THE EFFECT OF HYDROXYL CONTAINING TABLET EXCIPIENTS ON THE ADHESIVE DURATION OF SOME MUCOADHESIVE POLYMERS

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ABSTRACT

In order to investigate the effect of hydroxyl group containing tablet excipients on the duration of adhesion of mucoadhesive polymers, discs containing Carbopol 934 (C934), polycarbophil (PC), sodium carboxymethyl cellulose, hydroxypropylmethyl cellulose (HPMC), tragacanth (trag.) and sodium alginate (Na alg.), either alone or in the presence of various amounts of excipients were prepared. The duration of adhesion of the prepared discs were determined in pH 7.0 phosphate buffer at 37°C. All the excipients examined reduced the duration of adhesion and the relative durability of the polymer containing discs. HPMC discs despite showing the longest duration of mucoadhesion, suffered the greatest reduction in adhesive properties in the presence of excipients which were examined. Following HPMC, Na alg. and then trag. discs showed the greatest sensitivity to the presence of excipients. The least reduction in the duration of adhesion was observed with PC and C934. Among the excipients tested, spray-dried lactose produced the greatest reduction in the duration of adhesion, followed by polyethylene glycol 6000 and pregelatinized starch. The smallest reduction in the adhesive properties of the test polymers was due to talc powder. Hence, it seems that addition of the tablet excipients adversely reduce the adhesive properties of mucoadhesive dosage forms, which should be carefully considered during their formulation.

Key words: Mucoadhesion, Duration of adhesion, Tablet excipients, Mucoadhesive polymers, Relative durability

INTRODUCTION

The use of mucoadhesive polymers as means of delivering therapeutically active drugs, including proteins and peptides, to or via mucosal membranes has been the focus of attention in recent years (1-5). The term "mucoadhesion" refers to the attachment of synthetic or natural macromolecules to a mucus-coated mucosal membrane (6). The process of mucoadhesion initially involves the formation of an intimate contact between the mucosal surface/muco-adhesive polymer chains. Mucosal dehydration which is 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, that contain numerous hydrogen bond forming groups. These polymers will hydrate and swell in contact with an aqueous medium, and as a result adhere to the mucosal surfaces. However, their overhydration could lead to the formation of a slippery mucilage and a loss of the adhesive properties. Anionic polymers are 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, sodium alginate and tragacanth. The nonionic polymers, such as hydroxypropylmethyl cellulose and methyl cellulose, have shown exceedingly lower strengths of mucoadhesion, in comparison with the anionic polymers (9-12).

Numerous formulation-related and physiological parameters should be considered to formulate a successful drug delivery system. Regarding the mucoadhesive drug delivery systems, especially tablets, the available published data on the effect of common formulation excipients on the adhesive properties of mucoadhesive polymers and formulations are rather scarce. In the only available publication of this type to us, preparation of tablets containing Carbopol 934 along with a number of common flow aids and diluents, only at concentrations of 5 and 50% respectively, has been reported (13). It was found that the hydrophobic lubricant magnesium stearate hinders the formation of a strong mucoadhesive bond between Carbopol 934 and the pig gastric mucosa, and as a result reducing its' muco-adhesive strength significantly. However the other

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two tested flow aids, which were talc and colloidal silica, had no significant effect on the mucoadhesive strength of Carbopol 934 tablets. On the other hand, all four tablet diluents that they tested could significantly reduce the mucoadhesive strength of Carbopol 934 tablets. It is very important to note that this study just focused on the mucoadhesive strength of Carbopol 934 tablets only in the presence of one concentration of flow aid or diluent and did not determine their duration of mucoadhesion. An effective mucoadhesive formulation not only should be able to adhere to the mucosal surface, but also should be remained in the place for an extended period of time. Hence, assessment of the duration of mucoadhesion of the test system is critical (9, 14, 15). Due to the deficiency of published data on the effect of common tablet excipients containing hydroxyl groups on the adhesive properties of mucoadhesive polymers, in the present study attempts were made to investigate their influences on the duration of adhesion of a number of common mucoadhesive polymers, invitro.

MATERIALS & METHODS

Materials

Carbopol 934 and polycarbophil were obtained as gifts from B.F. Goodrich, Hounslow, UK; sodium carboxymethyl cellulose and hydroxypropylmethyl cellulose were purchased from Hercules Chemicals Co., USA; talc powder, pregelatinized starch, tragacanth and sodium alginate were obtained from BDH Chemicals, Poole, UK; polyethylene glycol 6000 was purchased from Sigma Chemical Co., Poole, UK; spray-dried lactose obtained from DMV Lactose, Veghel, Netherlands.

