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PREPARATION AND IN VITRO ASSESSMENT OF VARIOUS MUCOSA-ADHESIVE FILMS FOR BUCCAL DELIVERY

SEYED-ALIREZA MORTAZAVI and REZA ABOOFAZELI

School of Pharmacy, Shaheed Beheshti University of Medical Sciences, Tehran, Iran

ABSTRACT

The aim of this study was to examine various polymers considered to have mucosa-adhesive properties for the preparation of buccal-adhesive films and their *in vitro* evaluation. A number of materials, such as cellulose derivatives, carbopols and natural polymers, were employed for the preparation of buccal-adhesive films. Aqueous solutions containing the mucosa-adhesive polymer and a plasticizer were prepared and used to prepare films by the "solvent cast" method. Prepared films were then evaluated in terms of their physical appearance and film forming ability, *in vitro* mucosa-adhesive strength and duration of mucosa-adhesion. Results showed that among the various materials examined, sodium carboxymethyl cellulose (CMC) formed very flexible films with the greatest mucosa-adhesive strength. Further studies showed that the combination of carbopols and CMC, along with glycerin as the plasticizer, resulted in the formation of films with desirable appearance and a relatively stronger mucosa-adhesive strength than films containing CMC alone. *In vitro* studies showed that films containing carbopol 934P, CMC and glycerin gave the greatest mucosa-adhesive strength and longer mucosa-adhesion. In conclusion, this formulation is proposed as a good base for the preparation of buccal-adhesive films and patches. Furthermore, it is suggested that in the development of buccal-adhesive drug delivery systems, and in particular films and patches, duration of mucosa-adhesion determined by *in vitro* experiments is a critical factor in the selection of the ultimate formulation.

Key words: Buccal films, Patches, Carbopol 934P, Mucoadhesion, Sodium carboxymethyl cellulose

INTRODUCTION

In recent years, significant interest has been expressed in development of controlled drug delivery to, or via mucous membranes by the use of bioadhesive polymers. These dosage forms can be administered by different routes, including ocular, nasal, rectal and vaginal, for local or systemic drug delivery (1-4). The term "bioadhesion" is defined as the attachment of synthetic or biological macromolecules to a biological tissue (5). When applied to a mucosal epithelium, bioadhesive interactions occur primarily with the mucus layer, and this phenomenon is referred to as "mucoadhesion" (1). Mucosal-adhesive materials have been investigated and identified in previous work (6-9). These materials are generally hydrophilic macromolecules that contain numerous hydrogen bond forming groups, and will hydrate and swell when placed in contact with an aqueous solution. These materials need to be in the hydrated form in order to become adhesive but overhydration usually results in the formation of a slippery mucilage and a loss of the adhesive properties. Among the various routes of delivering mucoadhesive dosage forms, the buccal route appear to offer advantages of good accessibility, robust epithelium, quick and easy removal of the dosage form in case of need, good drug absorption, reduction of the first pass hepatic metabolism, and satisfactory patient acceptance and compliance (2,3). Buccal-adhesive patches are a novel form of mucosa-adhesive systems, which are thin and flexible films and are usually prepared by dissolving the bioadhesive polymer (s) along with a plasticizer in a solvent, followed by solvent evaporation (10). It has been reported

Correspondence: S.A.Mortazavi, School of Pharmacy, Shaheed Beheshti University of Medical Sciences, Tehran, Iran, P.O. Box: 455-6153, Fax: 8795008

(11) that buccal patches prepared by casting different polymer solutions, including hydroxypropylmethyl cellulose, hydroxyethyl cellulose, polyvinyl alcohol and polyvinyl pyrrolidone, along with a plasticizer, onto an impermeable backing sheet adhere to buccal mucosa *in vivo* for up to one hour. In another study (12) mucoadhesive buccal patches were prepared for controlled release of benzydamine and lidocaine from tamarind gum. Prepared patches were well tolerated and adhered to the upper gum of human volunteers for over 8h. The aim of this study was to screen and evaluate various polymers for their ability to form buccal-adhesive films. Also, it was of interest to evaluate effects of polymer concentration as well as addition of the various amounts of plasticizer on film formation, *in vitro* mucosa-adhesive strength and duration of mucosa-adhesion of films having good adhesion *in vitro*.

