Evaluation of Polyoxyethylene Homopolymers for Buccal Bioadhesive Drug Delivery Device Formulations

Submitted April 8, 1999; Accepted: August 13, 1999; Published: September 15, 1999.

Deepak Tiwari, Robert Sause, and Parshotam L. Madan

College of Pharmacy & Allied Health Professions, St. John's University, Jamaica, New York 11439

David Goldman

Pharmaceutical Division, Bayer Corporation, West Haven, Connecticut 06516

ABSTRACT Our objective was to evaluate the application of polyoxyethylene homopolymers in buccal bioadhesive drug (BBD) delivery device formulations. The bioadhesive strength of four different molecular weight (MW) polyoxyethylene polymers was measured by Instron® tensile tester using glass plate and bovine sublingual tissue as substrate surfaces. Several BBD device formulations containing polyoxyethylene polymer (MW 7,000,000) were prepared by direct compression and compression molding processes. The prepared BBD devices were evaluated for their elasticity, in vitro adhesion and drug release characteristics. The in vivo bioadhesion characteristics of a placebo compression molded device were examined in 3 adult healthy male beagle dogs. The bioadhesive strength of polyoxyethylene polymers appeared to be directly related to their molecular weights. When bovine sublingual mucosa or a glass plate was used as model mucosal substrate surface, the rank order of bioadhesive strength of different molecular weight polyoxyethylene polymers was similar. The bioadhesive strength of devices prepared by the compression molding process was greater than those prepared by direct compression, but the kinetics of drug release were independent of the process used for the preparation of the devices. The drug release and the bioadhesive strength of the similarly prepared device formulations appeared to be dependent on the drug:polymer ratios. The elasticity of the BBD devices prepared by compression molding was improved by the inclusion of polyisobutylene polymer in the formulations. When adhered to the oral cavity of the dogs, the compression molded placebo BBD device exhibited adhesion for at least 4 hours and appeared to show no signs of local irritation. In conclusion, BBD devices containing polyoxyethylene polymer (MW 7,000,000) can be prepared by direct compression or compression molding process in order to provide controlled drug release to the oral cavity while maintaining appropriate bioadhesive characteristics.

INTRODUCTION

The oral cavity is viewed as a convenient and easily accessible site for the delivery of therapeutic agents (1). Within the oral cavity, drugs can be administered from the buccal gingiva or the sublingual space either for the treatment of local conditions (eg, thrush) or for the systemic treatment of diseases (eg, angina). The advances in bioadhesive and controlled release technology have stimulated a renewal of interest in the delivery of drugs to, or via, the buccal route (2). Buccal bioadhesive drug (BBD) devices can now be designed to remain in contact with the oral mucosa while providing controlled release characteristics over a prolonged period of time. A combination of these two attributes can be achieved by the use of suitable bioadhesive materials (3-6). Appropriate materials for the bioadhesive drug delivery consist mainly of hydrogel-forming polymers (7,8). They have been called "wet" adhesives because they require moisture to exhibit the adhesive property (9). This may be supplied by the saliva, which may also act as the dissolution medium. The various polymers considered suitable for the development of bioadhesive devices are cellulosic derivatives (methylcellulose, sodium carboxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose); natural gums (guar gum, karaya gum, xanthan gum, locust bean gum, veegum); sodium alginate; polyoxyethylenes; and polyacrylates (carbopol and polycarbophil) (10-12).

Polyacrylic acid polymers have received considerable attention in the development of bioadhesive drug delivery systems (5-9). The high concentration of carboxyl groups in a dry tablet of polyacrylic acid generates a low surface pH (between 2 and 3) on moistening (13). A low pH would be expected to damage the contacting mucosal surface, and this has been reported in an in vivo study involving human volunteers (14). Results of preliminary investigation in human volunteers on the

KEY WORDS: polyox, bioadhesion, compression molding, buccal patch, polyethyleneoxide