Methods

Preparation of polymer-containing solid discs

The test polymers used included, polycarbophil (PC), Carbopol 934 (C934), sodium carboxymethyl cellulose (CMC), hydroxypropylmethyl cellulose (HPMC), tragacanth (trag.) and sodium alginate (Na alg.). Flat-faced control and test discs with a diameter of 9 mm and containing 100 mg of each of the test polymers either alone or along with various amounts of only one excipient were prepared by compression, using an Erweka single-punch tablet press. Excipients used in this study included polyethylene glycol 6000 (PEG_{6000}) at amounts of 0.5, 1, 3, 5, 10, 15 and 20 %w/w; pregelatinized starch at amounts of 1, 3, 5, 10, 15, 20, 25 and 30 %w/w; spray-dried lactose at amounts of 1, 3, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60 and 70 %w/w; and talc powder at various amounts of 0.5, 1, 3, 5, 7 and 10 % w/w. All the prepared discs were kept in air tight containers until use.

Determination of the duration of mucoadhesion

Based on previous studies (9, 14, 16, 17), the model mucosal membrane used in this study was rat small intestine. The apparatus (Fig. 1) and method used for determination of the duration of mucoadhesion of discs which were prepared in this study were similar to those of the previous studies (9, 14, 15, 18). Solid polymer-containing discs were individually mounted on the upper platform of the test apparatus. Sections of the rat intestine were individually mounted securely in such a way that the mucosal sides were upward on the lower platform of the test apparatus. The test apparatus was then filled with pH 7 phosphate buffer medium at 37ºC. Next, the upper platform was lowered on to the lower platform until it touched the mucosal surface. After 5 min contact a constant tensile stress (a 15 g weight) was applied to the adhesive joint and the digital timer of the apparatus was activated to record the elapsed time intervals. As soon as the adhesive joint failed, the 15g weight dropped onto a photocell detector, which automatically stopped the timer device and recorded the duration of mucoadhesion of the tested disc. This experiment was conducted five times for each series of discs, which were tested. In addition, the relative durability of each series of the prepared discs was calculated as follows: $[D_{test} / D_{control}]$ in which D_{test} and $D_{control}$ are the mean values (n=5) obtained for the duration of mucoadhesion of the test and control discs, respectively.

RESULTS AND DISCUSSION

Common hydroxyl group containing tablet excipients could form hydrogen bonds with the hydrophilic functional groups (such as carboxyl and hydroxyl) of the mucoadhesive polymers, and as a result prevent their interactions with the mucosal surface. Formation of hydrogen bonds between the hydrophilic functional groups of the mucoadhesive polymers and the mucus layer or the mucosal surface is a prerequisite for extensive and durable mucoadhesion (6, 7, 19, 20).

In general, among the control discs which were tested, HPMC discs showed the greatest duration of mucoadhesion, being significantly [$P< 0.05$, one way analysis of variance (ANOVA) with tukey post test] greater than the other examined anionic polymers. This finding is in agreement with previously published data (18, 21), and results from a slower rate of hydration of HPMC as a non-ionic polymer. This could in turn prevent the disc from quick overhydration and formation of a slippery and weak mucilage, which could be

easily removed from the mucosal surface. Also similar to previous results (9, 18, 21) the tested Carbopols, PC and C934, were able to remain in contact with the mucosal surface longer than CMC, and the natural anionic polymers trag. and Na alg. This is again due to the greater rate of hydration and water uptake of CMC and the natural polymers which were tested (8, 18). Also, in agreement with the previous results (8, 9), PC discs were able to uptake water slower and remain in contact with the mucosal surface longer than the loosely cross-linked C934 discs.

