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Original Article

A Comparative Study Between the Strength and Duration of Mucosa-Adhesion of Transbuccal Carbomer Based Aqueous Gels

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Abstract

Mucosa-adhesive gels can be used as a useful mean of delivering drugs to or via mucosal membranes, and in particular buccal mucosa. Carbomers are among the best mucosa-adhesive materials known. The aim of this study was to compare the results obtained from the mucosa-adhesive strength of aqueous gels containing Carbomers, either alone or in combination, to the data obtained from assessing the duration of mucosa-adhesion of these gels. Based on initial studies, a total Carbomer concentration of 2.0%w/v forms the most desirable gel. Furthermore, it was found that gels containing a combination of Carbomers 934P (C934), 971P (C971) and 974P (C974) form clear and transparent gels with good spreadability. Next, using these Carbomers, gels containing either one, two or all three Carbomers with a total polymer concentration of 2.0%w/v were prepared and tested for their mucosa-adhesive strength to rat small intestine (as model mucosa) in pH6.8 isotonic phosphate buffer at 37 ºC. It was found that the presence of more than 0.4%w/v C971 in gels containing all three Carbomers, greatly reduce the mucosa-adhesive strength of the gel. Furthermore, it was found that a combination of C934 and C974 at a total concentration of 1.6-1.8%w/v, along with 0.2-0.4%w/v C971 form gels with good clarity and spreadability as well as strong mucosa-adhesive strengths. Gels showing the greatest mucosa-adhesive strength and good general appearance and spreadability were then assessed in terms of their duration of mucosa-adhesion to rat intestine in pH6.8 isotonic phosphate buffer at 37 ºC and under a constant applied force of 15.0g. The results obtained showed that a gel that has high mucosa-adhesive strength will not necessarily have a great duration of mucosa-adhesion. Hence, it is suggested that this important parameter should also be considered besides the test for assessing the mucosa-adhesive strength in the selection of an efficient transbuccal mucosa-adhesive drug delivery system.

Keywords: Transbuccal drug delivery; Mucosa-adhesive gel; Carbomers; Duration of mucosa-adhesion; Mucosa-adhesive strength.

Introduction

The use of bioadhesive polymers and copolymers as means of delivering therapeutically active drugs, including proteins and peptides, to or via mucous membranes has been the focus of attention in recent years (1-4). The term "bioadhesion" is defined as the attachment of synthetic or natural 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 "mucosa-adhesion" (1).

Mucosal-adhesive materials have been investigated and identified in previous work (e.g., 6-9). These materials are generally hydrophilic macromolecules that contain numerous hydrogen bonds forming groups, and

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will hydrate and swell when placed in contact with an aqueous solution. These materials need to hydrate to become adhesive but over-hydration usually results in the formation of a slippery mucilage and a loss of the adhesive properties.

Among the various routes of delivering mucosa-adhesive dosage forms, the buccal route appear to offer a series of advantages, including good accessibility, robust epithelium, quick and easy removal of the dosage form in case of need, good drug absorption, avoidance of first pass hepatic metabolism to a great extent, and satisfactory patient acceptance and compliance (3, 10, 11). Bioadhesive gels may be used locally for drug delivery within the buccal cavity, with the aim of prolonging the residence time of drugs (4, 10). One of the original buccal mucosa-adhesive delivery systems is "Orabase®", which consists of finely ground pectin, gelatin and sodium carboxymethyl cellulose dispersed in a polyethylene and a mineral oil gel base (4). This system has been used for the local application of steroids for the treatment of mucosal ulceration, and can remain at its site of application for 15-150min.

In a study by Ishida and co-workers (12) a high-viscosity gel ointment containing 12.5% Carbomer 934 within glycerin or polyethylene glycol was prepared. Sodium salicylate was then added to this formulation and its invivo absorption in hamster cheek pouch was investigated. The results obtained showed that the formulation could provide sustained drug absorption for 5h. They also found that the consistency of the gel ointment affects the rate of drug release, and should be taken into consideration.

In this study attempts were made to compare and contrast the results obtained from assessing the strength of mucosa-adhesion of various Carbomers (either alone or in combination) in the form of aqueous gels, with their duration of mucosa-adhesion, in order to see whether the data obtained from these two important parameters follow the same trend and are similar or not. This study will therefore clarify the need for conducting both these tests during the formulation of an effective and durable transbuccal mucosa-adhesive gel.

