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Original Article

Effect of Surfactant Type and Concentration on the Duration of Mucoadhesion of Carbopol 934 and HPMC Solid Compacts

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Abstract

In order to formulate an efficient and durable mucoadhesive drug delivery system, careful consideration of formulation-related parameters is critical. This study was conducted to investigate the effect of the presence of various types and concentrations of surfactants within or outside Carbopol 934 (C934) as well as hydroxypropylmethyl cellulose (HPMC) solid compacts, on their duration of mucoadhesion in vitro. Surfactants used in this study were chlorhexidine (CLH, cationic), sodium lauryl sulfate (SLS, anionic), and Poloxamer 407 (POL407, nonionic). These surfactants were individually dissolved in pH 7.0 phosphate buffer or added inside the solid compacts, and their effects on the duration of mucoadhesion of C934 and HPMC solid compacts determined at 37ºC, using rat small intestine as the model membrane. Results showed that the presence of CLH outside both C934 and HPMC compacts produces the greatest reduction in their duration of mucoadhesion among the three types of surfactants studied. Effect of the other two investigated surfactants, on reducing the duration of mucoadhesion of C934 and HPMC solid compacts was exceedingly less than that of CLH. For C934 compacts, the effect of SLS was to some extent more than POL407. However, the reverse was observed with HPMC compacts. With all the different types of surfactants investigated, increasing the concentration of surfactant resulted in a greater reduction in the duration of mucoadhesion of solid compacts. Furthermore, HPMC compacts were generally found to be more sensitive to the presence of various types and concentrations of surfactants within the external buffer medium. In fact the presence of CLH at a concentration of 0.2%, within the buffer medium, completely prevented their adhesion to the mucosal surfaces.

In conclusion, the presence of all three types of surfactants studied within C934 solid compacts reduced the duration of mucoadhesion greatly less than their presence within the buffer medium. This trend was also observed for HPMC compacts containing CLH and POL407. However, the presence of SLS (at concentrations above 0.5%) within HPMC compacts managed to reduce their duration of mucoadhesion more than when present in the outer buffer medium.

Keywords: Mucoadhesion; Duration of mucoadhesion; Mucoadhesivity ratio; Carbopol 934; Hydroxypropylmethyl cellulose; Surfactants.

Introduction

The use of mucoadhesive drug delivery systems for systemic or local delivery of various drugs has attracted a great deal of attention in recent years. These systems are capable of adhering to mucosal membranes for extended periods of time and releasing their drug content with a slow and gradual manner. A number of drugs, and in particular proteins and peptides, have been recognized as potential candidates for use in these systems (1-5).

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The process of mucoadhesion involves the formation of a tight and intimate contact between the mucosal surface and the polymeric chains of the mucoadhesive system. Dehydration of the mucosal surface, followed by the formation of physical entanglements and secondary chemical bonds (in particular hydrogen bonds) between these two surfaces, are of utter importance (6-8).

Mucoadhesive polymers are natural or synthetic hydrophilic macromolecules, usually containing hyroxyl or carboxyl groups. These functional groups help with the formation of hydrogen bonds with the mucosal surfaces. Anionic polymers are found to be amongst the best candidates for mucoadhesion. They include the Carbopol family of polymers, e.g. Carbopol 934 and polycarbophil, as well as other polymers such as sodium carboxymethyl cellulose and tragacanth. The nonionic polymers, such as hydroxypropylmethyl cellulose and methyl cellulose, are found to show exceedingly lower strengths of mucoadhesion, compared with the anionic polymers (9-14).

When formulating a successful drug delivery system, numerous formulation-related as well as physiological parameters should be taken into account. Regarding the mucoadhesive drug delivery systems, relatively few and rather limited studies have been conducted on the effect of various formulation additives on the adhesive-ability of mucoadhesive polymers and formulations (15, 16). These studies have shown that the use of common tablet excipients, as well as other formulation additives could influence the performance of mucoadhesive polymers. Neglecting the effect of the presence of these formulation additives on the strength and duration of adhesion of a formulated mucoadhesive system could alter its efficacy and residence time in vivo.