MATERIALS & METHODS

Materials: Carbopols including Carbopol 934P (C934), Carbopol 974P (C974) and polycarbophil (PC) were obtained as a gift from Noavar-Arash Co. (B.F. Goodrich sales agent), Tehran, Iran; Cellulose derivatives including methyl cellulose (MC), hydroxypropylmethyl cellulose (HPMC) and sodium carboxymethyl cellulose (CMC) were all of low-medium viscosity grade and manufactured by Hercules Chemical Co., USA. The natural polymers tragacanth and gelatin, sodium chloride, sodium dihydrogen phosphate, disodium hydrogen phosphate, sodium hydroxide and various plasticizers including propylene glycol, polyethylene glycol 400 and 600 and glycerin were obtained from Merck Chemical Co., Germany. Polyvinyl pyrrolidone (PVP) and polyvinyl alcohol (PVA) were prepared from Fluka Chemical Ltd., Derbyshire, U.K. Triethyl citrate (plasticizer) and the natural polymer acacia were purchased from Aldrich Chemical Co., Gillingham, England.

Preparation of the test films: For the purpose of this study various polymers were used. These polymers were divided into four main group. The polymers studied in each group and their preparation method is described below:

Cellulosic polymers: Aqueous solutions containing 0.5-3% v/v polymer and glycerin (1-9% w/v) were prepared and filled into glass molds with a height of 1.5cm and a diameter of 5cm and placed in a 37°C oven until completely dried.
Rectangular films with a dimension of 0.5X1.5 cm were then cut out and used for experimentation.

Carbopols: Aqueous solutions containing 0.1-0.2 %w/v carbopol and a plasticizer were prepared and pH was adjusted to 6.0 using 1N sodium hydroxide. Aqueous solutions containing carbopol, plasticizer and CMC (1% w/v) were also prepared and pH adjusted to 6.0 using 1N sodium hydroxide.

Natural polymers: Aqueous solutions containing acacia (2-10% w/v), gelatin (5-10% w/v) or tragacanth (0.5-2% w/v) and glycerin (1-10% v/v) or propylene glycol (5-7% v/v) were prepared and treated.

Other polymers: Aqueous solutions containing either PVA (5-15% w/v) or PVP (5-20% w/v) and glycerin or propylene glycol were prepared and treated.

Evaluation of the prepared films: Following the preparation of films and assessment of their physical appearance, following tests were undertaken:

Assessment of the mucosa-adhesive strength of films: In order to evaluate the mucosa-adhesive strength of the prepared films, an apparatus (Fig.1) principally similar to that described in previous studies (8,9,13) was designed and used. The upper stationary platform was linked to a balance for measuring the force needed to break contact between the film and mucosa. The model mucosal membrane used in this study was rat small intestine which was prepared according to the previous studies (8, 9). Sections of the rat intestine were placed and fixed over two platform in the test cells filled with pH6.8 isotonic phosphate buffer, maintained at 37°C, and allowed to equilibrate for 1 min. The prepared films were then individually sandwiched between the two mucosa covered platforms and kept in place for 5 min and then a constantly increasing force of 0.1 g/sec was applied on the adhesive joint formed between rat intestine and the test film, by gradual lowering of the lower platform.

This trend was continued until the contact between the test film and mucosa was broken and the maximum measured force was recorded.

Assessment of the duration of mucosa-adhesion of films: The apparatus designed (Fig. 2) for this study was based on the one that is described by Mortazavi and Smart (14) and composed of six upper and six lower cylindrical platforms within a clear jacketed perspex cell, filled with pH 6.8 isotonic phosphate buffer. Sections of rat intestine were mounted securely in place (mucosal side upwards) on each of the platforms and allowed to equilibrate for 1 min. The test films were sandwiched between the two platforms and allowed to stand for 5min. Then, through two pulley system a 2 g weight was applied on each upper platform. This weight was chosen, since it is not expected that buccal-adhesive films encounter very high stresses in the mouth. As soon as the contact between the film and the mucosal surface was broken, a small flap dropped onto a photocell detector, stopped the timer device (recording the elapsed time to 0.1 min) and measured the duration of mucosa-adhesion of films.