Experimental

Materials

Carbomer 934P, Carbomer 971P, Carbomer 974P and Polycarbophil were all obtained as a gift from No-avar-Arash Co. (B.F. Goodrich sales agent), Tehran, Iran. Sodium chloride, sodium dihydrogen phosphate, disodium hydrogen phosphate and sodium hydroxide were all purchased from Merck Chemical Co., Germany.

Methods

Preparation of gels

Carbomer containing gels were prepared using Carbomer 934P (C934), Carbomer 971P (C971), Carbomer 974P (C974) or Polycarbophil (PC) either alone or in combination. In the initial studies, gels containing 0.5-3.0%w/v Carbomer were prepared using distilled water and pH adjusted to 7.0 using 1N sodium hydroxide. Following the initial studies, it was found that gels containing 2.0%w/v Carbomer form the most desirable gels. Hence, further studies were performed using this concentration. For this purpose gels containing different amounts of one, two or three Carbomer were prepared in distilled water and in each case pH adjusted to 7.0. The gels prepared were then used for experimentation.

Preparation of the model mucosa (test surface)

The model mucosal membrane used in this study was rat intestine. The preparation method used was similar to that of previous studies (8, 9). The middle sections, discarding the first 40-50mm at either end, of fresh intestine were removed from male rat (approximately 220g weight and 6-8 weeks old), killed by cervical dislocation. These were frozen at -20 ºC until required, to inhibit muscle contraction, hence ensuring the flat and uniform surface essential for this type of adhesion testing. Before use the tissue was allowed to thaw at 4 ºC and cut into 5cm length pieces, which were then opened longitudinally to expose the inner mucosal surface. Each mucosal surface was washed gently with pH 6.8 isotonic phosphate buffer to remove any loose material, and then used for experimentation.

Mucosa-adhesive studies

The gels prepared underwent the following tests:

Assessment of the mucosa-adhesive strength of gels

In order to evaluate the mucosa-adhesive strength of the gels prepared (only those containing 2.0%w/v Carbomer), the apparatus shown in Figure 1 was used. This apparatus was principally similar to those described in previous studies (8, 9, 13-15). The upper stationary platform was linked to a balance, measuring the force needed to break contact between the gel and mucosa. The test cell was filled with pH6.8 isotonic phosphate buffer, maintained at 37 ºC, and sections of rat intestine placed and fixed in place over the two cylindrical platforms and allowed to equilibrate in this solution for 2min. 0.5g of the gels prepared were then individually sandwiched between the two mucosa-covered platforms. Gels were kept in place for 5min and then a constantly increasing force of 0.1 g/sec was applied on the adhesive joint formed between rat intestine and the test gel, by gradually lowering the lower platform. This trend was continued until the contact between the test gel and mucosa was broken and the maximum detachment force measured was recorded.

Assessment of the duration of mucosa-adhesion of gels

The apparatus used for this study was based on those described in previous studies (16, 17). The test apparatus (Figure 2) was composed of six upper and six lower cylindrical platforms within a clear jacketed perspex cell, filled with pH6.8 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 2min. The test gels were then sandwiched between the two platforms and allowed to stand for 5min. Next, through two pulley system a 15.0g weight was applied on each upper platform. This weight was chosen (through initial studies), since it is not expected that buccal-adhesive gels encounter very high stresses in the mouth. As soon as the contact between the gel and the mucosal surface broke, a small flap dropped onto a photocell detector, stopping the timer device (recording the elapsed time to 0.1min) and measuring the duration of mucosa-adhesion of the gel.

