INVESTIGATION OF VARIOUS PARAMETERS INFLUENCING THE DURATION OF MUCOADHESION OF SOME POLYMER CONTAINING DISCS

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ABSTRACT

The aim of this study was to evaluate the effect of some important parameters on duration of adhesion of discs containing mucoadhesive polymers. For this purpose discs containing carbopol 934P (C934), polycarbophil (PC), sodium carboxymethyl cellulose (CMC) and hydroxypropylmethyl cellulose (HPMC) were prepared and the duration of their *in vitro* mucoadhesion were evaluated. Also the effect of the addition of various amounts of HPMC to other polymers, the effect of the test medium and prehydration of the test discs for 2 and 5 min prior to their placement in contact with the mucosal surface, on the duration of mucoadhesion of test discs were investigated. Results show that the addition of 25% HPMC increases the duration of mucoadhesion of all the tested polymers. The greatest duration of mucoadhesion with the anionic polymers CMC, C934 and PC was found to be at pH values above 4.0. The duration of mucoadhesion of HPMC containing discs were not greatly affected by the pH values above 2.2. However, at a pH value of 2.2 all of the investigated polymers showed the lowest duration of mucoadhesion. Finally, prehydration of discs containing HPMC, CMC or their combination before their placement on the mucosal surface resulted in a significant reduction in their duration of mucoadhesion. Discs containing only C934 or PC were far less affected by prehydration, especially after 2 min. Addition of HPMC to these discs greatly reduced their duration of mucoadhesion.

Keywords: Mucoadhesion, Carbopols, HPMC, Prehydration.

INTRODUCTION

The term "bioadhesion" is used to describe attachment of synthetic or natural polymers to a biological surface. If the adhesion surface is a mucous membrane coated with a thin layer of mucus, then the term "mucoadhesion" is employed (1, 2). The use of mucoadhesive polymers and copolymers as platforms for the local or systemic controlled delivery of therapeutically active drugs, to or via mucous membranes, has been the focus of attention in the past two decades (3-8). This interest is mainly due to the following applications of bioadhesive drug delivery systems (6, 8-10): (i) adhesion to specific sites of the body such as the oral and nasal cavities, which enhances or increases the drug bioavailability, (ii) formation of an optimum contact with the adhesion surface which may increase absorption of the drug, and (iii) prolongation of the residence time of the dosage form within the gastrointestinal tract, which reduces the need for multiple dosing and as a result a better patient compliance. An effective mucoadhesive dosage form should be able to form strong interactions with the mucosal surface, in such a way that prevents its' displacement from the site of adhesion. Tensile testing systems are the most widely used *in vitro* methods for evaluation of the strength of the mucoadhesive interactions (11-17). These studies usually determine the strength of adhesion after a specific contact time, but do not provide information on the duration of adhesion. Mucoadhesive materials which are hydrophilic macromolecules need to take up water to become adhesive, but may overhydrate to form a slippery mucilage and this would result in their disposal from the adhesion surface (8, 18). Hence, it is clear that the duration of adhesion of an effective mucoadhesive dosage form is a critical factor in the design and formulation of

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these systems and should be taken into consideration. Relatively few studies have attempted to assess directly the durability of the mucoadhesive joint *in vitro* (12, 18-20). It has been reported that a mucoadhesive dosage form which adheres strongly to the mucosal surface and shows high mucoadhesive strength may not remain in contact with the mucosal surface for an extended period of time, emphasizing further the importance of these studies along with the usual mucoadhesive strength studies. The aim of this study was to evaluate the effect of a few important parameters on the *in vitro* duration of mucoadhesion of dry polymeric discs.

MATERIALS & METHODS

Materials

Carbopol 934P (C934), and polycarbophil (PC) were obtained as gifts from B.F. Goodrich, Hounslow, UK; cellulose derivatives including sodium carboxymethyl cellulose (CMC) and hydroxypropylmethyl cellulose (HPMC) were purchased from Hercules Chemical Co., USA; and disodium hydrogen phosphate and citric acid were purchased from Merck Chemical Co., Germany.

Preparation of the test disc

Flat-faced polymer containing discs with a diameter of 9 mm containing 100 mg of the mucoadhesive polymer(s) were prepared by direct powder compression using a single punch tablet press and kept in air tight containers until use. Polymers employed in this investigation were C934, PC, CMC and HPMC, which were used either alone or in combination.