Surfactants are among the most widely used additives in pharmaceutical formulations. They are used for various reasons, such as improving the solubility and dissolution rate of drugs present within formulations, uniform and thorough dispersion of particles present in a formulation, proper wetting of solid particles, stability of pharmaceutical formulations, antibacterial activity, detergency, etc. Hence, incorporation of surfactants within mucoadhesive formulations or even their presence in the physiological environment surrounding the mucoadhesive system could influence their adhesive-ability. In the latter instance, surfactants could be found naturally in the body or be released from a pharmaceutical product containing them. However, despite their potential impact on the adhesive-ability of mucoadhesive formulations, very few and limited studies have been carried out in this respect.

In a study performed, using the approach of dynamic oscillatory rheology, various polysorbates (nonionic surfactants) were found to reduce the viscosity and viscoelastic nature of the mucus gel. It is speculated that polysorbates show this characteristic by disrupting the mucus gel structure, and this could be found useful in improving drug absorption via mucous membranes (17). In another study carried out, using the method of contact angle measurement, it was found that the presence of cholesterol (as a surfactant) at a concentration of 1% w/v could reduce the mucoadhesive strength of Carbopol 934 discs. However, addition of span 60 (as surfactant) at the same concentration resulted in an increase in the mucoadhesive strength of Carbopol 934 discs (18). Finally, Tobyn and co-workers (16) prepared tablets containing Carbopol 934 along with various amounts (1, 5 and 10%) of some surfactants, including cholesterol, span 60, triton X705, sodium lauryl sulfate and cetyl pyridinium chloride. They showed that none of the surfactants studied significantly reduced the strength of adhesion of tablets prepared to pig gastric mucosa invitro. However, it is very important to note that in none of the studies mentioned, effects of the presence of surfactants within or outside (within the external medium) the mucoadhesive formulation have been assessed on its' duration of mucoadhesion. A putative and effective mucoadhesive formulation should not only be able to adhere to the mucosal surface, but should also be capable of remaining in place for an extended period of time. Hence, assessing the duration of mucoadhesion of test system is critical (6, 12, 19, 20).

Therefore, because of the lack of knowledge in this field, in this study attempts were made to investigate the influence of the presence of various amounts of anionic, cationic and nonionic surfactants within and outside

Carbopol 934 and hydroxypropylmethyl cellulose solid compacts, on their duration of mucoadhesion in vitro.

Experimental

Materials

Carbopol 934 was obtained as a gift from B.F. Goodrich Chemical Co. (U.K.). Hydroxypropylmethyl cellulose (Methocel K100 M) was purchased from Colorcon Ltd. (U.K.). Chlorhexidine digluconate was obtained from the Sigma-Aldrich Chemicals (Germany). Sodium lauryl sulfate was from Merck Chemical Co. (Germany). Poloxamer 407 was obtained from BASF ChemTrade (Germany).

Preparation of solid compacts

For this purpose a single punch tablet machine (Erweka AR-400, Germany), fitted with flat 9mm round punches, was employed. Polymers used were Carbopol 934 (C934) and hydroxypropylmethyl cellulose (HPMC). Control solid compacts (discs), containing 100mg of the test polymer alone and in the absence of any surfactant, were prepared by compression. Next, 100mg solid compacts containing either C934 or HPMC along with various amounts of surfactants, were prepared following thorough mixing. Surfactants used in this study included the anionic surfactant, sodium lauryl sulfate (SLS), at amounts of 0.5, 1 and 2% w/w; the cationic surfactant, chlorhexidine digluconate (CLH), at amounts of 0.01, 0.1 and 0.2% w/w; and the nonionic surfactant, Poloxamer 407 (POL407), at amounts of 0.5, 1, 2, 3, 6, 10 and 20% w/w. It should be noted that all the solid compacts were compressed under identical conditions and following preparation stored in airtight containers until use.

