Arch Pharm Res Vol 26, No 11, 973-978, 2003

Archives of Pharmacal Research
http://apr.psk.or.kr

Preparation of Buccal Patch Composed of Carbopol, Poloxamer and Hydroxypropyl Methylcellulose

Myung-Kwan Chun, Byoung-Tae Kwak, and Hoo-Kyun Choi
College of Pharmacy, Chosun University, Gwangju, Korea 501-759

(Received October 24, 2003)

A polymeric film composed of Carbopol, Poloxamer and hydroxypropyl methylcellulose was prepared to develop a buccal patch and the effects of composition of the film on adhesion time, swelling ratio, and dissolution of the film were studied. The effects of plasticizers or penetration enhancers on the release of triamcinolone acetonide (TAA) were also studied. The hydrogen bonding between Carbopol and Poloxamer played important role in reducing swelling ratio and dissolution rate of polymer film and increasing adhesion time. The swelling ratio of the composite film was significantly reduced and the adhesion time was increased when compared with Carbopol film. As the ratio of Poloxamer to hydroxypropyl methylcellulose increased from 0/66 to 33/33, the release rate of TAA decreased. However, no further significant decrease of release rate was observed beyond the ratio of 33/33. The release rate of TAA in the polymeric film containing polyethylene glycol 400, a plasticizer, showed the highest release rate followed by triethyl citrate, and castor oil. The release rate of TAA from the polymeric film containing permeation enhancers was slower than that from the control without enhancers. Therefore, these observations indicated that a preparation of a buccal patch is feasible with the polymeric film composed of Cabopol, Poloxamer and hydropropyl methylcellulose.

Key words: Adhesion time, Release rate, Penetration enhancer, Carbopol, Poloxamer, Hydroxypropyl methylcellulose

INTRODUCTION

Although the oral administration of drugs has been the preferred route of administration for the patients and clinicians, certain disadvantages such as hepatic first pass metabolism, gastric irritation, and enzymatic degradation within the gastrointestinal tract have been identified. Administration of drugs via the buccal mucosa as an alternative route of administration has several advantages over oral administration, such as avoiding presystemic metabolism in the gastrointestinal tract and hepatic first-pass elimination (de Vries *et al.*, 1991). The buccal mucosa has some advantages such as high permeability and high blood flow (de Vries *et al.*, 1991) and is easily accessible for both application and removal of a drug delivery device. Due to these advantages, the buccal mucosa has been investigated as a potential site for controlled delivery of hydrophilic macromolecular therapeutic agents, such as peptides, proteins, and polysaccharides (de Vries *et al.*, 1991).

One of the important factors to enhance the drug delivery through buccal administration is the extended adhesion time of the applied dosage form on the buccal mucosa. Since bioadhesive polymers are essential element to provide adhesive property, they have extensively been employed in buccal drug delivery systems (Remuñán-Lápez *et al.*, 1998; Langoth *et al.*, 2003). These include synthetic polymers such as poly(acrylic acid) (Burgalassi *et al.*, 1996) and hydroxypropyl methylcellulose (HPMC) (Choi *et al.*, 2000), as well as naturally occurring polymers such as hyaluronic acid (Lim *et al.*, 2000) and chitosan (Şenel *et al.*, 2000).

Carbopol 971 is a partially cross-linked poly(acrylic acid) and has been widely used as a bioadhesive polymer because it has a strong mucoadhesive force. However, it has some drawbacks such as high swelling ratio in water. The high swelling ratio of Carbopol 971 is a major limiting factor for its use as a matrix for transmucosal drug delivery system despite its strong adhesive force to the mucous

Correspondence to: Hoo-Kyun Choi, Ph.D., College of Pharmacy, Chosun University, 375, Seosuk-dong, Dong-gu, Gwangju 501-759, Korea
Tel: 82-62-230-6367, Fax: 82-62-228-3742
E-mail: hgchoi@chosun.ac.kr

membrane. The high swelling ratio of Carbopol could lessen its mucoadhesive force. It has been shown in our previous study that Poloxamer could reduce the aqueous solubility of poly(acrylic acid) without reduction in the adhesive force of poly(acrylic acid) owing to hydrogen bonding between poly(acrylic acid) and Poloxamer (Chun *et al.*, 2001). Carbopol 971 was selected as one of the matrix materials to develop buccal patch formulation and Poloxamer 407 and HPMC 2910 were added to reduce the swelling ratio of Carbopol 971.