1 **Corresponding author:** Deepak Tiwari, Bayer Corporation, West Haven, Connecticut 06516; telephone: (203) 812-2715, facsimile: (203) 812-5136; e-mail: deepak.tiwari.b@bayer.com

use of polyoxyethylene as a nonirritating buccal bioadhesive polymer appear promising (14,15). Polyoxyethylene homopolymers consisting of monomer $-\text{[CH}_2\text{-CH}_2\text{-O]}_n-$ are linear, nonionic, and water soluble polymers. Polyoxyethylene homopolymers (Polyox $\text{\textcircled{O}}$) are commercially available in different molecular weights ranging from about 100,000 to 8 million (16). Limited research on the use of polyoxyethylene homopolymers for buccal bioadhesive drug device formulations has been accomplished. Moreover, thermoplastic properties associated with polyoxyethylene homopolymers, which could be utilized to make a flexible buccal patch by compression molding, has not been explored. The objective of this study was to evaluate polyoxyethylene homopolymers as a platform for BBD device formulations. Four polyoxyethylene polymers of different molecular weights ranging from 200,000 to 7,000,000 were selected for initial bioadhesive strength screening using glass plate and bovine sublingual mucosa as substrate surfaces. A highly water soluble (160 mg/mL @ 25 $^{\circ}$ C) drug, chlorpheniramine maleate, was chosen as a model drug (17). Direct compression and compression molding processes were evaluated for the preparation of BBD devices.

MATERIALS AND METHODS

Polyoxyethylene (Polyox $\text{\textcircled{R}}$) and Polyethyleneglycol (Carbowax $\text{\textcircled{O}}$) were donated by Union Carbide (Danbury, CT). Polyisobutylene (Vistanex $\text{\textcircled{O}}$ LM-MS-LC) was donated by Exxon (Atlanta, GA). Chlorpheniramine maleate USP was purchased from Spectrum (Gardena, CA). Anhydrous lactose was purchased from Sheffield Products (Norwich, NY).

Preparation of the Polymer Disks

Compressed disks of the polymers were prepared by direct compression in a Carver $\text{\textcircled{R}}$ (Carver Inc., Wabash, IN) press using the flat, 10-mm diameter punches, under a 1,000 kg force for 6 seconds. The mean (SD) thickness of all the prepared disks was in the range of 1.29 (0.17) mm.

Preparation of Chlorpheniramine Maleate BBD Devices

The buccal devices of 10-mm diameter were prepared using a Carver $\text{\textcircled{R}}$ press either by direct compression or the compression molding process. In former, a 100-mg mixture of polymer and drug was compressed using flat tablet punches and dies under

a 1,000-kg force for 6 seconds. In the latter, sufficient amount of the mixture (drug, polymer, plasticizer, and/or elastomer polyisobutylene) was filled in a die of 1 mm thickness having a 5-cm internal diameter and a 6-cm external diameter. This mixture was then compressed under a 4,500-kg force between the two heated platens at 70 $^{\circ}$ C for 5 minutes. Disks of 10-mm diameter were then "cut" from the above compression-molded mixture with the help of a cork borer.

Bioadhesive Strength

A commercial bench-mounted vertical tensile/compression tester, Instron $\text{\textcircled{R}}$ 5569 (Instron Corp., Canton, MA), was used for the quantitative measurements of bioadhesive bond strength. The Instron $\text{\textcircled{R}}$ tester was directly controlled by the software Merlin $\text{\textcircled{R}}$ II, which provides full self-diagnostic, calibration, and analog data recording capabilities. Samples were tested between the stationary lower compression platen mounted to the main frame of the machine and the upper compression anvil fixed via the load cell to the moving crosshead. The compressed disks of the polymers or BBD devices were glued using cyanoacrylate adhesive to the compression anvil. Either glass plate or bovine sublingual tissue obtained from Animal Biotech Industries (Danboro, PA) and stored at - 20 $^{\circ}$ C was used as the model mucosal substrate surface. Before use, the tissue was thawed to room temperature in normal saline solution and then was cut to the dimensions of approximately 20 cm ^{2} surface. The substrate surface (bovine sublingual mucosa or a glass plate) was also fixed to the stationary base compression platen using cyanoacrylate adhesive. A constant volume of water was used to wet the above substrate surfaces (20 mL for the glass plate and 40 mL for the bovine tissue). The compressed disks were then adhered to the wet substrate by applying a constant force (1 N for glass plate and 5 N for the bovine tissue) with the help of Instron $\text{\textcircled{R}}$ for 5 minutes. The tensile test was then performed for adhesion strength characterization of the polymers by moving the compression anvil at a constant speed (0.2 mm/min for glass plate and 5 mm/min for bovine tissue). Data representing force as a function of displacement were obtained at 1-second intervals until the compressed disks were detached from the substrate surface (break point). The maximum force required to initiate the

detachment and area under the force-displacement curve was calculated for the quantification of the bioadhesive strength.