Preparation of surfactant containing solutions

For the purpose of this study, pH 7 phosphate buffer was used. The pH values of these buffer solutions were carefully measured with a digital pH meter (Hanna 8519N, Italy) at room temperature, and were found to be 7.0 ± 0.04. Next, the test surfactants were added to the buffer solution at different concentrations and mixed thoroughly at room temperature, using a mechanical stirrer (Heidoloph RZR50, Germany), to form the final solution. SLS was added at concentrations of 0.5, 1 and 2% w/v. CLH was added at concentrations of 0.01, 0.1 and 0.2% w/v. Finally, POL407 was added at concentrations of 0.5, 1, 2, 3, and 6% w/v. Addition of POL407 at concentrations higher than 6% w/v, resulted in its precipitation within the phosphate buffer solution. Hence, its effect within the buffer solution was only studied at concentrations up to 6% w/v.

Preparation of the model mucosa

Based on previous studies (11, 12, 19, 21), the model mucosal membrane used for assessing the duration of mucoadhesion of solid compacts prepared was rat small intestine. Male N.M.R.I. rats (obtained from Pasteur Institute of Iran), weighing between 200 ± 20 g and aged between 6-8 weeks, were used in this study. Rats were sacrificed by being placed in an ether containing desiccator, followed by cervical dislocation. Based on the above-mentioned studies, the middle section, discarding the first 40-50 mm at either ends of fresh intestine was removed, cut into 3 cm pieces, and frozen until required to inhibit muscle contraction. The night before experimentation, sections of rat intestine were placed at 4ºC to be thawed. Next, they were placed in distilled water for 30min in order to become hydrated, and then placed in pH 7 phosphate buffer for 15min to get adopted with this medium. Finally, they were opened longitudinally to expose the inner mucosal surface, gently washed with the phosphate buffer, and then mounted on the test apparatus.

Determination of the duration of mucoadhesion

In order to determine the duration of mucoadhesion of solid compacts prepared in

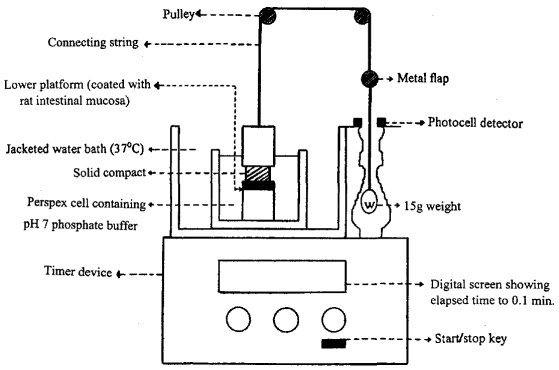

Figure 1. Apparatus used for measuring the duration of mucoadhesion of various solid compacts prepared to rat intestinal mucosa (model membrane) at 37°C.

Table 1. Effect of the presence of various amounts of the cationic surfactant, CLH, within or outside (pH 7 phosphate buffer medium) C934 solid compacts, on the duration of mucoadhesion of compacts to rat intestinal mucosa at 37°C (n=6, mean ± standard deviation).

Location of surfactant	Amount of surfactant added (%)	Duration of mucoadhesion (min)		Mucoadhesivity ratio
		Control (no surfactant)	With CLH	
Outside compact	0.01	1539.3 ± 36.4	1225.3 ± 26.7	0.796
	0.1		413.5 ± 19.1	0.269
	0.2		21.0 ± 7.4	0.014
Within compact	0.01	1577.8 ± 39.2	1556.4 ± 41.8	0.986
	0.1		1273.7 ± 37.9	0.807
	0.2		1118.0 ± 18.8	0.709

this study, the test apparatus shown in figure 1 was used.