The purposes of this study are to investigate the effect of various compositions of the polymeric film composed of Carbopol, Poloxamer and HPMC on swelling ratio, dissolution rate, and adhesion time of the polymeric film and to assess the feasibility of the film for the preparation of buccal patch delivery system. The effects of plasticizers and various penetration enhancers on the release of triamcinolone acetonide (TAA), a model drug, from the polymeric film composed of Carbopol, Poloxamer and HPMC are also investigated.

MATERIALS AND METHODS

Preparation of the polymeric film

TAA (0.01 g) was dissolved in ethanol/water mixture (4.65 g/4.65 g). Subsequently, 0.54 g of Carbopol 971, Poloxamer 407 and HPMC 2910 were successively added to the solution according to the predetermined weight ratio of Carbopol/Poloxamer/HPMC (33/66/0, 33/44/22, 33/33/33, 33/22/44 and 33/0/66). The solution was mixed for 24 h and the air-bubbles were removed. The polymeric film was prepared by casting the above solution in polyester film using a casting knife. It was dried at ambient temperature over 24 h to remove the residual solvents. The dried film was laminated onto ethyl cellulose film as a backing film.

To study the effect of the concentrations of TAA on the release of TAA, TAA was dissolved in ethanol/water mixture (4.65 g/4.65 g) according to the predetermined concentrations of TAA (0.3, 0.6, 0.9 or 1.2%). Subsequently, Carbopol 971 (0.18 g), Poloxamer 407 (0.18 g) and HPMC 2910 (0.18 g) were added to the solution. The polymeric film was prepared in the same way as described previously.

To study the effect of plasticizers on the release of TAA, TAA (0.01 g) was dissolved in ethanol/water mixture (4.65 g/4.65 g). Subsequently, 0.01 g of plasticizer (PEG 400, triethyl citrate or castor oil) was added. And then Carbopol 971 (0.18 g), Poloxamer 407 (0.18 g) and HPMC 2910 (0.18 g) were added to the solution. The polymeric film was prepared in the same way as described previously.

To study the effect of enhancers on the release of TAA, TAA (0.01 g) and 0.01 g of PEG 400 were dissolved in ethanol/water mixture (4.65 g/4.65 g) and 0.01 g of penetration enhancer (propylene glycol, taurocholic acid, Tween 80, Labrafill 1944, or Cremophor EL) was added. Subsequently, Carbopol 971 (0.18 g), Poloxamer 407 (0.18 g) and HPMC 2910 (0.18 g) were added to the solution. The polymeric film was prepared in the same way as described previously.

To study the effect of the concentration of PEG 400 on the adhesion time, TAA (0.01 g) and the predetermined concentrations of PEG 400 (1, 2 or 3%) were dissolved in ethanol/water mixture (4.65 g/4.65 g). Subsequently, Carbopol 971 (0.18 g), Poloxamer 407 (0.18 g) and HPMC 2910 (0.18 g) were added to the solution. The polymeric film was prepared in the same way as described previously.

Measurement of swelling ratio

Swelling ratios of the polymeric films were determined by placing the polymeric films in 5 mL of distilled water. The swelling ratio was measured as a function of time at room temperature. At predetermined time intervals, residual water was removed and the weight of the swelled film was measured. The swelling ratio was calculated by using $[(Wp - Ws)/Ws] \times 100$, where Ws and Wp are the weight of the dry film before testing and the weight of swelled film after testing, respectively.