RESULTS AND DISCUSSION

As mentioned in the experimental section, four group of polymers were investigated for their ability to form buccal-adhesive films. Carbopols, which are long chain acrylic acid based polymers, have been reported as strong mucosa-adhesives (7, 9, 15). In this study several carbopol and other polymers were investigated. The following results were obtained: A suitable mucosa-adhesive film with good adhesive strength should have a uniform thickness, to be free of any air bubble and should not have any apparent crack or fracture. Results of this study also indicate that none of the prepared films possessed these undesirable characters. When using CMC, it was found that polymer concentrations above 3% w/v, result in the formation of viscous and gelled systems, unsuitable for film formation. However, solutions containing up to 3%w/v CMC and 7% v/v glycerin, as plasticizer, produced clear and flexible films. Films which were prepared from 2 or 3% w/v CMC solutions had greater resistance to tearing than those prepared from the 1 %w/v solutions. When using HPMC, it was found that aqueous solutions of 1.5%w/v polymer (or less) and 5%v/v glycerin can form clear and flexible films. Finally, aqueous solutions of 2.5% w/v or less MC and 7% v/v glycerin formed slightly hazy and less flexible films than HPMC and CMC. Aqueous solutions containing 0.15% w/v (above that very viscous solutions were formed) carbopol and various plasticizers formed very brittle films, unsuitable for further studies.

Table 1. Mucosa-adhesive strength of cellulosic films in pH 6.8 isotonic phosphate buffer at 37°C, prepared from solutions containing various amounts of polymer and glycerin (n=3, mean±SD)

CMC (% w/v)	Glycerin (% v/v)	Mucosa-adhesive strength (mN)
1.0	7.0	200±2
2.0	7.0	480±1
3.0	7.0	500±2
2.0	3.0	250±5
2.0	5.0	683±2
2.0	7.0	480±1
2.0	9.0	473±3
HPMC (% w/v)	**Glycerin (% v/v)**	**Mucosa-adhesive strength (mN)**
0.5	5.0	300±1
1.0	5.0	321±2
1.5	5.0	380±1
1.5	1.0	431±1
1.5	3.0	400±2
1.5	5.0	380±1
1.5	7.0	241±3
1.5	9.0	220±2
MC (%w/v)	**Glycerin (%v/v)**	**Mucosa-adhesive strength (mN)**
0.5	7.0	55±2
1.0	7.0	152±2
2.0	7.0	221±1
2.5	7.0	182±2
2.0	5.0	161±1
2.0	7.0	221±1
2.0	9.0	211±3

However, it should be noted that as it is reported (16), the addition of polyisobutylene or polyisopropylene as plasticizers solve the problem and results in film formation, but we did not have access to any of these plasticizers. Therefore, it was decided to combine carbopols with CMC, which is a good film forming polymer and also has good mucosa-adhesion, comparable with carbopols (4, 7). In fact, the combination of

