded the negative charge of the carboxylic group, decreased the repulsion forces between carboxylic groups, led to recoiling of the carbopol on itself, and consequently made it difficult to diffuse and penetrate to form secondary chemical bonds with the biological tissues. This interaction was observed visually during casting process, where a viscous solution was formed upon the addition of lidocaine base to carbopol solution. Previous work supported the result, where the addition of metoprolol tartarate to a film composed of Eudragit NE40D and carbopol led to a decrease in the bioadhesive strength due to interaction between metoprolol tartarate (cation) and the latex (highly ionic) (Wong et al., 1999).

Figure 8 shows that loading carbopol film of 0.04 mm thickness with low amount of lidocaine hydrochloride up to 1 mg/cm^2 produced a decline in mucoadhesion force compared to unloaded film. While loading higher amount of lidocaine hydrochloride to carbopol film produced no further effect on the mucoadhesive strength. This could be explained according to the net summation of two processes that might happen. Protonated carboxyl group at low pH decreased the repulsion between the coiled chains, which means more coiled chains that lower interpenetration and adhesion. At the same time, higher protonated carboxyl groups, means higher hydrogen bond formation with mucus in the biological tissue and higher mucoadhesion strength. At low concentration (< 1 mg/cm^2), interpenetration limitation effect was more dominant, however, at higher concentration this limitation was not observed.

Effect of Plasticizers

The mechanical properties of carbopol films were dependent on the plasticizer/polymer composition. Without the addition of a plasticizer, carbopol could not be processed into an elastic film due to its high transition temperature (*Tg*) value. Plasticizers reduce the brittleness, impart flexibility, and increase toughness, strength, tear resistance, and impact resistance of the polymer (Xiang et al., 2002). Figure 9 shows that all the plasticized films, which have propylene glycol, glycerin or polyethylene glycol 400 showed a linear increase in the mucoadhesive force of adhesion with increasing the concentration of the plasticizer from (10–40% w/w polymer content). Films were applied to the mucosa in the non-hydrated glassy state. Plasticizers reduced the glass transition temperature (*Tg*) below ambient conditions, and the hydrogel became progressively rubbery that increased the mobility of molecules and facilitated the interpenetration with the mucus layer, that consequently, enhanced the mucoadhesive force. Plasticizers might disrupt the intermolecular attraction between the polymer chain by hydrogen bond formation. As the concentration of the plasticizers increased, hydrogen bond formation was increased, which led to higher force of adhesion.

The force of adhesion for non-plasticized carbopol film can not be practically measured, because of film inflexibility (brittleness). They could not be peeled off from the petri dishes. But it can be determined from the y-intercept of the typical linear regression equations of the straight lines obtained from force of adhesion and the concentration of the plasticizer used. Typical linear equations were: $y = 0.3281\ x - 4.175$ ($r^2 = 0.9993$), $y = 0.1784\ x - 3.745$ ($r^2 = 0.9998$), $y = 0.0998\ x - 3.905$ ($r^2 = 0.9996$) for glycerin, polyethylene glycol 400 and propylene glycol, respectively. The mean force of adhesion for the non-plasticized carbopol film was equal to 3.94 ± 0.22 N. Films plasticized with glycerol (40% w/w of polymer content) showed the strongest force of adhesion 17.4 ± 0.2 N, while the mucoadhesive force for a film plasticized with the same amount from polyethylene glycol 400 and propylene glycol were 10.87 ± 0.5 N and 7.89 ± 0.4 N, respectively. Films plasticized with glycerol had significantly higher force of adhesion than the one plasticized with propylene glycol ($P = 0.03$), and the one plasticized with polyethylene glycol 400 ($P = 0.04$). These significant differences could be attributed to the differences in the chemical structure between the plasticizers, which