Measurement of dissolution rate

Dissolution rate of the polymeric film was determined by placing the polymeric film in 15 mL of distilled water. At predetermined time intervals, a sample film was removed and dried to determine its weight. The degree of dissolution was calculated by using $[(Wp - Ws)/Wp] \times 100$, where Ws and Wp are the dry weights of sample films after testing and before testing, respectively.

Measurement of adhesion time

The discs with the same area as commercial Aftach® tablet were wetted with pH 7.4 phosphate buffer solution at room temperature before the testing, and then placed on the polypropylene plate. The specimens were pressed under 19.6 N/cm^2 for 60 s before the measurement. The plate, to which the specimen was adhered, was attached to the wall of beaker and pH 7.4 phosphate buffer solution was added until the specimen was submerged. The solution was stirred with a paddle at 150 rpm at room temperature. The adhesion time of the specimen was determined by measuring the time required for the specimen to be detached from the plastic plate.

In vitro release of TAA from the polymeric film

A flow-through diffusion cell system consisting of a multichannel peristaltic pump, a fraction collector, a circulating water bath, and flow-through diffusion cells, was used to investigate *in vitro* release of TAA from the polymeric film.

The temperature was maintained at 37°C. The receiver cell was filled with the mixture of pH 7.4 phosphate buffer solution and propylene glycol (70/30). An aliquot of the release medium was automatically withdrawn at predetermined time intervals and equivalent amount of fresh medium was added to the receiver cell. Collected samples were analyzed by UV spectrophotometer (UV-1602, Shimadzu, Japan) at 238nm to determine the amount of TAA released.

RESULTS AND DISCUSSION

The limited aqueous solubility and adequate adhesive force are two important requirements in developing transmucosal drug delivery system. The high aqueous solubility of poly(acrylic acid) was a limiting factor for its use as a matrix of transmucosal drug delivery system despite of its strong adhesive force to the mucous membrane. It has been shown in our previous study that Poloxamer could reduce the aqueous solubility of poly(acrylic acid) without reduction in the adhesive force of poly(acrylic acid) owing to hydrogen bonding between them (Chun *et al.*, 2001). Carbopol 971 is a partially cross-linked poly(acrylic acid) and has been widely used as a pharmaceutical excipients. Carbopol 971 has a strong mucoadhesive force, however, it swells in water and lose its mucoadhesive force. Carbopol 971 was selected as one of the matrix materials to develop buccal patch formulation and Poloxamer 407 and HPMC 2910 were added to reduce the swelling of Carbopol 971. In addition, a plasticizer was used to improve the flexibility of the film and an enhancer was added to increase the permeation rate of TAA.

Fig. 1 shows the effect of various compositions of Carbopol, Poloxamer and HPMC on the swelling ratio of the film. The Carbopol film swelled quickly within 1 h and swelled more than 500 times. After 1 h, no further swelling was observed. When Carbopol 971 and HPMC 2910 were used to prepare the film without Poloxamer, it dissolved so quickly that it was not possible to measure the swelling ratio. There were no significant difference in the swelling ratio between films containing Carbopol 971 and Poloxamer 407. The penetration of water molecule into the polymer network was significantly reduced due to the hydrogen bonding between Poloxamer and Carbopol 971, resulting in lower swelling ratio. The presence of HPMC 2910 did not show significant effect on the swelling of Carbopol 971.