Assessment of the duration of mucoadhesion

The apparatus (Fig.1) and the experimental details used in this study were based on that described by Mortazavi and Aboofazeli (12). The model mucosal surface used in this study was rat small intestine. Test discs were placed in contact with the mucosal surface for a period of 2 min in order to allow the mucoadhesive bonds to form and consolidate (17). Next, based on a previous study (17), a constant tensile stress of 10 g was applied and the duration of mucoadhesion of the test discs were determined using a photocell detector capable of recording the elapsed time to 0.1 min.

Effect of combining polymers

Discs containing the test polymer either alone or in combination were prepared and individually placed in contact with the mucosal surface (in the presence of a pH 6.0 citrate-phosphate buffer) and the duration of mucoadhesion of the test discs were determined as stated above.

Influence of the test medium pH

For this purpose citrate-phosphate buffers with various pH values, ranging from 2.2-8.0, were prepared and individually placed within the perspex cell of the test apparatus. The duration of mucoadhesion of the test discs in the presence of individual buffer solutions were then determined in the manner stated above.

Effect of prehydration on the test discs

The prepared test discs were prehydrated by placing them in a pH 6.0 citrate-phosphate buffer for either 2 or 5 min prior to their placement in contact with the mucosal surface. Duration of mucoadhesion of the prehydrated test discs in the pH 6.0 citrate-phosphate buffer solution were then determined in a similar fashion as described above.

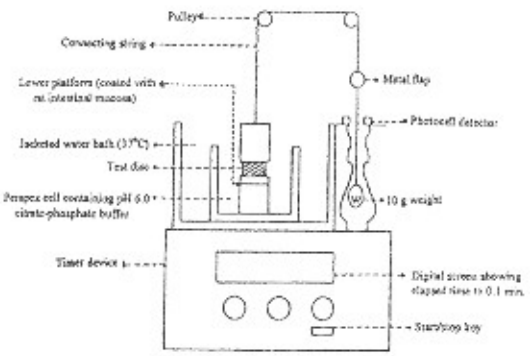

Fig1. Apparatus used for measuring the duration of mucoadhesion of various polymer containing discs to rat intestinal mucosa (as the model mucosa) at 37 °C, using a constant tensile stress (weight) of 10 g.

RESULTS AND DISCUSSION

The results of the assessment of duration of mucoadhesion of various test discs are shown in Table 1. As can be seen, and similar to a previous study (17), discs containing HPMC alone in spite of reports (17, 20, 21) on its' relatively weak mucoadhesion have shown the greatest duration of mucoadhesion, which is significantly ($P<0.05$, student's t-test) more

than other discs containing only one polymer. This finding could be explained in terms of the relatively slow swelling rate of HPMC. In contrast CMC, which is reported to be a good mucoadhesive, quickly overhydrates and easily dislodges from the mucosal surface and hence has the least duration of mucoadhesion. Combination of CMC with HPMC helps to improve the duration of mucoadhesion of CMC, presumably because of the reduction in the rate of water uptake by CMC. A similar trend has also been observed with the highly adhesive carbopols (8, 10, 17, 21).

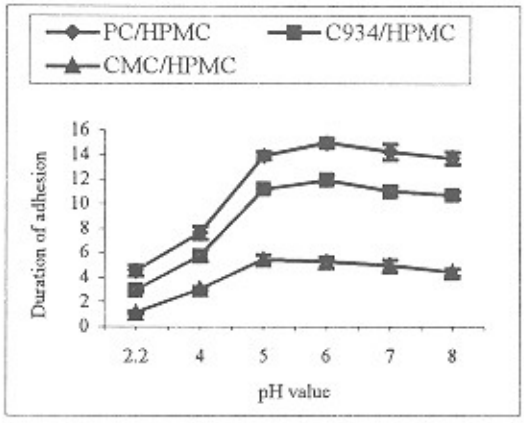

Fig. 2. The effect of the surrounding medium pH on the duration of mucoadhesion of various polymer/HPMC (ratio of 4:1) discs to rat intestinal mucosa, under a constant tensile stress of 10 g (n=6; mean±SD).