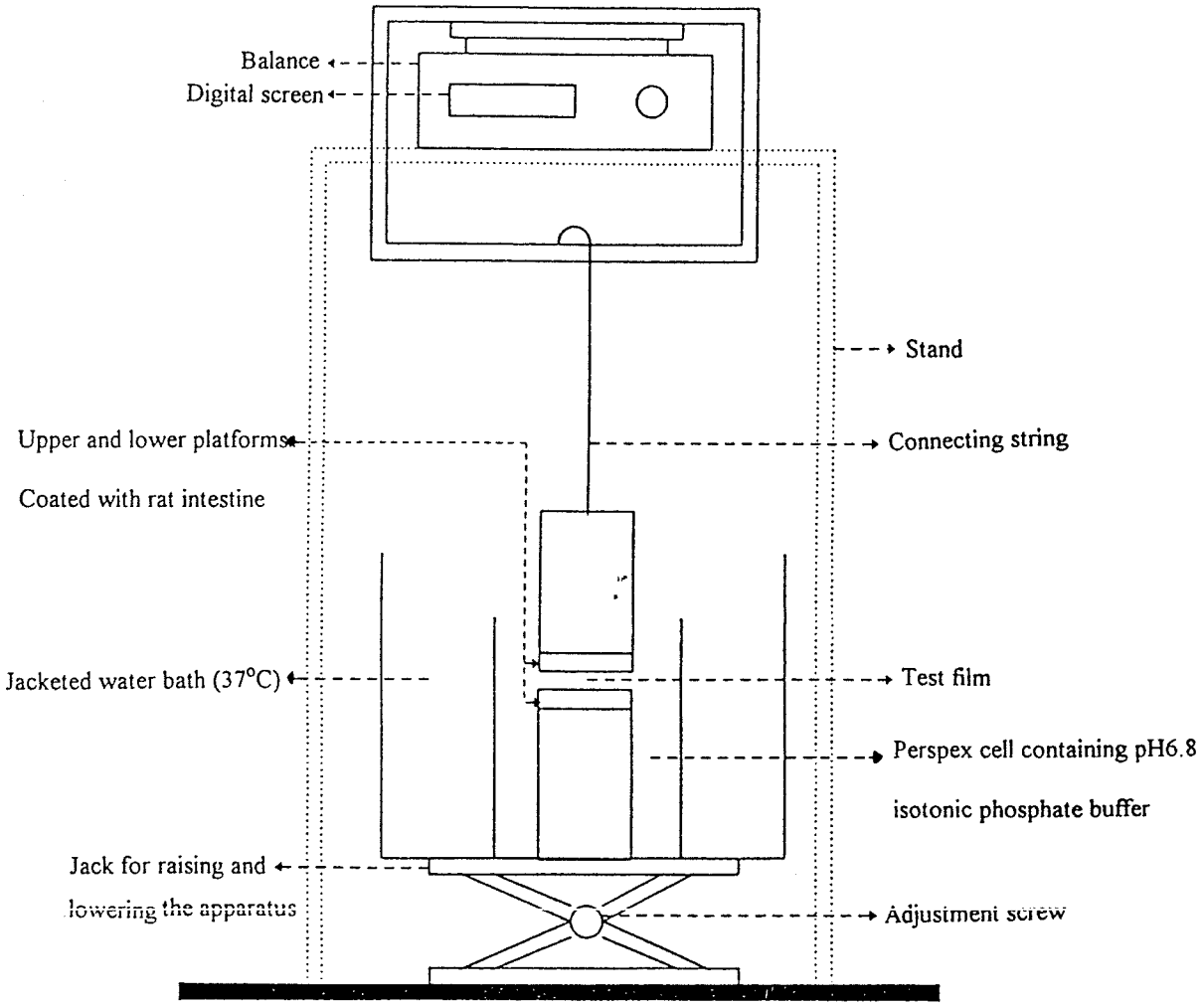

Fig. 1. Schematic drawing of the apparatus used for assessing the mucosa-adhesive strength of test film

carbopols and cellulose derivatives has been used by other researchers (8,17) as putative mucosal-adhesives, and it has been suggested that cellulosic polymers can be used in appropriate amounts without significant effect on the mucosa-adhesive ability of carbopols. It was found that formulations containing 0.075, 0.1 or 0.15% w/v carbopol, 1% w/v CMC and 2% v/v glycerin could form clear and flexible gels. Furthermore, it was found that films prepared from solutions containing 0.075% w/v carbopol were looser and break easier than those prepared from solutions with higher carbopol concentration. The results obtained with aqueous solutions containing 5-20% w/v acacia and 5-10% v/v glycerin, showed a lack of film forming ability. Hence, the plasticizer used was changed into propylene glycol. The results showed that solutions containing 5-20% w/v acacia and 7% v/v propylene glycol can form clear, slightly yellow and reasonably flexible films. The presence of less than 7%v/v propylene glycol in solution resulted in the formation of brittle films. With gelatin, it was shown that solutions containing 5-10% w/v gelatin and 5% v/v glycerin can form clear yellow-brown and flexible films. Finally, with solutions containing tragacanth, it was found that a polymer concentration of 0.5% w/v and 2% v/v glycerin can form slightly hazy and reasonably flexible films. However, increasing the amount of tragacanth in solution, resulted in the formation of very viscous or even gelled formulations, making them unsuitable for further studies. Both PVA and PVP have been reported to have weak mucosa-adhesive properties (7,18). All attempts to form suitable films with PVP failed, and hence this polymer was not used for further studies. With PVA, aqueous solutions containing 5 or 10% w/v polymer and 5% v/v propylene glycol were found to form suitable films. However, glycerin was found to be unsuitable as a plasticizer when used in combination with PVA. The results obtained with cellulose containing films are shown in Table 1. As shown in Table 1, increasing the amount of CMC, HPMC or MC (up to 2% w/v) in the formulation, results in an increase in the mucosa-adhesive strength of the films. In addition, the ranking order of mucosa-

Table 2. Mucosa-adhesive strength of carbopol/ CMC containing films in pH 6.8 isotonic phosphate buffer at 37°C, prepared from aqueous solutions containing different amounts of polymers and glycerin (n=3, mean±SD)