Elasticity Evaluation

The Instron® tensile tester with a standard 3-mm diameter puncture probe-chuck assembly at a crosshead speed of 0.2 mm/min was used for the quantitative measurement of elasticity of the prepared devices. The elasticity of the device was characterized by measuring the maximum penetration force and corresponding displacement required by the probe to cause failure of the device.

Drug Release Kinetics

A standard USP dissolution apparatus I (Vankel Industries Inc., Edison, NJ) without the basket fixture was used to evaluate drug release kinetics from the prepared device formulations. In order to mimic the in vivo adhesion of the devices to the gum area, each prepared device was affixed to the bottom flat end of the stirring rod instead of the basket fixture. The wet adhesive properties of the bioadhesive devices were utilized to affix the prepared bioadhesive devices. The flat bottom surface of the rod was moistened with the deionized water. The devices were affixed onto this moistened surface by maintaining a gentle fingertip pressure for 5 minutes. Deionized water at $37 \pm 0.5^\circ\text{C}$ was used as the dissolution medium, and the dissolution apparatus was operated at 100 rpm. Samples representing 10-mL aliquots were collected at predetermined time intervals and replaced with an equal volume of fresh dissolution medium. The samples were filtered through a 0.45- μm filter and then assayed for drug content using a Beckman DU-650 UV spectrometer (Vankel Industries Inc., Edison, NJ) at 261 nm.

Animal Studies

An experimental protocol was designed to evaluate bioadhesion characteristics of the prepared placebo BBD device formulation in three healthy adult male beagle dogs, 4 years of age, and having a weight in the range of 15 to 17 kg. This experimental protocol was reviewed and approved by the Institutional Animal Care and Use Committee. Placebo device formulations were placed in the oral cavity of the dogs, on the gum adjacent to upper canine teeth. The devices were adhered to the gum area by maintaining gentle fingertip pressure for 1 minute. The oral cavity of each dog was examined every hour for

possible dislocation of the adhered devices from the gum area. At the end of a 4-hour period, the devices were removed from each dog and the gum mucosa visually examined for any symptom of local skin irritation (redness or inflammation) that may have been caused by the device.

RESULTS AND DISCUSSION

Effect of Substrate Surfaces on Bioadhesive Strength

Bioadhesive strengths of four different molecular weight (MW) polyoxyethylene polymers, Polyox 80 (MW 200,000), Polyox 1105 (MW 900,000), Polyox 301 (MW 4,000,000), and Polyox 303 (MW 7,000,000) were determined using bovine sublingual tissue and glass plate as substrate surfaces. Preliminary studies using glass plate as substrate surface indicated that the optimal results of the bioadhesive strength measurements were obtained at 0.2 mm/min crosshead speed, 1 N pretest force, and 20 mL of the deionized water for wetting the substrate surface. Preliminary studies using bovine sublingual mucosa as substrate surface at 0.2 mm/min crosshead speed, 1 N pretest force, and 20 mL of the deionized water for wetting the substrate surface showed no apparent differences in the bioadhesive strength of the four different polyoxyethylene polymers. Further studies using bovine sublingual mucosa as substrate surface indicated that the optimal results of the bioadhesive strength measurements were obtained at 5.0 mm/min crosshead speed, 5 N pretest force, and 40 mL of the deionized water for wetting the substrate surface. Therefore, the bioadhesive strength determinations of polymers using bovine sublingual mucosa as substrate surface were conducted by employing 5.0 mm/min crosshead speed, 5 N pretest force, and 40 mL of deionized water.