One of the major requirements in developing buccal patch system is the maintenance of the morphology of the film, i. e., the film should not be dissolved for a certain period of time. Fig. 2 shows the effect of various compositions of Carbopol, Poloxamer and HPMC on the dissolution rate of the film. Carbopol 971 film and Carbopol 971/HPMC 2910 film completely dissolved within 1 h. All the films containing both Carbopol 971 and Poloxamer maintained the shape for more than 4 h. As was discussed in swelling ratio study, hydrogen bonding seemed to play a major role in reducing dissolution of the film. Another important factor in developing buccal patch system is the maintenance of adhesive force on the mucous surface. The effect of various compositions of Carbopol, Poloxamer and HPMC on the adhesion time was investigated after attaching the system on the polypropylene surface. The adhesion time is closely related to the ability of the system in limiting interpenetration of water. The interpenetration of water can be measured on the polypropylene surface, since once enough amount of water penetrate into the film, then the system will be detached from the polypropylene wall. Also, it has been shown in our previous study that adhesive force between polypropylene and mucoadhesive

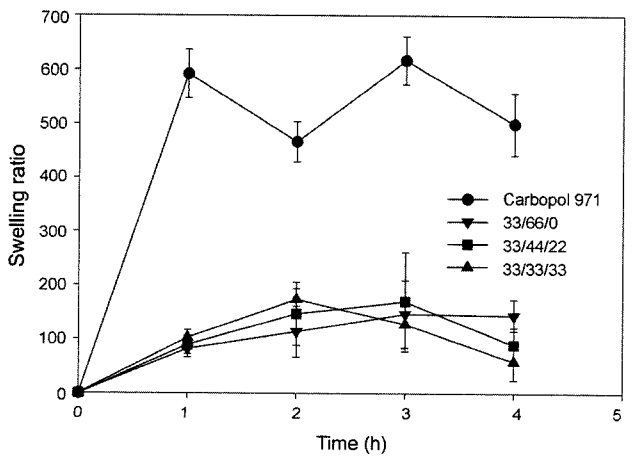

Fig. 1. Effect of various ratios of Carbopol 971/Poloxamer 407/HPMC 2910 on the swelling ratio of the polymeric films. (n = 3)

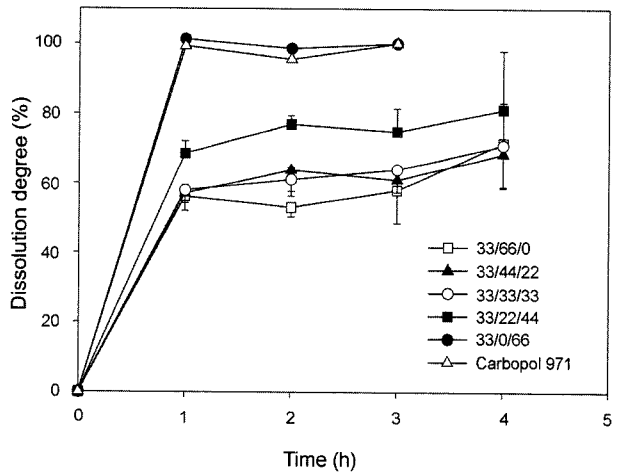

Fig. 2. Effect of various ratios of Carbopol 971/Poloxamer 407/HPMC 2910 on the dissolution rate of the polymeric films. (n = 3)

polymer was similar to adhesive force between mucous membrane and mucoadhesive polymer (Chun *et al*, 2001). The results are shown in Fig. 3. The Carbopol 971 film was detached from the surface in less than 3 h. The Carbopol 971/Poloxamer/HPMC (33/33/33) film was remained on the surface for more than 8 h. All other films containing both Carbopol 971 and Poloxamer were remained on the surface significantly longer than Carbopol 971 film due to hydrogen bonding. Although the dissolution rate of Carbopol 971/Poloxamer/HPMC (33/0/66) was faster than that of other films, the water-insoluble backing membrane on the film seemed to significantly retard the dissolution rate of the film.

To investigate the effect of various formulation factors on the release rate of TAA from the polymeric films composed of Carbopol 971, Poloxamer 407 and HPMC 2910, cellulose membrane was used as a barrier between the film and the release medium. When pH 7.4 phosphate buffer was used as the receiver cell medium, the flux was extremely low due to the low solubility of TAA, i.e., sink condition may have not been attained. To increase the solubility of TAA, 30% propylene glycol was added to the receiver cell medium.