In agreement with previous reports (22, 23), in this study carbopols showed a relatively high duration of mucoadhesion which was less than HPMC discs alone, because of its greater rate of water uptake compared to HPMC. Furthermore it was found that the duration of mucoadhesion of carbopols is improved by the addition of HPMC. However, presence of more than 25% HPMC within the formulation could dramatically reduce the mucoadhesive strength, which means that it can be easily displaced from its site of adhesion under low stresses. It should also be noted that among the carbopols studied, the duration of mucoadhesion of PC was found to be significantly ($P<0.05$, student's t-test) more than C934 discs, which suggests a lower rate of water uptake and overhydration and hence a delayed displacement from the site of adhesion by PC.

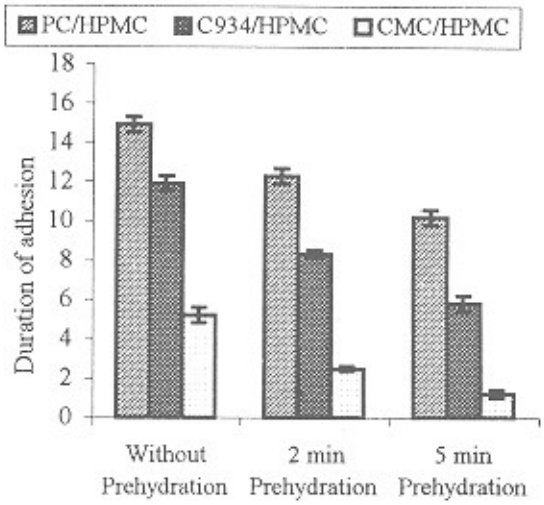

Fig. 3. The effect of prehydration of various polymer/HPMC (ratio of 4:1) discs in pH 6.0 citrate-phosphate buffer solution on their duration of mucoadhesion to rat intestinal mucosa under a constant tensile stress of 10 g (n=6; mean±SD).

Table 1. The duration of mucoadhesion of various polymer containing discs to rat intestinal mucosa in a pH 6.0 citrate-phosphate buffer at 37°C, under a constant tensile stress of 10 g (n=6, mean ±SD)

Test disc	Duration of mucoadhesion (h)
HPMC alone	21.3 ± 0.6
PC/HPMC (1:2)	17.4 ± 0.5
PC/HPMC (1:1)	16.8 ± 0.3
PC/HPMC (2:1)	15.6 ± 0.6
PC/HPMC (4:1)	14.9 ± 0.4
PC alone	13.1 ± 0.2
C934/HPMC (1:2)	14.9 ± 0.7
C934/HPMC (1:1)	13.6 ± 0.6
C934/HPMC (2:1)	12.7 ± 0.3
C934/HPMC (4:1)	11.9 ± 0.4
C934 alone	10.1 ± 0.5
CMC/HPMC (1:2)	8.1 ± 0.3
CMC/HPMC (1:1)	6.7 ± 0.4
CMC/HPMC (2:1)	5.8 ± 0.2
CMC/HPMC (4:1)	5.2 ± 0.4
CMC alone	4.0 ± 0.2

Therefore, based on this study the presence of about 25% of HPMC in a mucoadhesive formulation, along with carbopols (C934 or PC) may provide a suitable base with desirable mucoadhesive properties.

Table 2. Effect of pH of the surrounding medium on the duration of mucoadhesion of various polymer containing discs to rat intestinal mucosa at 37°C, under a constant tensile stress of 10 g (n=6, mean ±SD)