C934 (% w/v)	CMC (% w/v)	Glycerin (% v/v)	Mucosa-adhesive strength (mN)
0.075	1.0	2.0	502±4
0.10	1.0	2.0	521±5
0.15	1.0	2.0	541±3
0.15	0.5	2.0	480±2
0.15	1.0	2.0	541±3
0.15	2.0	2.0	593±5
0.15	2.0	1.0	560±2
0.15	2.0	2.0	593±5
0.15	2.0	3.0	823±3
PC (% w/v)	CMC (% w/v)	Glycerin (% v/v)	Mucosa-adhesive strength (mN)
0.075	1.0	2.0	523±6
0.10	1.0	2.0	550±1
0.15	1.0	2.0	672±2
0.15	0.5	2.0	630±1
0.15	1.0	2.0	672±2
0.15	2.0	2.0	700±1
0.15	2.0	1.0	601±2
0.15	2.0	2.0	700±2
0.15	2.0	3.0	721±5
C974 (% w/v)	CMC (% w/v)	Glycerin (% v/v)	Mucosa-adhesive strength (mN)
0.075	1.0	2.0	530±9
0.10	1.0	2.0	550±8
0.15	1.0	2.0	609±5
0.15	0.5	2.0	537±3
0.15	1.0	2.0	609±5
0.15	2.0	2.0	630±9
0.15	2.0	1.0	751±6
0.15	2.0	2.0	630±9
0.15	2.0	3.0	590±7

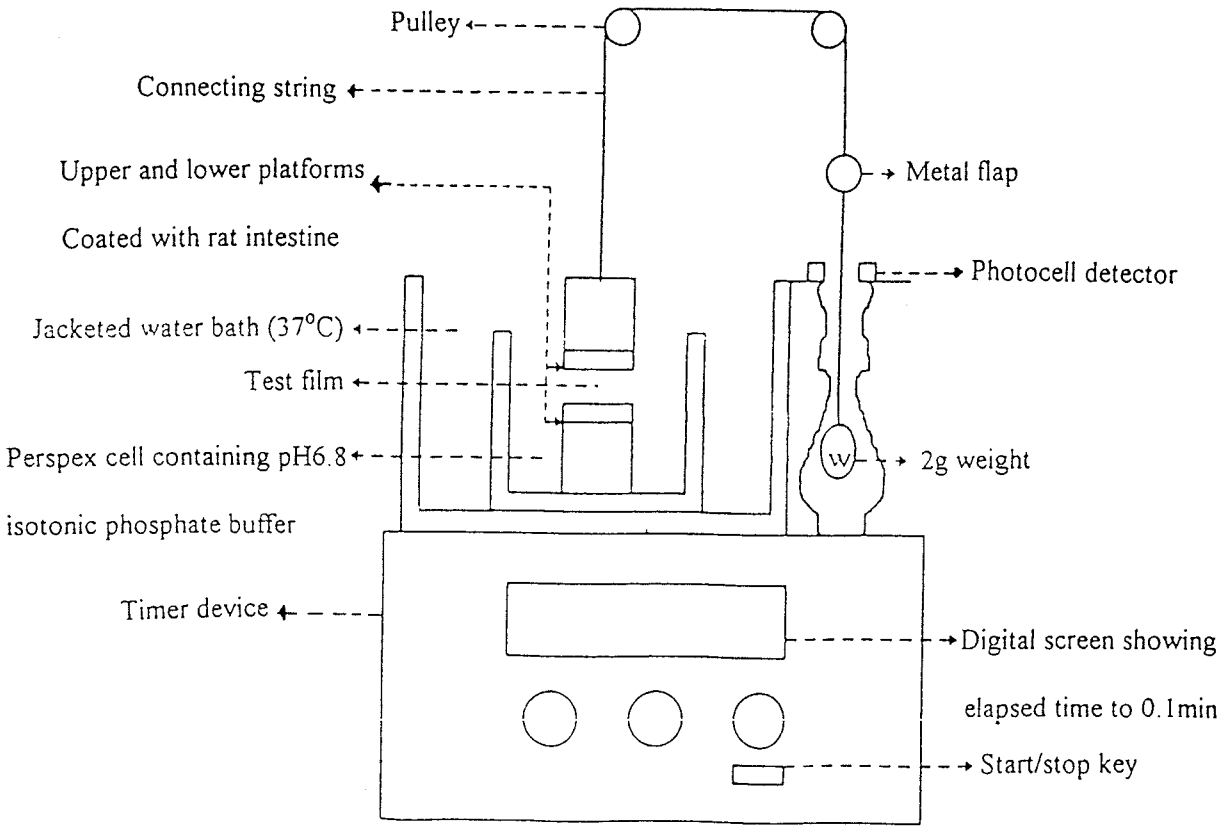

Fig. 2. Schematic drawing of one compartment of the apparatus used for assessing the duration of mucosa-adhesion of test films.