Figures 1 and 2 show the results of mean detachment force and energy evaluations using glass plate and bovine sublingual mucosa as the model substrate surfaces, respectively. The results indicated that irrespective of the model mucosal substrate used (glass plate or bovine sublingual tissue), mean detachment force and energy was increased significantly ($P < 0.05$) with increasing molecular weight of the polyoxyethylene polymer from molecular weight 200,000 to 4,000,000. No significant difference ($P > 0.05$) in the mean detachment force and energy was observed when the

molecular weight of the polymer was increased from 4,000,000 to 7,000,000. Also, from both evaluations (glass plate and bovine sublingual tissue), the same rank order correlation of the polymer's bioadhesive strength was obtained, which could be arranged in descending rank order of their adhesiveness as follows:

Polyox303 = Polyox301 > Polyox1105 > Polyox80.

For the same polymer, higher mean detachment force was obtained when glass plate was used as the model substrate surface in comparison to the bovine sublingual tissue (Figure 1). However, higher mean detachment energy was obtained when bovine sublingual tissue was used as the model mucosal substrate in comparison to the glass plate (Figure 2). This could be due to the different elastic characteristics of the two-substrate surfaces. Because bovine sublingual tissue is highly elastic in nature in comparison to the glass plate, it stretches to the maximum in the beginning before the force is applied to break the adhesive bond. On the other hand, the surface of the glass plate is not elastic and does not stretch. Hence, the surface of the device is pulled as soon as force is applied, resulting in the breakage of adhesive bond. Bovine sublingual tissue stretched easily with the applied force; therefore, higher detachment energy and lower detachment force was obtained for bovine sublingual tissue in comparison to the glass plate.

Table 1. BBD device formulations of model drug chlorpheniramine maleate

Formulation	Polyox 303	Drug	PIB	PEG 600
DC-1	70	30	-	-
DC-2	30	30	30	10
CM-3	70	30	-	-
CM-4	60	30	-	10
CM-5	60	30	5	5
CM-6	50	30	15	5
CM-7	30	30	30	10
CM-Placebo	30	30*	30	10

Numbers are percentages. BBD, buccal bioadhesive drug; PIB, polyisobutylene; PEG, polyethyleneglycol; DC, direct compression; CM, compression molding. *Drug was replaced with anhydrous lactose.

Figure 1. Mean detachment force of Polyox polymers using two model mucosal substrate surfaces

Figure 2. Mean detachment energy of Polyox polymers using two model mucosal substrate surfaces.

Formulation and In Vitro - In Vivo Evaluation

A high-molecular-weight polyoxyethylene polymer Polyox 303 showing good bioadhesive characteristic was chosen for the formulation of BBD device formulations. A highly water soluble (160 mg/mL @ 25°C) drug chlorpheniramine maleate, was chosen as a model drug. Direct compression and compression molding processes were evaluated for the preparation of the devices. Table 1 shows the concentrations of the polymers and drug used for the two formulations prepared by direct compression (DC) and five formulations prepared by the compression molding process (CM).

Elasticity Evaluation

The elasticity of the BBD devices was evaluated by measuring the maximum force required to puncture the device and the corresponding displacement at the maximum force. The results of this evaluation for the all the prepared device formulations are listed in Table 2. The DC device formulations showed lower displacement values in comparison to CM device formulations and were expectedly brittle. The fracture of these devices was visually observed when the puncture was attempted. Higher force was required for fracturing the device formulation DC-1 than the formulation DC-2. The CM devices showed higher values of displacement in comparison to DC devices and did not appear to fracture when the puncture was attempted, indicating the elastic or plastic behavior.

Table 2. Elasticity evaluation of BBD device formulations

Formulation	Force, N	Displacement, mm
DC-1	8.9 (1.02)	0.46 (0.02)
DC-2	0.90 (0.18)	0.45 (0.19)
CM-3	21.81 (1.09)	1.26 (0.15)
CM-4	20.79 (1.21)	1.24 (0.16)
CM-5	11.77 (0.42)	1.67 (0.07)
CM-6	8.64 (0.28)	1.66 (0.24)
CM-7	0.62 (0.14)	1.66 (0.25)
CM-Placebo	0.60 (0.12)	1.67 (0.14)

All values are expressed as mean $\pm$ SD, $n = 3$.
DC, direct compression; CM, compression molding.