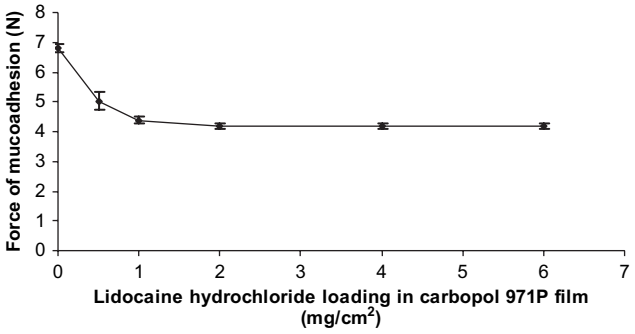

FIGURE 8. Effect of lidocaine hydrochloride loading on the force of mucoadhesion between glycerol plasticized carbopol 971P film (0.04 mm thickness) and chicken pouch. The films were composed of 0.225 g carbopol, 0.0.0675 g glycerol and 0, 1.57, 3.14, 6.28, 12.56, and 18.84mg of lidocaine hydrochloride (Each bar represents the standard deviations of 3–5 experiments).

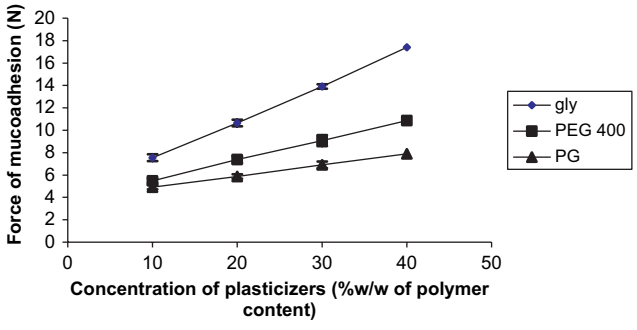

FIGURE 9. Effect of plasticizers on the force of mucoadhesion between non-medicated carbopol 971P film (0.06 mm thickness) and chicken pouch (Each bar represents the standard deviations of 3–5 experiments). (Gly: glycerol, PEG 400: polyethylene glycol 400, PG: propylene glycol).

played a major factor in the consolidation process of mucoadhesion (Liabot et al., 2002) (capability of hydrogen bond formation with the mucus).

Effect of Additives

Adding pluronic-F127 to carbopol 971P film led to a linear decrease in the mucoadhesive force (r^2 = 0.9994). This could be contributed to many factors: (1) Pluronic is a triblock copolymer has the ability to self assemble of individual block copolymer (unimers) into micelles in aqueous solutions at a concentration above the critical micelle concentration (CMC), which ranges from 2.8×10^{-6} to 1% w in aqueous solution at 37°C (Kabanov et al., 2003). During casting process the surfactant probably preferred to orient themselves at the film-air interface with its polar part in the mucoadhesive solution, and hydrophobic part away from it. This orientation decreased the amount of functional hydrophilic group available at the interface with the mucus, which led to a weak force of adhesion between the film and the biological tissue. (2) Micelles solubilized the lipophilic chains to such a large extent that interactions between lipophilic modifications no longer contribute to the elasticity of the gel, similar to the decrease in carbopol gels elasticity upon adding Brij 58 (polyoxyethylene 20 cetyl ether) as a surfactant (Paulsson & Edsman, 2001). A decrease in film elasticity, chain mobility lowered the mucoadhesive bond strength. (3) Pluronic F-127 has a large molecular weight of 12600, and when intermediate to large molecular weight (> 500) compound were loaded in bioadhesive polymeric matrices, the compound with their micelles might act as a physical cross-linker (Shojaei et al., 1998).

CONCLUSIONS

In the present study, buccal film using lidocaine and its hydrochloride salt (LDHCL) as a model drug was investigated. LDHCL and its base were present in carbopol 971P films in a molecular dispersion state without exerting any effect on the glass transition of these films. The flexibility required for a good compliance and optimum content was achieved employing glycerol at 40% w/w of polymer rather than PEG 400 or propylene glycol.

Drug concentration was found to affect mucoadhesive properties of the films. Lidocaine concentration up to 6 mg/cm^2 decreased linearly the mucoadhesive properties while LDHCL behaved differently, firstly decreased and then plateau was obtained at concentrations above 1 mg/cm^2. These effects could be correlated with drug - carbopol interaction where lidocaine interacted via salt formation while LDHCL interacted via hydrogen bonding. Pluronic F-127 as a nonionic surfactant negatively affected the mucoadhesive properties of carbopol films, solubilize the lipophilic chains of carbopol, decreased film elasticity, chain mobility and consequently mucoadhesive forces.