adhesion were CMC>HPMC>MC, which is in agreement with the previous studies (7, 19). Beside of anionic nature of CMC, which is required for strong mucosa-adhesion, its greater ability in absorbing water and being wetted by mucosal surface enhances spreading of the film over the mucosal surface and the formation of an intimate contact needed for strong mucosal-adhesion. With CMC containing films, since there was no significant (P>0.05) difference between the mucosa-adhesion of formulations containing 2 and 3% w/v CMC, and because of the better appearance of the formed films, they were chosen

Table 3. Mucosa-adhesive strength of films, prepared from aqueous solutions of natural polymers in pH 6.8 isotonic phosphate buffer at 37°C (n=3, mean±SD)

Acacia (% w/v)	PG (% v/v)	Mucosa-adhesive strength (mN)
5.0	5.0	---- (brittle film)
5.0	6.0	---- (brittle film)
5.0	7.0	87±2
5.0	7.0	87±2
10.0	7.0	193±1
15.0	7.0	229±3
20.0	7.0	---- (brittle film)
Gelatin (% w/v)	Glycerin (% v/v)	Mucosa-adhesive strength (mN)
5.0	5.0	200±1
7.0	5.0	184±2
10.0	5.0	173±2
5.0	3.0	185±3
5.0	5.0	200±3
5.0	7.0	250±1
5.0	9.0	232±4
Tragacanth (% w/v)	Glycerin (% v/v)	Mucosa-adhesive strength (mN)
0.5	2.0	234±3
0.5	1.0	251±2

for further studies. Addition of various amounts of glycerin to these formulations showed that the greatest mucosa-adhesion is achieved with a formulation containing 2% w/v CMC and 5% v/v glycerin. Films containing 3% v/v glycerin were found to have much weaker (250±5 mN) mucosa-adhesive strength than the 5% v/v film (683±2 mN), which might be attributed to the lesser flexibility of 3% v/v glycerin containing films, which prevents the formation of intimate contact with the mucosal surface needed for strong adhesion. The presence of less than 3% v/v glycerin in formulation resulted in the formation of brittle films, whereas, films with higher than 5% v/v glycerin were looser and had weaker physical strength. This finding suggests the importance of suitable film flexibility in the formation of strong mucosa-adhesive bonds. With films prepared from HPMC, the formulation of 1.5% w/v HPMC and 5% v/v glycerin was found to give the greatest mucosa-adhesion. On the other hand, decreasing the amount of glycerin in the formulation to 1% v/v, resulted in an increase in the mucosa-adhesion of the formed films. However, these films were found to be slightly less flexible than the formulation containing 3% v/v glycerin. Elimination of glycerin from the formulation resulted in the formation of brittle films, suggesting the importance of presence of a plasticizer in the film forming ability of HPMC. With MC containing films, the greatest mucosa-adhesion was observed with formulations of 2% w/v polymer and 7% v/v glycerin. Lowering the amount of glycerin in this formulation resulted in the formation of less flexible and slightly brittle films, and increasing the amount of glycerin in the formulation had no significant effect (P>0.05) on the mucosa-adhesion of prepared films. It should also be noted that formulation containing 2.5% w/v MC and 7% v/v glycerin had a lower mucosa-adhesive strength than films prepared from the 2% w/v MC solution. This could be due to the lesser chain flexibility of the former films, which reduces the chance of formation of an intimate polymer/mucosa contact required for good mucosa-adhesion. As it was mentioned before, no film was formed by the use of carbopols by itself. Hence it was decided to combine carbopols with CMC, which have both good film forming ability and mucosa-adhesive strength. Furthermore CMC could improve the wettability and the ease of spreading of the formed films, which results in greater adhesion. The results are shown in Table 2. It was shown that films prepared from solutions containing