The first excipient investigated was spray-dried lactose, which could be used as a common diluent in mucoadhesive tablet formulations (22). The effect of various amounts of lactose on the duration of adhesion of the tested mucoadhesive polymers is shown in table 1. Based on the results, spray-dried lactose was found to reduce significantly ($P< 0.05$, ANOVA with tukey post test) the duration of adhesion of all the investigated mucoadhesive polymers at amounts greater than 1%, in comparison with the corresponding control discs. Furthermore, by the use of HPMC containing discs it was found that even in the presence of 1% spray-dried lactose there was a significant fall in the duration of adhesion of the test disc and at concentrations above 5%, discs completely lost their adhesive properties. Following HPMC containing discs, Na alg. and then trag containing discs were affected mostly by the presence of spray-dried lactose. In fact, the presence of spray-dried lactose at a concentration of 15% or above, completely prevented their adhesion to the mucosal surface. In the case of the other three tested polymers (PC, C934 and CMC), presence of spray-dried lactose at a concentration of 50% or more prevented discs from adhesion to the mucosal surface totally. In this case, despite the fact that the control HPMC discs remained in contact with the mucosal surface much longer than the other tested control polymeric discs, the presence of spray-dried lactose produced the smallest relative durability values among the examined polymers. Following HPMC, the natural polymers trag. and Na alg. were more susceptible to the presence of spray-dried lactose. However, interestingly, the relative durabilities of the CMC discs were found to be larger than the Carbopols C934 and PC, despite CMC's shorter duration of mucoadhesion. Spray-dried lactose is a hydrophilic compound and it is speculated to increase the rate of water uptake and swelling of the mucoadhesive polymer containing discs. This could result in their quicker overhydration and dislodgment from the adhesion site. By the use of higher amounts of spray-dried lactose (it is not an intrinsically adhesive material), a reduction in the amount of mucoadhesive polymer which were present and other possible mechanisms which were mentioned before, contributed to an undesirable durability or even lack of adhesion. In a report (13), it has been demonstrated that the presence of 50% lactose within C934 tablets could significantly reduce the mucoadhesive strength of tablets to pig gastric mucosa in comparison with the control tablets (pure C934). The present study shows that at a lactose concentration of 50%, the mucoadhesive strength of the C934 disc is too weak to withstand the constant 15 g tensile stress exerted, and soon after application mucoadhesive bonds would be broken and as a result the C934 disc detaches from the mucosa. Furthermore, results of the present study show that lactose concentrations in C934 discs lower than 50%, down to 3%, can also significantly ($P< 0.05$, ANOVA with tukey post test) reduce their duration of mucoadhesion, in comparison with the control C934 discs.

The next excipient examined was pregelatinized starch, which could be used as a binder and adhesive in mucoadhesive tablets (22). Again, similar to spray-dried lactose, pregelatinized starch (1% and above with HPMC discs, and 3% or more with the other polymeric discs) also significantly ($P< 0.05$, ANOVA with tukey post test) reduced the duration of adhesion of the all tested mucoadhesive polymers, in comparison with the corresponding control discs (Table 2). In addition, the presence 10, 15 and 20% pregelatinized starch, within HPMC, Na alg. and trag. discs respectively, completely prohibited their mucoadhesive properties. However, the effect of pregelatinized starch in lowering the duration of mucoadhesion and relative durabilities of all the tested polymers was less than spray-dried lactose. Pregelatinized starch by itself is used as an adhesive in tablets and it was expected to keep the polymeric disc in contact with the mucosal surface slightly longer than the non-adhesive spray-dried lactose. Nevertheless, due to the possible formation of hydrogen bonds between the hydroxyl groups of pregelatinized starch and the functional groups of the tested mucoadhesive polymers, as explained for spray-dried lactose, as well as an increase in the swelling of the discs, adhesive properties and the durability of the mucoadhesive discs could be reduced. Similar to spray-dried lactose, HPMC containing discs first and then Na alg. and trag discs showed the greatest sensitivity to the presence of pregelatinized starch among the tested polymers. However, in contrast to the data found with spray-dried lactose, duration of adhesion and relative durability of C934 and PC containing discs were less influenced by the presence of

Table 1. In vitro effects of various amounts of spray-dried lactose on the duration of adhesion (D_{adh}) and relative durability (D_{rel}) of some well-known mucoadhesive polymers at 37°C (n=5, mean ± standard deviation).