The method used for setting up the apparatus and determining the duration of mucoadhesion of solid compacts prepared was similar to that adopted in previous studies (19, 20, 22). Briefly, the solid compacts prepared were individually mounted on the upper platform of the test apparatus. Sections of rat intestine prepared as explained in the previous part of this study were individually mounted securely in place, mucosal side upwards, on the lower platform of the test apparatus. The test apparatus was then filled with the test medium (phosphate buffer containing various surfactants or without surfactant) and its temperature maintained at 37ºC throughout the experiment. The upper platform was then lowered onto the lower platform, until contacted with the mucosal surface of rat intestine. After 5min contact, under a light pressure of fingertip, a constant tensile stress (a 15g weight) was applied to the adhesive joint (solid compact/mucosal interface) and the digital timer of test apparatus activated to record the time intervals elapsed. As soon as the adhesive joint detached, the 15g weight dropped onto a photocell detector, which automatically stopped the timer device and recorded the duration of mucoadhesion of compact tested. This experiment was run six times on each series of solid compacts prepared. The mean duration of mucoadhesion of each series was then calculated. In addition the mucoadhesivity ratio of each series was calculated using equation 1:

$$Mucoadhesivity\ ratio = Duration_{test}/Duration_{control} \quad \textit{(equation 1)}$$

In this equation the mean duration of mucoadhesion of solid compacts tested in the presence of a surfactant has been termed "$Duration_{test}$", and the mean duration of mucoadhesion of solid compacts tested in the absence of surfactants as "$Duration_{control}$".

Results and Discussion

As mentioned earlier, effect of the presence of surfactants within or outside mucoadhesive formulations on their duration of adhesion, has not been studied. Hence, in this study attempts were made to investigate the effect of various types and concentrations of surfactants on the duration of mucoadhesion of C934 and HPMC solid compacts. These two polymers are well-known mucoadhesive materials. In fact, the anionic C934 is ranked among the strongest mucoadhesive materials. On the other hand HPMC, which is a nonionic cellulose derivative, is known to be a moderate mucoadhesive polymer. However, under moderate stresses, HPMC has been found to remain in contact with the mucosal surface much longer than C934. In fact, results obtained from this study are also in agreement with this statement. This behaviour has been proposed to be due to the slower rate of hydration within HPMC, preventing it from being over-hydrated at shorter time intervals (11, 19, 20).

Table 2. Effect of the presence of various amounts of the cationic surfactant, CLH, within or outside (pH 7 phosphate buffer medium) HPMC solid compacts, on the duration of mucoadhesion of compacts to rat intestinal mucosa at 37°C (n=6, mean ± standard deviation).

Location of surfactant	Amount of surfactant added (%)	Duration of mucoadhesion (min)		Mucoadhesivity ratio
		Control	With CLH (no surfactant)	
Outside compact	0.01	3270.8 ± 37.5	2421.3 ± 41.7	0.740
	0.1		820.8 ± 35.6	0.251
	0.2		(no adhesion)	0.000
Within compact	0.01	3305.2 ± 45.7	3279.6 ± 38.6	0.992
	0.1		2304.5 ± 32.5	0.697
	0.2		1436.2 ± 29.7	0.435

Table 3. Effect of the presence of various amounts of the anionic surfactant, SLS, within or outside (pH 7 phosphate buffer medium) C934 solid compacts, on the duration of mucoadhesion of compacts to rat intestinal mucosa at 37°C (n=6, mean ± standard deviation).

Location of surfactant	Amount of surfactant added (%)	Duration of mucoadhesion (min)		Mucoadhesivity ratio
		Control (no surfactant)	With SLS	
Outside compact	0.5	1547.5 ± 38.7	1119.4 ± 30.6	0.723
	1.0		724.8 ± 28.1	0.468
	2.0		239.7 ± 16.2	0.155
Within compact	0.5	1562.5 ± 49.4	1540.7 ± 41.1	0.986
	1.0		1228.0 ± 35.4	0.786
	2.0		1091.2 ± 37.8	0.698