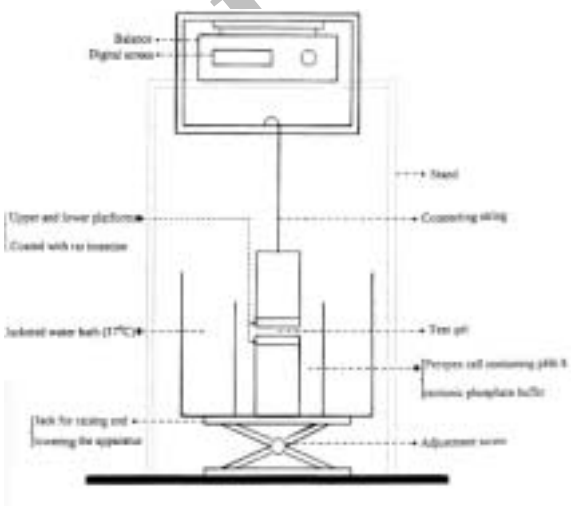

Figure 1. Schematic drawing of the apparatus used for assessing the mucosa-adhesive strength of test gels.

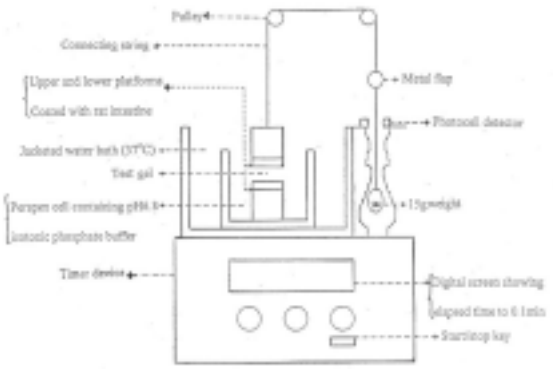

Figure 2. Schematic drawing of one compartment of the apparatus used for assessing the duration of mucosa-adhesion of test gels.

Results and Discussion

As mentioned earlier, buccal cavity provides a very useful route for local and systemic delivery of drugs. Because of the rather limited studies performed on transbuccal mucosa-adhesive gels, in this study attempts were made to investigate the efficacy of Carbomer containing gels as a base for transbuccal drug delivery, and to compare and contrast the results obtained from the mucosa-adhesive strengths of these gels with their duration of mucosa-adhesion, in order to find out whether they follow a similar trend or not.

Carbomers, which are long chain polymers made of acrylic acid units, have been recognized as strong mucosa-adhesives (1, 4, 6, 9, 15, 18). In this study aqueous gels at pH7.0

(this pH was chosen in order to make the pH of the gel close to that of the buccal cavity, hence preventing discomfort in the mouth during use) were prepared and assessed.

In the initial studies gels were prepared using four Carbomer, which were C934, C971, C974 and PC. Gels were prepared using each Carbomer alone at a polymer concentration of 0.5-3.0%w/v. Results showed that except for PC containing gels, with the other Carbomers investigated a polymer concentration of 2.0%w/v produced the most suitable gel. PC containing gels formed hazy and non-uniform gels with poor spreadability at all the concentrations studied and felt rough when spread on the buccal mucosa. Hence, this polymer was left out of further studies. As mentioned above, with the other Carbomers studied, gels containing 2.0%w/v polymer formed the best gels. Among these gels, gels containing C971 formed the most clear and transparent gels and had the least apparent viscosity and would easily spread on the buccal mucosa. C934 containing gels were found to be the least clear of all gels studied and were slightly hazy and had the greatest apparent viscosity and the worst spreadability on the buccal mucosa. C974 also formed slightly hazy gels, which were found to be in between C934 and C971 containing gels in terms of their visual characteristics and spreadability. Gels containing less than or greater than 2.0%w/v Carbomer were found to have unsuitable apparent viscosity and spreadability and hence left out of further studies.

Based on the results obtained, it was decided to add C971 to gels containing C934 or C974 alone or their combination, in order to produce desirable gels, which are not only clear and transparent, but also have an adequate apparent viscosity and spreadability on the buccal mucosa, which is a critical factor in improving patient acceptance.