Polymer	Control		1% Lactose		3% Lactose		5% Lactose		10% Lactose		15% Lactose		20% Lactose		25% Lactose		30% Lactose		40% Lactose	
	D_{adh} (h)	D_{rel}	D_{adh} (h)	D_{rel}	D_{adh} (h)	D_{rel}	D_{adh} (h)	D_{rel}	D_{adh} (h)	D_{rel}	D_{adh} (h)	D_{rel}	D_{adh} (h)	D_{rel}	D_{adh} (h)	D_{rel}	D_{adh} (h)	D_{rel}	D_{adh} (h)	D_{rel}
PC	30.4±0.9	1.0	29.4±0.8	0.967	26.9±0.9	0.885	25.0±0.6	0.822	21.2±0.7	0.697	16.6±0.4	0.546	11.0±0.5	0.362	8.4±0.4	0.276	6.1±0.3	0.201	2.8±0.4	0.092
C934	26.0±0.7	1.0	24.9±0.6	0.958	21.6±0.7	0.831	18.9±0.5	0.727	15.7±0.3	0.604	12.1±0.4	0.465	6.6±0.3	0.254	4.4±0.5	0.169	2.9±0.2	0.112	0.8±0.1	0.031
CMC	20.4±0.9	1.0	19.8±0.6	0.971	18.3±0.7	0.897	17.4±0.5	0.853	14.8±0.4	0.725	11.4±0.6	0.559	7.8±0.3	0.382	6.1±0.5	0.299	4.3±0.2	0.211	2.1±0.3	0.103
HPMC	47.5±1.8	1.0	18.6±1.3	0.392	5.8±0.4	0.122	0.7±0.1	0.015	no adhesion		no adhesion		no adhesion		no adhesion		no adhesion		no adhesion	
trag.	9.3±0.5	1.0	8.1±0.6	0.871	6.7±0.3	0.720	4.7±0.4	0.505	1.9±0.2	0.204	no adhesion		no adhesion		no adhesion		no adhesion		no adhesion	
Na alg.	7.7±0.6	1.0	6.5±0.4	0.844	4.9±0.3	0.636	2.8±0.2	0.364	0.7±0.1	0.091	no adhesion		no adhesion		no adhesion		no adhesion		no adhesion	

*(no adhesion was observed in any of the test discs in the presence of 50% or more spray-dried lactose)

Table 2. In vitro effects of various amounts of pregelatinized starch on the duration of adhesion (D_{adh}) and relative durability (D_{rel}) of some well-known mucoadhesive polymers at 37°C (n=5, mean ± standard deviation).

Polymer	Control		1% Starch		3% Starch		5% Starch		10% Starch		15% Starch		20% Starch		25% Starch		30% Starch	
	D_{adh} (h)	D_{rel}	D_{adh} (h)	D_{rel}	D_{adh} (h)	D_{rel}	D_{adh} (h)	D_{rel}	D_{adh} (h)	D_{rel}	D_{adh} (h)	D_{rel}	D_{adh} (h)	D_{rel}	D_{adh} (h)	D_{rel}	D_{adh} (h)	D_{rel}
PC	30.2±0.8	1.0	29.8±0.9	0.987	27.9±0.6	0.924	26.4±0.7	0.874	23.0±0.5	0.762	18.4±0.6	0.609	13.1±0.4	0.434	10.5±0.7	0.348	8.3±0.3	0.275
C934	25.9±1.0	1.0	25.2±0.7	0.973	22.0±0.8	0.849	19.5±0.6	0.753	16.2±0.5	0.625	12.8±0.6	0.494	7.4±0.5	0.286	5.9±0.3	0.193	3.7±0.4	0.143
CMC	20.3±0.7	1.0	19.5±0.8	0.961	17.1±0.6	0.842	14.8±0.7	0.729	11.2±0.4	0.552	7.7±0.5	0.379	4.5±0.3	0.222	2.0±0.2	0.098	no adhesion	
HPMC	47.0±1.6	1.0	19.2±1.8	0.408	8.0±0.5	0.170	2.6±0.2	0.055	no adhesion		no adhesion		no adhesion		no adhesion		no adhesion	
trag.	9.4±0.4	1.0	8.5±0.6	0.904	7.2±0.3	0.766	5.8±0.4	0.617	3.0±0.3	0.319	0.2±0.1	0.021	no adhesion		no adhesion		no adhesion	
Na alg.	7.7±0.5	1.0	6.9±0.8	0.896	5.6±0.5	0.727	3.9±0.2	0.506	1.8±0.2	0.234	no adhesion		no adhesion		no adhesion		no adhesion	

Table 3. In vitro effects of various amounts of talc powder on the duration of adhesion (D_{adh}) and relative durability (D_{rel}) of some well-known mucoadhesive polymers at 37°C (n=5, mean ± standard deviation).