Presence of the cationic surfactant, CLH, outside both the C934 (Table 1) and HPMC (Table 2) solid compacts was found to result in the greatest amount of reduction in their duration of mucoadhesion and the lowest mucoadhesivity ratios, among all the surfactants studied. For both C934 and HPMC solid compacts, this reduction was statistically significant ($P<0.05$, ANOVA and Tukey post-test), compared with the control compacts, at all CLH concentrations studied. In both cases, at higher CLH concentrations the reduction observed in the duration of mucoadhesion was more drastic. In addition, HPMC solid compacts were found to be exceedingly more sensitive to the presence of CLH within the exterior phosphate buffer medium, than C934 compacts. In fact at a CLH concentration of 0.2%, HPMC compacts completely failed to adhere to the mucosal surface. However, the presence of CLH within C934 and HPMC solid compacts reduced the duration of mucoadhesion of these compacts greatly less than their presence in the external medium (outside compacts). In fact with both C934 and HPMC compacts, the presence of CLH at amounts greater than 0.01% produced a statistically significant ($P<0.05$, ANOVA and Tukey post-test) reduction in the duration of mucoadhesion of compacts. Nevertheless, the reduction observed in the duration of mucoadhesion of C934 and HPMC compacts in the presence of CLH within them, was immensely less than the presence of CLH in the external buffer medium.

CLH is a cationic surfactant. Hence, it can bind to the negatively charged mucosal surface, preventing the polymer chains from being attached to this surface. Therefore, CLH can help to reduce the formation of strong adhesive bonds required to keep the compact in contact with the mucosal surface for an extended period of time. In other word, CLH hinders the formation of mucoadhesive polymer chains-mucosal surface interactions (such as hydrogen bond formation), needed to produce a strongly adhesive and durable compact. In addition CLH molecules can also form cation-anion complexes with the ionized carboxyl groups present within the C934 polymeric chains. These complexes can also hinder full stretching and opening of the C934 chains, needed for the formation of a close and intimate contact with the mucosal surface, and hence reduce the overall extent of adhesive bonds formed with the mucosal surface. However, it seems that despite the disrupting effect of CLH, C934 polymeric chains can encounter the presence of

Table 4. Effect of the presence of various amounts of the nonionic surfactant, POL407, within or outside (pH 7 phosphate buffer medium) C934 solid compacts, on the duration of mucoadhesion of compacts to rat intestinal mucosa at 37°C (n=6, mean ± standard deviation).

Location of surfactant	Amount of surfactant added (%)	Duration of mucoadhesion (min)		Mucoadhesivity ratio
		Control (no surfactant)	With POL407	
Outside compact	0.5	1514.4 ± 40.3	1490.4 ± 37.1	0.984
	1.0		1327.2 ± 39.6	0.876
	2.0		1169.9 ± 24.6	0.773
	3.0		1054.5 ± 27.1	0.696
	6.0		840.1 ± 23.4	0.555
Within compact	0.5	1509.1 ± 53.7	1496.5 ± 41.3	0.992
	1.0		1490.4 ± 45.7	0.988
	2.0		1481.7 ± 40.4	0.982
	3.0		1480.2 ± 18.9	0.981
	6.0		1470.9 ± 41.3	0.975
	10.0		1458.5 ± 43.8	0.967
	20.0		1107.2 ± 31.4	0.734

Table 5. Effect of the presence of various amounts of the nonionic surfactant, POL407, within or outside (pH 7 phosphate buffer medium) HPMC solid compacts, on the duration of mucoadhesion of compacts to rat intestinal mucosa at 37°C (n=6, mean ± standard deviation).

Location of surfactant	Amount of surfactant added (%)	Duration of mucoadhesion (min)		Mucoadhesivity ratio
		Control (no surfactant)	With POL407	
Outside compact	0.5	3202.4 ± 48.6	2368.7 ± 32.9	0.740
	1.0		1958.8 ± 40.7	0.612
	2.0		1296.3 ± 30.6	0.405
	3.0		825.9 ± 35.1	0.258
	6.0		341.5 ± 26.4	0.107
Within compact	0.5	3282.3 ± 54.5	3274.2 ± 44.7	0.998
	1.0		3255.6 ± 36.5	0.992
	2.0		3247.4 ± 41.6	0.989
	3.0		3245.9 ± 56.8	0.989
	6.0		3239.2 ± 47.4	0.987
	10.0		3230.7 ± 41.2	0.984
	20.0		2060.5 ± 30.9	0.628

CLH better than HPMC, and form stronger adhesive bonds with the mucosal surface.