REFERENCES

Artusi, M., Santi, P., Colombo, P., & Junginger, H. (2003). Buccal delivery of thiocolchicoside: In vitro and in vivo permeation studies. *Int. J. Pharm., 250*, 203–213.

Bommareddya, G., Paker-Leggs., Saripella, K., & Neaua, S. (2006). Extruded and spheronized beads containing Carbopol 974P to deliver nonelectrolytes and salts of weakly basic drugs. *Int. J. Pharm., 321*, 62–71.

Burgalassi, S., Panichi, L., Saettone, M. F., Jacobsen, J. B., & Rassing, M. R. (1996). Development and in vitro/in vivo testing of mucoadhesive buccal patches releasing benzydamine and lidocaine. *Int. J. Pharm., 133*, 1–7.

Cui, Z., & Mumper, R. (2002). Bilayer films for mucosal (genetic) immunization via the buccal route in rabbits. *Pharm. Res., 19*(7), 947–953.

Elkheshen, S. (2001). Interaction of verapamil hydrochloride with Carbopol 934P and its effect on the release rate of the drug and the water uptake of the polymer matrix. *Drug Dev. Ind. Pharm., 27*(9), 925–934.

Eouani, C., Piccerelle, P. H., Prinderre, P., Bourret, E., & Joachim, J. (2001). In-vitro comparative study of buccal mucoadhesive performance of different polymeric films. *Eur. J. Pharm. Biopharm., 52*, 45–55.

Guo, J. (1994). Bioadhesive polymer buccal patches for buprenorphine controlled delivery: Formulation, in vitro adhesion and release properties. *Drug Dev. Ind. Pharm., 20*(18), 2809–2821.

Jay, S., Fountain, W., Cui, Z., & Mumper, R. (2002). Transmucosal delivery of testosterone in rabbits using novel bi-layer mucoadhesive wax film composite disks. *J. Pharm. Sci., 91*(9), 2016–2025.

Jimenez-Kairuz, A., Allemandi, D., & Manzo, R. (2002). Mechanism of Lidocaine Release From Carbomer – Lidocaine. *J. Pharm. Sci., 91*(1), 267–272.

Jones, D., Woolfson, A., & Brown, A. (1997). Textural analysis and flow rheometry of novel, bioadhesive antimicrobial oral gels. *Pharm. Res., 14*(4), 450–457.

Kabanov, A., Batrakova, E., & Miller, D. (2003). Pluronic block copolymers as modulators of drug efflux transporter activity in the blood-brain barrier. *Adv. Drug Del. Rev., 55*, 151–164.

Kang, L., Jun, H., & McCall, J. (1999). HPLC assay of Lidocaine in plasma with solid phase extraction and UV detection. *J. Pharm. Bio. Anal., 19*, 737–745.

Katzung, B. (1998). Basic and clinical pharmacology, 7 th edition, Chapter 14.

Khan, T., Peh, K., & Ch'ng, H. (2000). Mechanical, bioadhesive strength and biological evaluations of chitosan films for wound dressing. *J. Pharm. Pharmaceut. Sci., 3*(3), 303–311.

Khanna, R., Agarwal, S., & Ahuja, A. (1997). Muco-adhesive buccal tablets of clotrimazole for oral candidiasis. *Drug Dev. Ind. Pharm., 23*(8), 831–837.

Kohda, Y., Kobayashi, H., Baba, Y., Yuasa, H., Ozeki, T., Kanaya, Y., & Sagara, E. (1997). Controlled release of lidocaine hydrochloride from buccal mucosa-adhesive films with solid dispersion. *Int. J. Pharm., 158*, 147–155.

Liabot, J., Manzo, R., & Allemandi, D. (2002). Double layered mucoadhesive tablets containing nystatin. AAPS. *Pharm. Sci. Tech., 3*(3) article 22.

Minghetti, P., Colombo, A., Montanari, L., Gaeta, G., & Gombos, F. (1998). Buccoadhesive slow release tablets of acitretin: Design and in vivo evaluation. *Int. J. Pharm., 169*, 195–202.