Fig. 4 shows the effect of various compositions of Carbopol, Poloxamer and HPMC on the release rate of TAA from the polymeric film across the cellulose membrane. The ratio of Poloxamer to HPMC varied with the ratio of Carbopol fixed. The release profile showed the typical release pattern of matrix system, i. e., the amount released was proportional to square root of time. As the ratio of Poloxamer to HPMC increased from 0/66 to 33/33 the release rate of TAA was decreased, whereas no significant changes were observed beyond the ratio of 33/33. As was discussed previously, the formation of complex

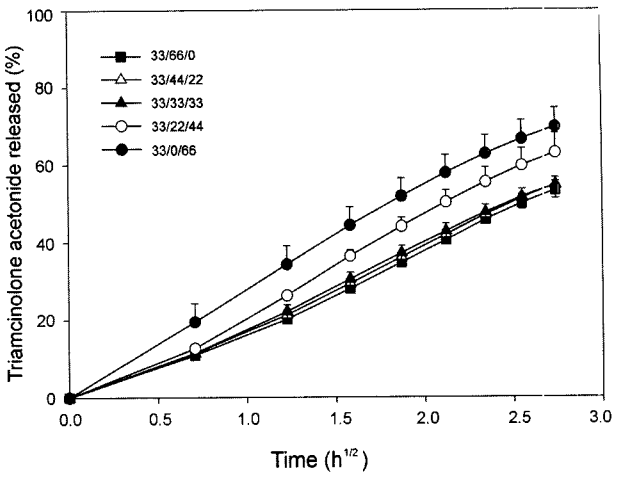

Fig. 4. Effect of various ratios of Carbopol 971/Poloxamer 407/HPMC 2910 on the release rate of TAA across the cellulose membrane from the polymeric film. (n = 3)

between Carbopol 971 and Poloxamer due to hydrogen bonding decreased the swelling rate of Carbopol 971 and the release rate of TAA (Chun *et al*, 2001). Further increase in the ratio of Poloxamer did not seem to increase the degree of complexation in the composite film, resulting in no further decrease in the release rate of TAA.

The effect of the concentrations of TAA on the release rate of TAA from the polymeric film across the cellulose membrane is shown in Fig. 5. As the concentration of TAA was increased, the release rate of TAA increased. The flux is proportional to the concentration gradient across the membrane. The results indicate that TAA is solubilized within the matrix and the flux can be controlled by adjusting the amount of TAA loaded in the film.

The polymeric film is supposed to be applied to buccal mucous membrane, which requires adequate flexibility of

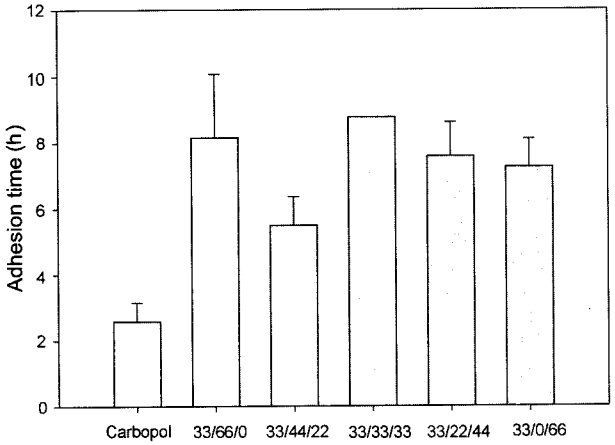

Fig. 3. Effect of various ratios of Carbopol 971/Poloxamer 407/HPMC 2910 on the adhesion time of the polymeric films in the pH 7.4 phosphate buffer solution. (n = 3)