Test disc	Duration of mucoadhesion (h)					
	pH=2.2	pH=4.0	pH=5.0	pH=6.0	pH=7.0	pH=8.0
HPMC alone	12.5 ± 0.5	21.4 ± 0.8	20.9 ± 0.4	21.3 ± 0.6	21.5 ± 0.7	20.7 ± 0.3
PC/HPMC (1:2)	7.4 ± 0.3	10.1 ± 0.5	16.8 ± 0.6	17.4 ± 0.5	16.9 ± 0.3	16.4 ± 0.4
PC/HPMC (1:1)	6.0 ± 0.2	9.4 ± 0.4	15.9 ± 0.5	16.8 ± 0.3	16.2 ± 0.6	15.8 ± 0.1
PC/HPMC (2:1)	5.3 ± 0.1	8.8 ± 0.4	14.7 ± 0.3	15.6 ± 0.6	15.2 ± 0.5	14.9 ± 0.2
PC/HPMC (4:1)	4.5 ± 0.4	7.6 ± 0.5	13.9 ± 0.3	14.9 ± 0.4	14.2 ± 0.6	13.7 ± 0.5
PC alone	4.2 ± 0.4	6.5 ± 0.3	12.3 ± 0.1	13.1 ± 0.2	12.5 ± 0.3	12.1 ± 0.4
C934/HPMC (1:2)	5.9 ± 0.3	9.6 ± 0.5	14.3 ± 0.4	14.9 ± 0.7	14.4 ± 0.4	14.0 ± 0.1
C934/HPMC (1:1)	4.0 ± 0.5	7.5 ± 0.7	12.9 ± 0.2	13.6 ± 0.6	13.0 ± 0.3	12.8 ± 0.6
C934/HPMC (2:1)	3.3 ± 0.3	7.1 ± 0.2	12.2 ± 0.5	12.7 ± 0.3	12.1 ± 0.6	11.8 ± 0.4
C934/HPMC (4:1)	2.9 ± 0.1	5.7 ± 0.5	11.2 ± 0.1	11.9 ± 0.4	11.0 ± 0.4	10.7 ± 0.3
C934 alone	2.2 ± 0.2	4.3 ± 0.2	9.6 ± 0.3	10.1 ± 0.5	9.7 ± 0.2	9.1 ± 0.4
CMC/HPMC (1:2)	1.7 ± 0.1	4.2 ± 0.3	8.0 ± 0.5	8.1 ± 0.3	7.5 ± 0.4	7.3 ± 0.2
CMC/HPMC (1:1)	1.4 ± 0.2	3.7 ± 0.1	6.7 ± 0.2	6.7 ± 0.4	6.2 ± 0.3	6.0 ± 0.5
CMC/HPMC (2:1)	1.2 ± 0.2	3.3 ± 0.4	5.9 ± 0.3	5.8 ± 0.2	5.4 ± 0.1	5.0 ± 0.4
CMC/HPMC (4:1)	1.1 ± 0.1	3.0 ± 0.2	5.4 ± 0.4	5.2 ± 0.4	4.9 ± 0.5	4.4 ± 0.3
CMC alone	0.8 ± 0.2	2.1 ± 0.3	4.3 ± 0.3	4.0 ± 0.2	3.5 ± 0.2	3.1 ± 0.4

In the next part of this study the effect of environmental (surrounding) pH on the duration of mucoadhesion was investigated. The results (Table 2 and Fig. 2) show that pH may influence the duration of mucoadhesion of ionic polymers. As can be seen with discs containing a carbopol, duration of mucoadhesion increased at pH values above 4.0 and reached to its' maximum value at pH=6.0. At higher pH values the duration of mucoadhesion gradually decreased and reached to its minimum value at pH=2.2, which is significantly ($P<0.05$, one way analysis of variance) less than the results obtained at higher pH values. At this pH value most of the carboxyl groups present within carbopols will be in their unionized form, which prevents the formation of an extended polymer network required for good water permeation and mucoadhesion. Addition of HPMC reduces the rate of water uptake by carbopols, which increases the durability of mucoadhesive matrices in situations when they encounter high pH values. Nevertheless, since HPMC is a relatively weak mucoadhesive material, its use in amounts greater than 25% can reduce the overall mucoadhesive strength of formulation, and displaces it easily from the site of adhesion. Similar results were found with CMC, an anionic polymer. With HPMC, a nonionic polymer, pH values above 2.2 had no significant effect ($P>0.05$, one way analysis of variance) on mucoadhesion. However at a pH value of 2.2, the duration of mucoadhesion significantly ($P<0.05$, student's t-test) decreased because of the coiling of mucus gel network, which hinder the penetration of polymer chains and hence formation of tight and strong mucoadhesive bonds. On the basis of previous studies (1, 10, 24, 25), this phenomenon is a critical factor in the process of mucoadhesion.

In the final part of this study the effect of prehydration of the test discs before their placement on the mucosal surface was investigated. This is a rather important study because once the mucoadhesive dosage form enters the gastrointestinal tract it will not be able to reach the mucosal surface immediately, and hence would be exposed to the surrounding fluid which could hydrate the dosage form, and as a result affects the duration of its mucoadhesion.