Nurkeeva, Z., Mun, G., Khutoryanskiy, V., Bitekenova, A., & Dzhusupbekova, A. (2002). Polymeric complexes of lidocaine hydrochloride with poly(acrylic acid) and poly(2-hydroxyethyl vinyl ether). *J. Biomater. Sci. Polymer Edn., 13*(7), 759–768.

Parodi, B., Russo, E., Caviglioli, G., Cafaggi, S., & Bingnardi, G. (1996). Development and characterization of a buccoadhesive dosage form of Oxycodone Hydrochloride. *Drug Dev. Ind. Pharm., 22*(5), 445–450.

Paulsson, M., & Edsman, K. (2001). Controlled drug release from gels using surfactant aggregates: I. Effect of lipophilic interactions for a series of uncharged substances. *J. Pharm. Sci., 90*(9), 1216–1225.

Peh, K., & Wong, C. (1999). Polymeric films as vehicle for buccal delivery: Swelling, Mechanical, and Bioadhesive properties. *J. Pharm. Pharmaceut. Sci., 2*(2), 53–61.

Perry, D. A., Gansky, S. A., & Loomer, P. M. (2005). Effectiveness of a transmucosal lidocaine delivery system for local anaesthesia during scaling and root planing. *J. Clin. Periodontol., 32*(6), 590–4.

Pharmaceutical Excipients, Edited by: Raymond C Rowe, Paul J Sheskey and Siân C Owen. (2006). Published jointly by the Pharmaceutical Press and the American Pharmacists Association.

Repka, M., Gutta, K., Prodduturi, S., Munjal, M., & Stodghill, S. (2005). *Eur. J. Pharm. Biopharm., 59*(1), 189–196.

Salamat-Miller, N., Chittchang, M., & Johnston, T. (2005). The use of mucoadhesive polymers in buccal drug delivery. *Adv. Drug Del. Rev., 57,* 1666–1691.

Shojaei, A., Paulson, J., & Honary, S. (2000). Evaluation of poly(acrylic acid-co-ethylhexyl acrylate) films for mucoadhesive transbuccal drug delivery: factors affecting the force of mucoadhesion. *J. Control. Rel., 67,* 223–232.

Shojaei, A., & Zhou, S., & Li, X. (1998). Transbuccal delivery of acyclovir (II): Feasibility, system design, and in vitro permeation studies. *J. Pharm. and Pharmaceut. Sci., 1*(2), 66–73.

Singh, B., & Ahuja, N. (2002). Development of controlled release buccoadhesive hydrophilic matrices of diltiazem hydrochloride: optimization of bioadhesion, dissolution, and diffusion parameters. *Drug Dev. Ind. Pharm., 28*(4), 431–442.

Singla, A., Chawla, M., & Singh, A. (2000). Potential applications of Carbomer in oral mucoadhesive controlled drug delivery system: Review. *Drug Dev. Ind. Pharm., 26*(9), 913–924.

Tamburic, S., & Craig, D. (1997). A comparison of different in vitro methods for measuring mucoadhesive performance. *Eur. J. Pharm. Biopharm., 44,* 159–167.

Tiwari, D., Sause, R., & Madan, P. (1999). Evaluation of polyoxyethylene homopolymers for buccal bioadhesive drug delivery device formulations. *AAPS Pharmsci., 1*(3), article 13.

Torres-lugo, M., & Peppas, N. (2000). Transmucosal delivery systems for calcitonin: A review. *Biomaterials, 21,* 1191–1196.

Wise, D. (2000). Handbook of pharmaceutical controlled release technology (chap. 12). Marcel Dekker.

Wong, C., Yuen, K., & Peh, K. (1999). Formulation and evaluation of controlled release Eudragit buccal patches. *Int. J. Pharm., 178,* 11–22.

Wong, C., Yuen, K., & Peh, K. (1999). An in-vitro method for buccal adhesion studies: importance of instrument variables. *Int. J. Pharm., 180,* 47–57.

Xiang, J., Fang, X., & Li, X. (2002). Transbuccal delivery of 2′,3′-dideoxycytidine: In vitro permeation study and histological investigation. *Int. J. Pharm., 231,* 57–66.