0.15% w/v carbopol, 1% w/v CMC and 2% v/v glycerin give the highest mucosa-adhesive strength. Among the carbopols which were studied, PC containing films gave the highest mucosa-adhesion, followed by C974 and C934. Further studies showed that by keeping the amount of carbopol in solution to 0.15% w/v and glycerin to 2% v/v, but changing the amount of CMC, solution containing 2% w/v CMC gave films with the highest mucosa-adhesive strength. Furthermore, by keeping the amount of carbopol and CMC to 0.15 and 2% w/v respectively, and varying the amount of glycerin, it was found that solutions containing 3% v/v glycerin (1% v/v for C974 containing films) gave films with the highest mucosa-adhesive strength. It is therefore suggested that combination of a carbopol and a good film forming and strongly adhesive cellulosic polymer such as CMC result in the formation of desirable buccal films. Presence of suitable amounts of a plasticizer in this combination also appears to be critical for giving good mucosa-adhesion. None of the investigated natural polymers produced films with mucosa-adhesive strengths as high as carbopol/CMC combination or CMC alone films (Table 3). With acacia containing films, it was found that the presence of at least 7% v/v propylene glycol in the initial solution is critical for the formation of flexible films for overcoming the problems of film brittleness. Furthermore, it was found that increasing the amount of acacia within the formulation increases the mucosa-adhesive strength of the formed films. However, by exceeding the amount of acacia to 15% w/v, the solution becomes viscous and results in the formation of non-uniform and brittle films. With gelatin containing films, it was found that the most desirable amount of gelatin within the initial solution is 5% w/v. Increasing the amount of gelatin beyond this level reduced the mucosa-adhesive strength of the films, which might be due to the reduction in film flexibility and formation of intimate polymer/mucosa contact. Finally, the films prepared with PVA were found to have relatively low mucosa-adhesive strengths. Among the PVA containing films, a solution containing 10% w/v PVA and 7% v/v propylene glycol resulted in the highest mucosa-adhesive strength (71 ± 2mN). In the literature (18), PVA is ranked as a weak mucosa-adhesive material. This study also suggests the unsuitability of PVA for the preparation of buccal adhesive films, because of its weak mucosa-adhesive properties. Overall, it is suggested that, among the various polymers studied, a combination of a carbopol and CMC can produce films with the greatest mucosa-adhesive strength. Based on the results of assessment of the mucosa-adhesive strength of various films, and since carbopol/CMC containing films, among the evaluated films, achieved the highest rank, attempts were made to investigate their duration of mucosa-adhesion. In fact, Mortazavi and Smart (14) have suggested the importance of assessing this parameter in mucosa-adhesive formulations. The results of this study are shown in Table 4. As can be seen, films containing C934 and C974, which also have higher mucosa-adhesive strengths than PC containing films, remain in contact with the mucosal surface for a longer period of time. In addition, C934 and C974 containing films have much longer duration of mucosa-adhesion than PC containing films. Hence, based on the results obtained, films prepared from C934 or C974 appear to be more suitable for the preparation of buccal-adhesive films and patches. Finally, it should be noted that it is not expected that the films containing a combination of carbopol/CMC pose a serious threat and major discomfort for patients. In fact, placement of these films within the buccal cavity of authors for a period of 5h showed no sign of discomfort or pain. Other studies (6,20,21) on buccal formulations containing even greater amounts of cellulose derivatives and carbopols, than the amount used in this study, have also shown a lack of irritation or discomfort during use.

CONCLUSION

Buccal-adhesive films and patches can open a new horizon in mucoadhesive drug delivery systems. These rather thin and flexible films adhere to the buccal mucosa, remain in place and release their drug content steadily for a reasonable length of time and as a result improve patient compliance. In this study various polymers were screened for their film forming

Table 4. Mucosa-adhesive strength and duration of mucosa-adhesion of selected films to rat intestine in pH 6.8 isotonic phosphate buffer at 37°C, under a constant breaking force of 2g (n=3, mean±SD).

Composition in initial solution			Mucosa-adhesive strength (mN)	Duration of mucosa-adhesion (min)
Carbopol (% w/v)	CMC (% w/v)	Glycerin (% v/v)		
0.15% C934	2.0	3.0	823±3	235.0±5.8
0.15% C974	2.0	1.0	751±6	211.7±7.1
0.15% PC	2.0	3.0	721±5	111.7±7.6
0.15% PC	2.0	2.0	700±2	138.0±0.5

and mucosa-adhesive potential. Based on the results, formulations containing a combination of carbopols and CMC produced films with the highest mucosa-adhesive strength. This finding which is in agreement with other studies (7,8), suggests the suitability of carbopols as excellent mucosa-adhesive materials. In addition, it was found that the duration of mucosa-adhesion of the films can be used as a useful indication of their efficacy, along with the mucosa-adhesive strength of the films. Also it was found that films containing C934 or C974 along with CMC remain longer in contact with the mucosal surface than PC/CMC containing films. It should also be noted that the rate and amount of water uptake by a film can greatly affect its duration of mucosa-adhesion (22). Hence, effective buccal-adhesive films can be prepared by using a copolymer which beside of having good adhesive properties can avoid quick hydration and formation of a loose mucilage, which can be easily dislodged from the site of adhesion.