The results obtained from this study are shown in Table 3 and Fig. 3. Mucoadhesion of discs containing only HPMC was significantly ($P<0.05$, student's t-test) decreased by prehydration because of the formation of an uneven and rough surface, which will hinder the formation of a close and intimate contact

Table 3. The effect of prehydrating polymer containing discs in pH 6.0 citrate-phosphate buffer solution on the duration of their mucoadhesion to rat intestinal mucosa in a pH 6.0 citrate-phosphate buffer at 37°C, under a constant tensile stress of 10 g (n=6, mean ± SD)

Test disc	Duration of mucoadhesion (h)		
	Without Prehydration	2 min Prehydration	5 min Prehydration
HPMC alone	21.3 ± 0.6	3.7 ± 0.3	1.4 ± 0.1
PC/HPMC (1:2)	17.4 ± 0.5	7.6 ± 0.4	5.9 ± 0.2
PC/HPMC (1:1)	16.8 ± 0.3	9.9 ± 0.5	7.1 ± 0.4
PC/HPMC (2:1)	15.6 ± 0.6	11.2 ± 0.2	8.9 ± 0.3
PC/HPMC (4:1)	14.9 ± 0.4	12.3 ± 0.4	10.2 ± 0.4
PC alone	13.1 ± 0.2	12.8 ± 0.4	11.3 ± 0.5
C934/HPMC (1:2)	14.9 ± 0.7	4.2 ± 0.3	2.2 ± 0.2
C934/HPMC (1:1)	13.6 ± 0.6	6.1 ± 0.5	3.0 ± 0.1
C934/HPMC (2:1)	12.7 ± 0.3	7.3 ± 0.4	4.1 ± 0.3
C934/HPMC (4:1)	11.9 ± 0.4	8.3 ± 0.2	5.8 ± 0.4
C934 alone	10.1 ± 0.5	9.2 ± 0.3	7.6 ± 0.6
CMC/HPMC (1:2)	8.1 ± 0.3	4.2 ± 0.1	2.6 ± 0.4
CMC/HPMC (1:1)	6.7 ± 0.4	3.5 ± 0.2	2.2 ± 0.1
CMC/HPMC (2:1)	5.8 ± 0.2	2.8 ± 0.3	1.9 ± 0.3
CMC/HPMC (4:1)	5.2 ± 0.4	2.5 ± 0.1	1.2 ± 0.2
CMC alone	4.0 ± 0.2	1.7 ± 0.2	0.8 ± 0.1

required for good mucoadhesion. The prehydrated CMC containing discs showed a significant ($P<0.05$, student's t-test) reduction in their duration of mucoadhesion for the same reason. On the other hand, the duration of mucoadhesion of carbopol (alone) containing discs decreased slightly following 2 min prehydration. However, prehydration of carbopol containing discs for 5 min significantly ($P<0.05$, Student's t-test) reduced their duration of mucoadhesion. In spite of this finding, it should be noted that the reduction in the duration of mucoadhesion of discs containing carbopols alone is significantly less than those observed with HPMC and CMC discs. This means that even after 5 min of prehydration, the carbopol containing discs could have a reasonable duration of mucoadhesion. The PC containing discs are again less affected by prehydration than C934 containing discs. Addition of HPMC, especially in amounts greater than 25%, to carbopol containing discs significantly ($P<0.05$, Student's t-test) reduced their duration of mucoadhesion, particularly following 5 min prehydration, which makes it unsuitable for use in such cases.

CONCLUSION

Results of this study show that the use of HPMC along with PC or C 934 at a ratio of 1:4 help to provide a strong and durable mucoadhesive matrix. However, prehydration of such a combination as a result of water uptake from the surrounding medium before adhesion could greatly reduce the duration of mucoadhesion of the dosage form. Hence, the use of such a combination is more suitable in cases where the dosage form could be directly placed on the mucosal surface (e.g. buccal cavity). Finally, it should be noted that the pH of the surrounding medium could also alter the duration of mucoadhesion and in pH values around 6.0, discs containing a combination of an anionic polymer (carbopol or CMC) along with the nonionic polymer HPMC remain in contact with the mucosal surface for the longest period of time. In contrast, in highly acidic or alkaline pH values these polymers do not show desirable mucoadhesive properties, which emphasize the need for careful evaluation of the effect of surrounding pH on the durability of a putative mucoadhesive dosage form.

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