Presence of CLH within C934 and HPMC solid compacts has not been able to produce the same extent of reduction in the duration of mucoadhesion of compacts, compared to that seen when CLH was present outside the solid compacts. It is speculated that in contrast to the situation when CLH is present outside the solid compacts, when CLH molecules are present within the compacts they can not quickly reach out and bind to the mucosal surface. In fact, a solid compact requires more time to be hydrated and let the external medium to get into the compact to dissolve all the CLH molecules. Hence, this lag time will allow the formation of stronger adhesive bonds between the polymer chains and the mucosal surface. This would in turn create a stronger and more durable mucoadhesive joint. However, by increasing the amount of CLH present within the solid compact, a greater number of CLH molecules can get out of the compact, and hence exert a more pronounced effect.

Presence of the anionic surfactant, SLS, and the nonionic surfactant, POL407, outside the C934 and HPMC solid compacts have not been able to produce the same reduction in the duration of mucoadhesion of compacts, compared with the solid compacts placed in contact with CLH. The presence of SLS outside the C934 compacts (Table 3) has reduced the duration of mucoadhesion more than POL407 (Table 4). Hence, the mucoadhesivity ratios of C934 compacts placed in contact with SLS are less than those placed in contact with POL407.

Presence of SLS and POL407 within the buffer medium at all the concentrations studied, resulted in a significant ($P<0.05$, ANOVA and Tukey post-test) reduction in the duration of mucoadhesion of both C934 and HPMC solid compacts, compared with the corresponding control compacts. However, interestingly and unlike the C934 solid compacts, the presence of POL407 outside the HPMC compacts (Table 5) managed to reduce the duration of mucoadhesion of HPMC compacts more than SLS (Table 6). In other word in C934 solid compacts, following CLH, the presence of SLS outside the compacts results in the greatest reduction in mucoadhesion, whereas in HPMC solid compacts POL407 stands after CLH in this respect. Regardless of this finding, both SLS and POL407 were able to further reduce the duration of mucoadhesion of C934 and HPMC compacts, by increasing their concentration within the phosphate buffer medium. Also, the mucoadhesivity ratio of both the C934 and

Table 6. Effect of the presence of various amounts of the anionic surfactant, SLS, within or outside (pH 7 phosphate buffer medium) HPMC solid compacts, on the duration of mucoadhesion of compacts to rat intestinal mucosa at 37°C (n=6, mean ± standard deviation).

Location of surfactant	Amount of surfactant added (%)	Duration of mucoadhesion (min)		Mucoadhesivity ratio
		Control	With SLS (no surfactant)	
Outside compact	0.5	3264.0 ± 40.3	2698.6 ± 34.5	0.827
	1.0		2021.4 ± 48.7	0.619
	2.0		1430.7 ± 33.9	0.438
Within compact	0.5	3255.8 ± 39.1	3239.1 ± 49.4	0.995
	1.0		2005.9 ± 41.6	0.616
	2.0		1286.3 ± 32.7	0.395

HPMC solid compacts placed in contact with SLS or POL407 containing buffer medium were greater than their corresponding compacts placed in the buffer medium containing CLH.