Table 3. Bioadhesive strength of DC and CM BBD device formulations

Formulation	Force, N	Energy, mJ
DC-1	4.60 (0.10)	0.211 (0.031)
DC-2	2.70 (0.17)	0.063 (0.009)
CM-3	6.90 (0.19)	0.302 (0.026)
CM-4	7.36 (0.54)	0.386 (0.109)
CM-5	7.69 (0.33)	0.320 (0.052)
CM-6	7.67 (0.74)	0.309 (0.006)
CM-7	3.81 (0.19)	0.308 (0.016)
CM-Placebo	2.77 (0.33)	0.143 (0.027)
AftachÒ	2.29 (0.14)	0.067 (0.016)

All values are expressed as mean $\pm$ SD, $n = 5$. BBD, buccal bioadhesive drug; DC, direct compression; CM, compression molding.

The force required for puncturing the device formulation containing polyethyleneglycol (CM-4) did not appear to be different in comparison to the formulation containing no polyethyleneglycol (CM-3). Similarly, the force required for puncturing the placebo device formulation containing anhydrous lactose (CM-Placebo) did not appear to be different in comparison to the formulation containing drug chlorpheniramine maleate (CM-7).

The device formulations containing no polyisobutylene (CM-3 and CM-4) showed significantly higher values of the force required to puncture the device in comparison to the formulations containing polyisobutylene (CM-5, CM-6, and CM-7). The force required to puncture the device for formulations CM-5, CM-6, and CM-7 decreased as polyisobutylene concentration increased from 5 to 30% w/w. Polyisobutylene, a commonly used elastomeric polymer in chewing gum formulations (18-22), appeared to improve the elasticity of the CM device formulations.

Bioadhesive Strength Evaluation

The bioadhesive strength of all the prepared formulations was characterized with the Instron® tensile tester using a glass plate as the model mucosal substrate surface. AftachÒ was included in this study for the purpose of the comparison. AftachÒ is a commercial mucosal adhesive tablet of triamcinolone acetonide developed for the treatment of aptha (23). It utilizes a mixture of hydroxypropyl cellulose and carbopol in order to provide

appropriate adhesion property to the oral mucous membrane and to control drug release from the tablet. The results of this evaluation are summarized in Table 3. In general, the bioadhesive strength of similarly prepared formulations was directly proportional to their polyoxyethylene polymer concentrations. Formulations CM-5 and CM-6, containing higher concentrations of the polymer, showed higher detachment forces and energies in comparison to formulation CM-7. Similarly, formulation DC-1, containing higher concentrations of the polymer, showed higher detachment force and energy in comparison to formulation DC-2.

The bioadhesive strength of the formulations containing similar drug and polymer concentrations but prepared by compression molding appeared to show higher detachment force and energy in comparison to the formulations prepared by direct compression. Formulation CM-3, containing similar drug and polymer concentrations, showed higher detachment force and energy in comparison to formulation DC-1. Similarly, formulation CM-7, containing similar drug and polymer concentrations, showed higher detachment force and energy in comparison to formulation DC-2. The apparent increase in the bioadhesive strength of the CM devices could probably be explained by the compression molding process, which plasticizes the polymer and may affect the physical characteristics (such as hydration and plastic/elastic nature) of the devices.

The bioadhesive strength of CM-Placebo formulation (30% w/w anhydrous lactose and 30% w/w Polyox 303) was lower than the CM-7 formulation (30% w/w drug and 30% w/w Polyox 303), probably because of the different solubilities of anhydrous lactose and the drug. However, the bioadhesive strength of all the prepared device formulations was higher in comparison to the commercial preparation AftachO.

Drug Release Kinetics

The release kinetics of the drug appeared to be independent of the process used for preparation of the devices. Figure 3 shows percentage of drug released as a function of time for the formulations DC-1 and CM-3 containing similar concentrations of drug and polymer. Drug-release profiles of the formulations DC-1 and CM-3, prepared by direct compression and compression molding, respectively, appeared to be

similar. Approximately 80% of the drug was released in 5.5 hours. Some differences in the dissolution profile were observed after 6 hours, where rate of release was higher for the device formulation CM-3 in comparison to the DC-1 formulation.