The results obtained from assessing the mucosa-adhesive strength of gels prepared are shown in Table 1. As can be seen, among gels containing only one Carbomer, the C934 containing gel resulted in the greatest mucosa-adhesive strength, followed by C974 and C971. In fact the mucosa-adhesive strength of C971 containing gels was greatly less than that of C934 and C974 containing gels. In a previous study (19), C971 has also been found to have weaker mucosa-adhesive strength than C934. Furthermore, it was found that the addition of C971 to gels containing either C934 or C974 resulted in a reduction in the mucosa-adhesive strength of gel. This reduction was found to be greater with increasing the amount of C971 in gel. On the other hand, since gels containing C974 alone showed good mucosa-adhesive strength, its addition to C934 containing gels resulted in a small reduction in the mucosa-adhesive strength of gel. However, it should be noted that even though gels containing both C934 and C974 were less hazy and had better spreadability than gels containing C934 alone, but still were not completely clear and transparent, and this could affect their patient acceptance during use. Hence, it was decided to prepare gels containing all three Carbomers in order to form gels, which not only have good

Table 1. Mucosa-adhesive strength of various Carbomer containing aqueous gels to rat small intestine in pH= 6.8 isotonic phosphate buffer at 37 °C (n=3, mean ± standard deviation).

Carbomer composition within the gel (%w/v)			Mucosa-adhesive strength (mN)	Carbomer composition within the gel (%w/v)			Mucosa-adhesive strength (mN)
C934	C974	C971		C934	C974	C971	
2.0	--	--	878 ±16	1.2	0.4	0.4	596 ±21
--	2.0	--	783 ±24	1.0	0.8	0.2	668 ±17
--	--	2.0	256 ± 5	1.0	0.5	0.5	532 ±15
1.5	--	0.5	503 ±12	1.0	0.2	0.8	445 ±11
1.0	--	1.0	366 ±13	0.8	1.0	0.2	711 ±28
0.5	--	1.5	287 ±18	0.8	0.8	0.4	621 ±22
--	0.5	1.5	310 ±12	0.8	0.2	1.0	412 ±22
--	1.0	1.0	539 ±18	0.6	1.2	0.2	715 ±25
--	1.5	0.5	683 ± 9	0.4	1.4	0.2	723 ±25
0.5	1.5	--	810 ±22	0.4	1.2	0.4	680 ±22
1.0	1.0	--	839 ±18	0.4	0.2	1.4	333 ±15
1.5	0.5	--	855 ±15	0.2	1.6	0.2	732 ±26
1.6	0.2	0.2	696 ±17	0.2	1.4	0.4	695 ±32
1.2	0.6	0.2	676 ±22	0.2	0.9	0.9	531 ±10

Table 2. A comparison between the mucosa-adhesive strength and duration of mucosa-adhesion of selected Carbomer containing gels to rat small intestine in pH6.8 isotonic phosphate buffer at 37 ºC (n=3, mean ± standard deviation).

Formulation code	Carbomer composition within the gel (%w/v)			Mucosa-adhesive strength (mN)	Duration of mucosa-adhesion (min)
	C934	C974	C971		
F1	0.2	1.6	0.2	732 ±26	121.1 ± 4.7
F2	0.4	1.4	0.2	723 ±25	145.2 ± 9.8
F3	0.6	1.2	0.2	715 ±25	162.5 ± 6.8
F4	0.8	1.0	0.2	711 ±28	193.3 ± 12.4
F5	1.6	0.2	0.2	696 ±17	151.4 ± 9.7
F6	0.2	1.4	0.4	695 ±32	83.6 ± 3.1
F7	0.4	1.2	0.4	680 ±22	95.4 ± 5.5
F8	1.2	0.6	0.2	676 ±22	130.9 ± 3.3
F9	1.0	0.8	0.2	668 ±17	112.4 ± 4.5

mucosa-adhesive strengths, but also are clear and have desirable visual characteristics and spreadability. For this purpose, using an overall polymer concentration of 2.0%w/v, gels containing all three Carbomers selected (C934, C971 and C974) were prepared and assessed in terms of their mucosa-adhesive strength. It was found that increasing the amount of C971 in gels containing C934 and C974 improves the clarity and ease of spreading of the gel, but greatly reduces the mucosa-adhesive strength. In fact, it was found that the presence of more than 0.4%w/v C971 in these formulations, in spite of improving gels clarity, greatly reduces the mucosa-adhesive strength of the gel, compared with gels containing C934, C974 or their combination. With gels containing 0.2-0.4%w/v C971, it was found that the presence of a greater amount of C934 in gel than C974, as expected slightly increases the mucosa-adhesive strength of the gel, because of the greater mucosa-adhesive nature of C934 than C974. Overall, it could be said that gels containing 0.2%w/v C971 and 1.8%w/v C934 and C974 not only have good mucosa-adhesive strength, but also are clear, and have good spreadability. Hence, the presence of small amounts of C971 in these gel formulations appear to be critical.