On the other hand, the presence of SLS and POL407 within C934 solid compacts (Tables 3 and 4), could not produce the same reduction in the duration of mucoadhesion of compacts, compared to the situation when they were added to the external buffer medium. Hence, the corresponding mucoadhesivity ratios were also higher for C934 solid compacts containing these surfactants. Nevertheless, the presence of SLS within C934 solid compacts was able to significantly ($P<0.05$, ANOVA and Tukey post-test) reduce the duration of mucoadhesion of compacts, compared with the control compacts, when present at amounts greater than 0.5%. As mentioned above this reduction was greatly less than when SLS was present outside the C934 compacts. With POL407, its presence within C934 solid compacts only at a concentration of 20%, was found to significantly reduce the duration of mucoadhesion of compacts. Hence, it seems that the presence of SLS within C934 compacts can reduce the duration of mucoadhesion of compacts more than POL407. This was also reflected in the mucoadhesivity ratios obtained. However, with HPMC solid compacts, the presence of SLS (except for 0.5% concentration) within these compacts (Table 6) was found to reduce their duration of mucoadhesion more than when SLS was present outside the HPMC compacts. This finding was also supported with the mucoadhesivity ratios obtained with these compacts. In fact at SLS concentrations above 0.5% within HPMC compacts, the reduction observed in the duration of mucoadhesion of compacts was found to be significant ($P<0.05$, ANOVA and Tukey post-test), compared with the control HPMC compacts. Finally, the presence of POL407 within HPMC solid compacts (Table 5) was only found to significantly ($P<0.05$, ANOVA and Tukey post-test) reduce the duration of mucoadhesion of compacts, compared with the control compacts, when present at a concentration of 20%. Furthermore, this reduction observed was greatly less than that obtained when POL407 was present in the buffer medium. Also, the effect of SLS in reducing the duration of mucoadhesion of HPMC, when present within these compacts, seems to be greater than that of POL407.

As mentioned earlier, the presence of CLH outside C934 and HPMC compacts, can quickly cover and form complexes with the mucosal surface, preventing the formation of strong and durable mucoadhesive bonds between the polymer chains and the mucosal surface. The anionic surfactant, SLS, and the nonionic POL407 are not expected to be able to exert such an effect. Hence, it does not seem strange that their ability to reduce the duration of mucoadhesion of C934 and HPMC compacts is less than that of CLH. With C934 compacts, the presence of SLS outside the compacts was found to reduce the duration of mucoadhesion more than POL407. It is speculated that the presence of the anionic surfactant, SLS, in the buffer medium surrounding the C934 compacts can form a repulsive layer of surfactant in the interface between polymer chains and the mucosal surface. These repulsive forces are formed because of the presence of negative charges within both the C934 polymeric chains (ionized carboxyl groups) as well as the mucosal surface. Hence, the process of nearing of the C934 chains towards the mucosal surface, followed by the formation of a close and intimate contact, required for consolidation of the mucoadhesive joint, can not properly take place. This could in turn result in the formation of weaker mucoadhesive bonds, leading to a quicker dislodgment of compacts from the mucosal surface. The nonionic surfactant, POL407, is not expected to create such a repulsive layer. Hence, its ability to reduce the duration of mucoadhesion of C934 solid compacts is less than CLH and SLS.

Neither the presence of SLS nor POL407 within the C934 solid compacts reduced the duration of mucoadhesion of compacts, as much as their corresponding compacts placed in buffer media containing these surfactants. Just like CLH, these two surfactants are also not able to quickly and completely diffuse out of the C934 compact, and come into contact with the mucosal surface. This is because of the time period required for the solid compacts to hydrate and allow the external medium to get into the dry compact and dissolve the surfactant molecules. Following this stage, these two surfactants can exert their effects in a similar manner to that described above. However,

because of this lag time, stronger adhesive joints would be formed between the polymer chains and the mucosal surface, leading to a longer duration of mucoadhesion.