Figure 3. Dissolution profile of directly compressed DC-1 and compression-molded CM-3 formulations.

Figure 4. Dissolution profile of directly compressed DC-2 and compression-molded CM-7 formulations.

In Vivo Adhesion Characteristics

The in vivo adhesion characteristics of the placebo compression molded device formulation containing 30% w/w Polyox 303 were evaluated in three adult healthy male beagle dogs. The results exhibited a reasonably good adhesion of the device in the oral cavity of dogs for at least 4 hours as no dislocation of the device was observed during this period. At the end of 4-hour experiment, the devices were removed and mucosal tissue underneath the device visually examined. The placebo device appeared to be well tolerated by all three dogs, and no signs of local irritation or untoward effect of the device on oral mucosa was observed.

CONCLUSION

The bioadhesive strength of polyoxyethylene polymers increased with increasing polymer molecular weights, exhibiting a direct relationship between bioadhesive strength and molecular weight. When bovine sublingual mucosa or glass plate was used as the model mucosal substrate surface, similar rank order of polymer bioadhesive strength was observed, indicating that the glass plate provides a suitable model for the evaluation of the BBD device formulations. The bioadhesive strength of BBD devices prepared by compression molding was greater than those prepared by direct compression, but the kinetics of drug release appeared to be independent of the process used for the preparation of the devices. Elasticity of the BBD devices prepared by compression molding was improved by the inclusion of polyisobutylene polymer in the formulations. A placebo BBD device prepared by compression molding exhibited adhesion for at least 4 hours and appeared to show no signs of local irritation in the oral cavity of dogs.

In conclusion, the BBD devices containing polyoxyethylene polymer (MW 7,000,000) can be prepared by compression molding or direct compression in order to provide controlled drug release to the oral cavity while maintaining appropriate bioadhesive characteristics.

ACKNOWLEDGEMENTS

This work was supported by a grant from Bayer Corporation. The authors wish to thank Robert Thurston, Chris Town, and William Brubaker for assistance with the animal work.

Figure 4 shows percentage of drug released versus time for the formulations DC-2 and CM-7 containing similar concentrations of drug, polymer, elastomer, and plasticizer. Drug-release profiles of these two formulations prepared by direct compression and compression molding, respectively, also appeared to be similar. However, less than 60% of the drug was released from these devices in 5.5 hours. No further increase in the percentage of drug released was observed for these formulations up until 12 hours. Formulations DC-2 and CM-7 contained 30% w/w of the elastomer polyisobutylene, which is commonly used as a chewing gum base. The inability of these formulations to release the remaining 40% drug is similar to those observed with chewing gum formulations (24,25).

Drug-release kinetics of the four device formulations prepared by compression molding are shown in Figure 5. The results of this evaluation indicated that drug-release kinetics depend on the complex interplay between the polymer (Polyox 303), elastomer (polyisobutylene), and plasticizer (polyethyleneglycol) concentrations.

Figure 5. Dissolution profile of compression-molded formulations.