Polymer	Control		0.5% Talc		1% Talc		3% Talc		5% Talc		7% Talc		10% Talc	
	D_{adh} (h)	D_{rel}	D_{adh} (h)	D_{rel}	D_{adh} (h)	D_{rel}	D_{adh} (h)	D_{rel}	D_{adh} (h)	D_{rel}	D_{adh} (h)	D_{rel}	D_{adh} (h)	D_{rel}
PC	30.6±0.8	1.0	30.3±1.1	0.990	29.9±0.7	0.977	28.9±0.5	0.944	27.9±0.6	0.912	26.5±0.4	0.866	24.3±0.2	0.794
C934	25.8±0.6	1.0	25.5±0.5	0.988	25.3±0.8	0.980	24.0±0.6	0.930	22.4±0.3	0.868	20.8±0.5	0.806	19.1±0.4	0.740
CMC	20.3±0.9	1.0	19.9±0.7	0.980	19.7±0.7	0.970	18.5±0.4	0.911	16.9±0.5	0.832	15.1±0.2	0.744	13.0±0.4	0.640
HPMC	46.9±1.4	1.0	45.8±1.6	0.976	45.1±1.7	0.962	40.4±1.0	0.861	31.8±0.8	0.678	24.9±0.9	0.531	17.3±0.7	0.369
trag.	9.5±0.7	1.0	9.1±0.5	0.958	8.9±0.4	0.937	8.1±0.2	0.853	6.7±0.3	0.705	5.6±0.2	0.589	4.4±0.2	0.463
Na alg.	7.6±0.4	1.0	7.3±0.6	0.960	7.0±0.5	0.921	6.2±0.3	0.816	5.2±0.2	0.684	4.1±0.1	0.539	2.9±0.3	0.382

Table 4. In vitro effects of various amounts of PEG_{6000} on the duration of adhesion (D_{adh}) and relative durability (D_{rel}) of some well-known mucoadhesive polymers at 37°C (n=5, mean ± standard deviation).

Polymer	Control		0.5% PEG_{6000}		1% PEG_{6000}		3% PEG_{6000}		5% PEG_{6000}		10% PEG_{6000}		15% PEG_{6000}		20% PEG_{6000}	
	D_{adh} (h)	D_{rel}	D_{adh} (h)	D_{rel}	D_{adh} (h)	D_{rel}	D_{adh} (h)	D_{rel}	D_{adh} (h)	D_{rel}	D_{adh} (h)	D_{rel}	D_{adh} (h)	D_{rel}	D_{adh} (h)	D_{rel}
PC	30.4±1.0	1.0	30.0±0.8	0.987	29.5±0.9	0.970	27.1±0.6	0.891	25.3±0.4	0.832	21.9±0.5	0.720	18.0±0.6	0.592	12.3±0.3	0.405
C934	25.9±0.7	1.0	25.4±0.5	0.981	24.9±0.8	0.961	21.8±0.7	0.842	19.1±0.6	0.737	16.4±0.3	0.633	12.8±0.4	0.494	7.1±0.5	0.274
CMC	20.1±0.8	1.0	19.4±0.7	0.965	18.9±0.9	0.940	16.0±0.5	0.796	13.8±0.4	0.697	9.2±0.5	0.458	5.4±0.2	0.269	1.7±0.3	0.085
HPMC	47.2±1.6	1.0	26.5±1.4	0.561	18.7±0.9	0.396	6.1±0.4	0.129	0.9±0.2	0.019	no adhesion		no adhesion		no adhesion	
trag.	9.4±0.8	1.0	8.9±0.9	0.947	8.2±0.5	0.872	6.9±0.6	0.734	5.1±0.7	0.543	2.4±0.3	0.255	no adhesion		no adhesion	
Na alg.	7.8±0.6	1.0	7.2±0.5	0.923	6.6±0.6	0.846	5.1±0.4	0.654	3.2±0.2	0.410	1.1±0.2	0.141	no adhesion		no adhesion	