In contrast to the results found for C934 compacts placed in contact with buffer media containing SLS or POL407, the presence of POL407 was able to reduce the duration of mucoadhesion of HPMC compacts more than SLS. In here, the SLS molecules are not able to repel the polymer chains of the nonionic HPMC and exert their repulsive layer effect (like that mentioned for C934) properly. Hence, these polymeric chains could get near the mucosal surface, resulting in the formation of durable mucoadhesive bonds. However, POL407 molecules can reside in the interfacial layer formed between the HPMC solid compact and the mucosal surface. Hence, by partially disrupting this layer as well as reducing the interfacial tension, POL407 can more effectively (compared with SLS) reduce the number of mucoadhesive bonds formed between HPMC chains and the mucosal surface. As a result the HPMC compact would not be able to remain in contact with the mucosal surface for a long period of time. Again, in here the presence of POL407 within the HPMC compacts was not able to reduce the duration of mucoadhesion of compacts, as well as when present in the external buffer medium. The reason for this finding is exactly similar to that mentioned for C934. However, the presence of SLS (at concentrations above 0.5%) within the HPMC solid compacts was found to reduce their duration of mucoadhesion more than when present outside the compacts. This finding was concentration dependent, and the presence of 2% SLS within HPMC compacts was able to exert a greater effect in reducing the duration of mucoadhesion. It is presumed that the presence of SLS anionic molecules within HPMC compacts can result in a more expanded polymeric network compared with POL407. This could in turn increase the rate of hydration of HPMC compact. Hence, as the time passes on, HPMC compact would hydrate faster and eventually reach the point of over-hydration and failure to remain in contact with the mucosal surface. Presence of SLS molecules outside the HPMC compact can not exert a similar effect, because the hydration rate of the compact is less in this situation.

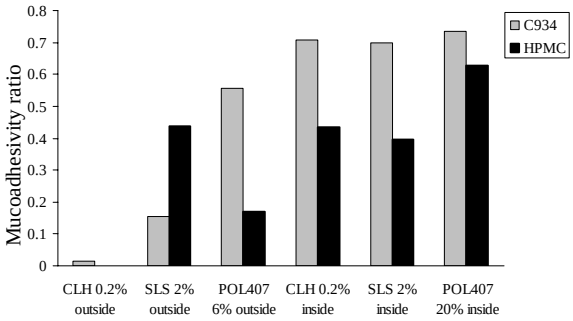

Figure 2. The least mean (n=6) mucoadhesivity ratios of C934 and HPMC solid compacts obtained in the presence of the greatest amounts of each of the surfactants used within and outside them (note: value for HPMC in CLH 0.2% outside is zero).

It is worth mentioning that in the only similar study Tobyn and co-workers (16) found that the presence of various surfactants, including cholesterol, span 60, triton X705, sodium lauryl sulfate and cetyl pyridinium chloride, at concentrations of 1, 5 and 10% within Carbopol 934 tablets, resulted in no significant reduction in their strength of mucoadhesion. Determination of the strength of mucoadhesion is a quick test; merely measuring the maximum force required for breaking apart the adhesive joint formed between the mucoadhesive system and the mucosal surface. In this test tablets will not have the chance to hydrate extensively. Therefore, the surfactant molecules will not have the chance to exert their effects properly. However by determining the duration of mucoadhesion, as performed in this study, a better view of what would happen to the mucoadhesive system over a long period of time could be assessed. Hence in this study, in contrast to Tobyn and co-workers study, the presence of surfactants such as CLH and SLS within C934 and HPMC solid compacts was found to significantly reduce their duration of mucoadhesion. Therefore, as mentioned earlier, determining the duration of adhesion of a putative mucoadhesive system is a critical test.

Figure 2 summarizes the least mucoadhesivity ratios of C934 and HPMC compacts obtained in the presence of the greatest amounts of each of the surfactants used within and outside the compacts. It is clear that the presence of the cationic surfactant, CLH, outside both these discs can result in the lowest mucoadhesivity ratios obtained.

In conclusion, it seems that the presence of surfactants within or outside a mucoadhesive

formulation made of C934 and/or HPMC can affect the adhesion-ability of the system. Presence of various surfactants, and in particular cationic surfactants, outside the mucoadhesive system appears to be more effective in this respect. This would mean that, for example using products such as toothpaste or mouthwashes (both containing surfactants) in the presence of a buccoadhesive tablet (attached to the buccal cavity), could alter the durability of the mucoadhesive system. The Presence of lower amounts of nonionic surfactants within mucoadhesive formulations is not expected to drastically reduce their duration of mucoadhesion, making them a better choice for use in these formulations.

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