REFERENCES

1. Veillard MM, Longer MA, Martens TW, Robinson JR. Preliminary studies of oral mucosal delivery of peptide drugs. *J Controlled Release*. 1987;6:123-131.
2. Ponchel G. Formulation of oral mucosal drug delivery systems for the systemic delivery of bioactive materials. *Adv Drug Delivery Rev*. 1994;13:75-87.
3. Jimenez-Castellanos MR, Zia H, Rhodes CT. Mucoadhesive drug delivery systems. *Drug Dev Ind Pharm*. 1993;19:143-194.
4. Duchene D, Touchard F, Peppas NA. Pharmaceutical and medical aspects of bioadhesive systems for drug administration. *Drug Dev Ind Pharm*. 1988;14:283-318.
5. Park K, Robinson JR. Bioadhesive polymers as platforms for oral-controlled drug delivery: method to study bioadhesion. *Int J Pharmacol*. 1984;19:107-127.
6. Helliwell M. The use of bioadhesives in targeted delivery within the gastrointestinal tract. *Adv Drug Delivery Rev*. 1993;11:221-251.
7. Gupta A, Garg S, Khar RK. Interpolymer complexation and its effect on bioadhesive strength and dissolution characteristics of buccal delivery systems. *Drug Dev Ind Pharm*. 1994;20:315-325.
8. Satoh K, Takayama K, Machida Y, Suzuki Y, Nakagaki M, Nagai T. Factors affecting the bioadhesive property of tablet consisting of hydroxy propyl cellulose and carboxyvinyl polymer. *Chem Pharm Bull*. 1989;37:1366-1368.
9. Chen JL, Cyr GN. Compositions producing adhesion through hydration (Chapter 10). In: Manly RS, ed. *Adhesive Biological Systems*. New York, NY: Academic Press; 1970:163-181.
10. Merkle HP, Wolany G. Buccal delivery of peptide drugs. *J Controlled Release*. 1992;21:155-164.
11. Mortazavi SA, Smart JD. An in vitro method for assessing the duration of mucoadhesion. *J Controlled Release*. 1994;31:201-212.
12. Smart JD. An in vitro assessment of some mucosa-adhesive dosage forms. *Int J Pharmacol*. 1991;73:69-74.
13. Smart JD. Drug delivery using buccal-adhesive systems. *Adv Drug Delivery Rev*. 1993;11:253-270.
14. Bottenberg P, Cleymae R, Muynck C, Remon JP, Coomans D, Michotte Y, Slop D. Development and testing of bioadhesive fluoride-containing slow-release tablets for oral use. *J Pharm Pharmacol*. 1991;43:457-464.
15. Bottenberg P, Cleymae R, Muynck C, Remon JP, Coomans D, Slop D. Comparison of salivary fluoride concentrations after administration of a bioadhesive slow-release tablet and a conventional fluoride tablet. *J Pharm Pharmacol*. 1992;44:684-686.
16. Sentry® Polyox® WSR, NF- Polyethylene oxide [product literature]. Danbury, Conn: Union Carbide; 1995.
17. Eckhart CG, McCorkle T. Chlorpheniramine maleate. In: Florey K, ed. *Analytical Profiles of Drug Substances-Volume 7*. New York, NY: Academic Press; 1978:45-80.
18. Schott H. Polymer Science. In: Martin A, Bustamante P, Chun AHC, eds. *Physical Pharmacy*. Malvern, PA: Lea & Febiger; 1993:578-579.
19. Cherukuri SR, Friello DR, Ferroti M, Jewell W, D'Amelia RP, inventors; Nabisco Brands Inc. New York, NY. Gum base, chewing gum containing same and method. US patent 4,352,822. Oct. 5, 1982.
19. Mackay DAM, Warren K, Witzel F, Schoenholz D, inventors; Life Savers Inc. New York, NY. Long-lasting flavored chewing gum including chalk-free gum base. US patent 4,062,274. Dec. 20, 1977.
20. Song JH, Greenberg MJ, Record DW, Zibell SE, Broderick K, Schnell PG, inventors; Wrigley, Jr. Co. Chicago, IL. Gum composition containing dispersed porous beads containing active chewing gum ingredients and methods, US patent 5,154,927. Oct. 13, 1992.
21. Broderick KB, Record DW, inventors; Wrigley, Jr. Co. Chicago, IL. Gum composition containing dispersed porous beads containing active chewing gum ingredients and method. US patent 5,139,787. Aug. 18, 1992.
22. K. Satoh, K. Takayama, Y. Machida, Y. Suzuki, M. Nakagaki and T. Nagai. Factors affecting the bioadhesive property of tablet consisting of hydroxy propyl cellulose and carboxyvinyl polymer. *Chem. Pharm. Bull*. 1989;37:1366-1368.
23. M. Pederson and M.R. Rassing. Miconazole chewing gum as a drug delivery system test of release promoting additives *Drug Dev. Ind. Pharm*. 1991;17:411-420.
24. T. Anderson, M. Gram-Hansen, M. Pedersen and M.R. Rassing. Chewing gum as a delivery system for nystatin influence of solubilizing agents upon the release of water insoluble drugs. *Drug Dev. Ind. Pharm*. 1990;16:1985-1994.