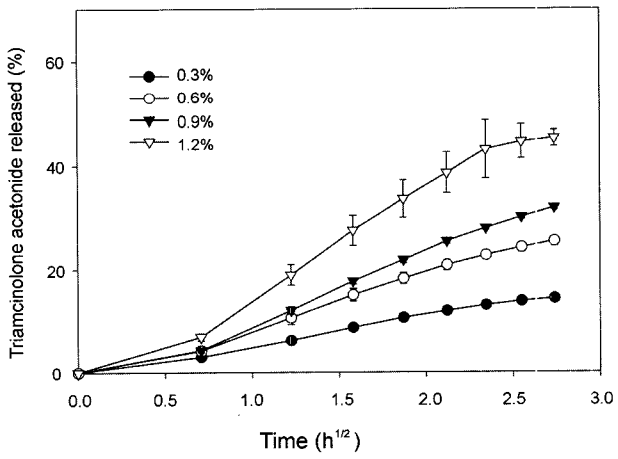

Fig. 5. Effect of various concentrations of TAA on the release rate of TAA across the cellulose membrane from the polymeric film. (n=3)

the membrane. If the film does not have adequate flexibility, it will be uncomfortable after the application. To improve the flexibility of the film, various plasticizers were incorporated in the film and their effects on the release rate of TAA were investigated. The results are shown in Fig. 6. The release rate of TAA from the polymeric film containing a plasticizer was higher than that from the film without a plasticizer. PEG 400 has shown the highest release rate followed by triethyl citrate and castor oil. PEG 400 is soluble in water, whereas triethyl citrate and castor oil are partially soluble and insoluble in water, respectively. This result suggested that water-soluble plasticizer might aid the release of TAA more than plasticizers with low aqueous solubility. When release medium diffuses into the polymeric film, water-soluble plasticizer, such as PEG 400, do not interfere with the movement of water molecule within the film. However, water-insoluble plasticizer, such as castor oil, may suppress the aqueous release medium from diffusing into the polymeric film.

Fig. 7 shows the effect of various penetration enhancers on the release rate of TAA from the polymeric film across the cellulose membrane. The release rate of TAA from polymeric film containing various enhancers was lower than that from the control without penetration enhancer except propylene glycol. In spite of lower release rate, the release rate *in vivo* might well be enhanced by these enhancers. Since the effect of most enhancers is not due to their effect on the release rate but due to their ability to change physicochemical properties of biological membrane. Propylene glycol tended to slightly increase the release rate. The drug is soluble in propylene glycol and propylene glycol is miscible with water, therefore, some of the drug dissolved in propylene glycol could diffuse out of the film easier. The effect of enhancer should be evaluated *in vivo*.

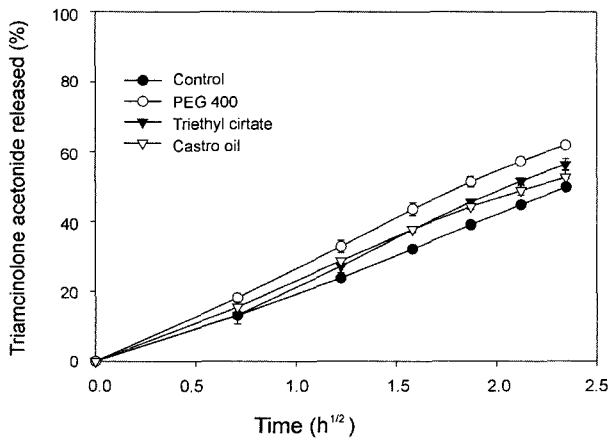

Fig. 6. Effect of various plasticizers on the release rate of TAA across the cellulose membrane from the polymeric film. (n=3)

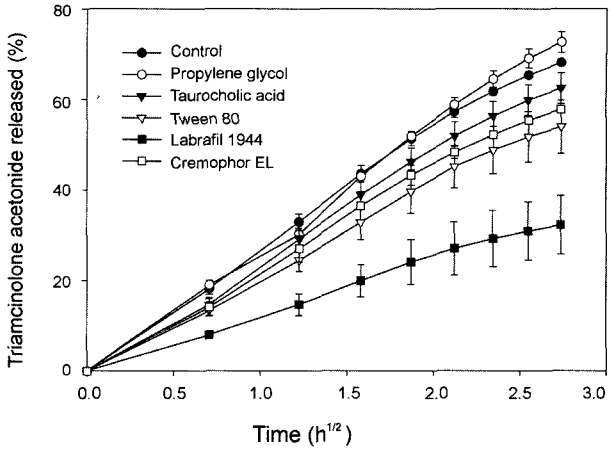

Fig. 7. Effect of various penetration enhancers on the release rate of TAA across the cellulose membrane from the polymeric film. (n=3)