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REFERENCES

1. Gu, J.M., Robinson, J.R., Leung, S.H.S. (1988) Binding of acrylic polymers to mucin/epithelial surfaces: structure-property relationships. CRC Crit. Rev. Ther. Drug Carrier Systems 5:21-67.
2. Jimenez-Castellanos, M.R., Zia, H., Rhodes, C.T. (1993) Mocoadhesive drug delivery systems. Drug Dev. Ind. Pharm. 19:143-194.
3. Smart, J.D. (1993) Drug delivery using buccal-adhesive systems. Adv. Drug Del. Rev. 11: 253-270.
4. Ahuja, A., Khar, R.K., Ali, J. (1997) Mucoadhesive drug delivery systems. Drug Dev. Ind. Pharm. 23:489-515.
5. Peppas, N.A., Buri, P.A. (1985) Surface, interfacial and molecular aspects of polymer bioadhesion on soft tissue. J. Control. Release 2:257-275.
6. Chen, J.L., Cyr, G.N. (1970) Compositions producing adhesion through hydration. In: Manly, R.S. (ed.) Adhesion in Biological Systems. Academic Press, London, pp 163-181.
7. Smart, J.D., Kellaway, I.W., Worthington, H.E.C. (1984) An in-vitro investigation of mucosa-adhesive materials for use in controlled drug delivery. J. Pharm. Pharmacol. 36:295-299.
8. Smart, J.D. (1991) An invitro assessment of some mucosa-adhesive dosage forms. Int. J. Pharm. 73: 69-74.
9. Mortazavi, S.A., Smart, J.D. (1995) An investigation of some factors influencing the invitro assessment of mucoadhesion. Int. J. Pharm. 116:223-230.
10. DeGrande, G., Benes, L., Horriere, F., Karsenty, H., Lacoste, C., McQuinn, R., Guo, J.H., Scherrer, R. (1996) Specialized oral mucosal drug delivery systems: patches. In: Rathbone, M.J. (ed.) Oral Mucosal Drug Delivery. Marcel Dekker Inc., New york, pp 285-317.
11. Anders, R., Merkle, H.P. (1989) Evaluation of laminated muco-adhesive patches for buccal drug delivery. Int. J. Pharm. 49:231-240.
12. Burgalassi, S., Panichi, L., Saettone, M.F., Jacobsen, J., Rassing, M.R. (1996) Development and invitro/invivo testing of mucoadhesive buccal patches releasing benzydamine and lidocaine. Int. J. Pharm. 133:1-7.
13. Ch'ng, H.S., Park, H., Kelly, P., Robinson, J.R. (1985) Bioadhesive polymers as platforms for oral controlled drug delivery II: synthesis and evaluation of some water-insoluble bioadhesive polymers. J. Pharm. Sci. 74(4):399-405..

14. Mortazavi, S.A., Smart, J.D. (1994) An in-vitro method for assessing the duration of mucoadhesion. J. Control. Release 31:207-212.
15. Harris, D., Robinson, J.R. (1990) Bioadhesive polymers in peptide drug delivery. Biomaterials. 11: 652-658.
16. Guo, J.H. (1994) Bioadhesive polymer buccal patches for buprenorphine controlled delivery: formulation, invitro adhesion and release properties. Drug Dev. Ind. Pharm. 20:18-25.
17. Satoh, K., Takayama, K., Machida, Y., Suzuki, Y., Nakagaki, M., Nagai, T. (1989) Factors affecting the bioadhesive property of tablets consisting of hydroxypropyl cellulose and carboxyvinyl polymer. Chem. Pharm. Bull. 37(5):1366-1368.
18. Mortazavi, S.A., Smart, J.D. (1994) Factors influencing gel-strengthening at the mucoadhesive-mucus interface. J. Pharm. Pharmacol. 46:86-90.
19. Mortazavi, S.A. (1993) An investigation into the mechanism of mucoadhesion. Ph.D Thesis, University of Portsmouth, England.
20. Nagai, T., Konishi, R. (1987) Buccal/gingival drug delivery systems. J. Control. Release 6:353-360.
21. Collins, A.E., Deasy, P.B. (1990) Bioadhesive lozenge for the improved delivery of cetylpyridinium chloride. J. Pharm. Sci. 79(2):116-119.
22. Mortazavi, S.A., Smart, J.D. (1993) An investigation into the role of water movement and mucus gel dehydration in mucoadhesion. J. Control. Release 25:197-203.