An effective mucosa-adhesive transbuccal gel formulation should besides having a desirable appearance and spreadability, must adhere strongly to the mucosal surface for an extended period of time. As stated before, in most cases only the mucosa-adhesive strength of a newly formulated mucosa-adhesive system is evaluated, despite the fact that it is possible that a mucosa-adhesive system could initially adhere strongly to the mucosal surface but in long term it could quickly overhydrate and get displaced from the site of adhesion. Hence, investigating both these parameters is critical in the development of an effective mucosa-adhesive dosage form. In this study the data obtained from the mucosa-adhesive strength studies carried out on Carbomer containing gels were compared and contrasted with the data on their duration of mucosa-adhesion, in order to see whether the patterns of adhesion obtained are similar in all case. For this purpose, formulations resulting in greater mucosa-adhesive strengths were selected and their duration of mucosa-adhesion to rat small intestine, under an applied force of 15.0g assessed. The results obtained are shown in Table 2. The greatest duration of mucosa-adhesion was observed with formulation F4, which had the fourth highest mucosa-adhesive strength among the selected gels investigated. Formulations F6 and F7, both containing 0.4%w/v C971, in contrast to the other formulations containing 0.2%w/v C971, resulted in the lowest duration of mucosa-adhesion among the selected gels studied. These findings clearly show that the results obtained from assessing the duration of mucosa-adhesion of gels prepared do not follow a similar trend to the data obtained from assessing the mucosa-adhesive strength of these gels (Table 1). This finding is in agreement with previous work (17), and hence suggests the importance of assessing the duration of mucosa-adhesion of a test system as an important parameter in the selection of the ultimate formulation. In previous studies (16, 20) the rate of water uptake by a polymer has been considered as an important parameter in its mucosa-adhesive ability and duration of

mucosa-adhesion. Therefore, it is speculated that in the duration of mucosa-adhesion test, C971 takes up water at a faster rate from the surrounding medium than C934 and C974, resulting in a quicker dilution of the gel, which can consequently reduce the structural strength and resistance to disruption of the gel. The gel will eventually break as a result of cohesive failure within its structure. It should be noted that when assessing the mucosa-adhesive strength of C971 containing gels, because the length of time in which gel remains in contact with the mucosa and surrounding medium is relatively short, the difference in the rate of water uptake will not have a great influence on the results obtained.

Finally, it appears that the presence of 1.0-1.2%w/v C974 within the gel, along with a maximum of 0.2%w/v C971 and 0.6-0.8%w/v C934 can form gels with strong mucosa-adhesive strength as well as a reasonable duration of mucosa-adhesion.

Overall, formulation F4 resulted in the formation of the most suitable gel, with desirable visual appearance, clarity and spreadability as well as suitable mucosa-adhesion. Furthermore, it is speculated that this formulation could remain longer in contact with the buccal mucosa invivo. In this study the gel was fully immersed in an aqueous environment in order to prevent it from dryness and resembles the presence of saliva. However, this condition could result in a quicker hydration and faster disruption of the gel, in contrast to buccal cavity which contains less fluid. At the end, it should be noted that in both the evaluation of mucosa-adhesive strength and duration of mucosa-adhesion tests, separation of the gel from the mucosal surface appeared to be a result of a cohesive failure within the gel structure. Therefore, the mucosal surface was found to be coated with a rather thin layer of gel at the end of each test (i.e. when gel-mucosa separation took place). This finding would mean that invivo, a thin layer of gel could still remain in contact with the buccal mucosa, even after the main bulk of the gel applied has been washed away by saliva, prolonging the residence time of the gel and allowing further drug release from it.

In conclusion, based on this study it could be said that the results obtained from the mere assessment of the mucosa-adhesive strength of a gel formulation do not provide an overview of the length of time this system remains on the mucosal surface and ignoring this rather important parameter could result in the formulation of a mucosa-adhesive formulation with a low duration of adhesion. Hence, these two tests should be used as complementary to each other in the formulation and selection of an effective and efficient transbuccal mucosa-adhesive gel.

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