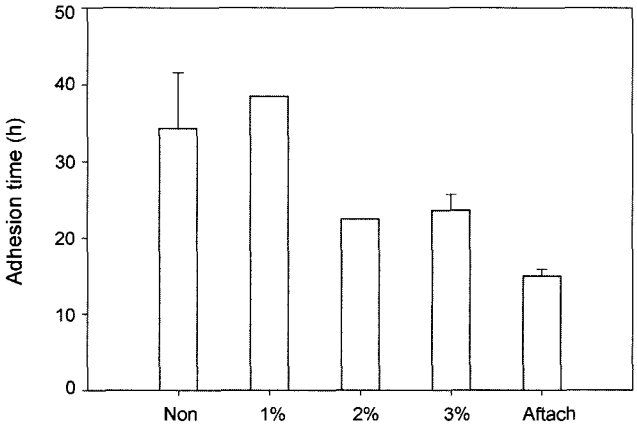

Fig. 8. Effect of various concentrations of PEG 400 as a plasticizer on the adhesion time of the polymeric film in the pH 7.4 phosphate buffer solution. (n=3)

The effect of various concentrations of PEG 400, a plasticizer, on the adhesion time of the film was measured in pH 7.4 phosphate buffer solution. When 1% of PEG 400 was incorporated in the polymeric film, the adhesion time of polymeric film was similar to the control without PEG 400. However, in the case of the polymeric films containing 2 or 3% of PEG 400, the adhesion time of the polymeric film decreased. Nonethe less, the adhesion time of all the polymeric films tested were longer than that of a commercial product, Aftach®.

REFERENCES

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

Choi, H. -G., Jung, J. -H., Yong, C. S., Rhee, C. -D., Lee, M. -K.,

Han, J. -H., Park, K, -M., and Kim, C. -K., Formulation and *in vivo* evaluation of omeprazole buccal adhesive tablet. *J. Control Release*, 68, 405-412 (2000).

Chun, M. -K., Cho, C. -S., and Choi, H. -K., A novel mucoadhesive polymer prepared by template polymerization of acrylic acid in the presence of poloxamer. *J. Appl. Polym. Sci.*, 79, 1525-1530 (2001).

Langoth, N., Kalbe, J., and Bernkop-Schnürch, A., Development of buccal drug delivery systems based on a thiolated polymer. *Int. J. Pharm.*, 252, 141-148 (2003).

Lim, S. T., Martin, G. P., Berry, D. J., and Brown, M. B., Preparation and evaluation of the *in vitro* drug release properties and mucoadhesion of novel microspheres of hyaluronic acid and chitosan. *J. Control Release*, 66, 281-292 (2000).

de Vries, M. E., Boddé, H. E., Verhoef, J. C., and Junginger, H. E., Developments in buccal drug delivery. *Crit. Rev. Ther. Drug Carrier Syst.*, 8, 271-303 (1991).

Remuñán-López, C., Portero, A., Vila-Jato, J. L., and Alonso, M. J., Design and evaluation of chitosan/ethylcellulose mucoadhesive bilayered devices for buccal drug delivery. *J. Control Release*, 55, 143-152 (1998).

Şenel, S., Kremer, M. J., Kaş, S., Wertz, P. W., Hincal, A. A., and Squier, C. A., Enhancing effect of chitosan on peptide drug delivery across buccal mucosa. *Biomaterials*, 21, 2067-2071 (2000).