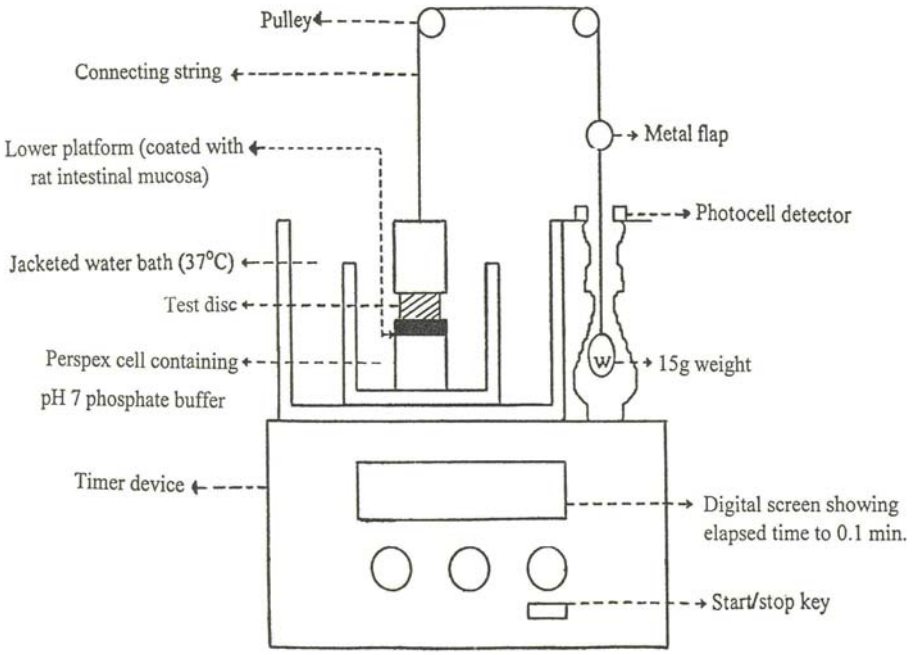

Figure 1. Apparatus used for measuring the duration of mucoadhesion of various solid test discs prepared to rat intestinal mucosa (model membrane) at 37 °C

pregelatinized starch than CMC discs. Overall, it seems that in comparison with spray-dried lactose, the use of pregelatinized starch results in a lower reduction in the duration of adhesion and relative durability of the tested mucoadhesive discs.

The results of the influence of the tablet flow aids, talc powder and PEG_{6000}, on the duration of mucoadhesion and relative durability of the tested mucoadhesive polymers are shown in tables 3 and 4 respectively. In both cases the general trends of reduction were similar to that of pregelatinized starch. At equal concentrations (3% and above) PEG_{6000} produced a more significant reduction ($P< 0.05$, student's t-test) in the duration of adhesion of all the mucoadhesive polymeric discs. With HPMC discs this difference was even significant at a flow aid concentration of 0.5%. Furthermore, presence of talc powder at concentrations below 3% resulted in a non-significant reduction ($P> 0.05$, one way analysis of variance) in the duration of adhesion of polymers in comparison with their corresponding control discs. Talc powder in spite of containing hydroxyl groups, only absorbs small amounts of water (22). However, PEG_{6000} is a hydrophilic material, capable of taking up greater amounts of water than talc powder. This difference could result in a reduced swelling and slower overhydration of the mucoadhesive polymer containing discs and a longer duration of mucoadhesion. This explanation could clearly be observed within HPMC discs, which show significantly ($P< 0.05$, student's t-test) smaller duration of adhesion in the presence of PEG_{6000}, compared with equal concentrations of talc powder. In fact HPMC discs fail to adhere to the mucosal surface at greater than 5% PEG_{6000} concentrations, unlike those containing 10% talc powder which remained adhesive for up to 17 h. Interestingly, it has been reported (13) that the presence of 5% talc within C934 tablets does not result in a significant reduction in the mucoadhesive strength of the tablet to pig gastric mucosa. This is in contrast with the significant reduction ($P< 0.05$, ANOVA with tukey post test) found in the duration of mucoadhesion in our study. This important finding shows the value of determination of the duration of adhesion of a putative and effective mucoadhesive test system. Based on this finding, it seems that the C934 disc containing talc powder can not remain in contact for the same length of time as the control discs, despite the fact that its' mucoadhesive strength as it has been reported (13) is not less than the control discs. In fact, the non-significant differences in the mucoadhesive strength of test and control discs appear to be magnified over an extended period of time which eventually results in a quicker displacement of the talc containing C934 discs from their sites of adhesion. Hence, the information obtained from evaluation of the duration of adhesion provides useful and

important complementary data regarding the efficacy of a mucoadhesive drug delivery system.

In conclusion, it seems that the presence of various common tablet excipients containing hydroxyl groups can influence the adhesive property and duration of mucoadhesion of such tablets. Hence, in the formulation of a strong and durable mucoadhesive tablet, beside choosing the most suitable mucoadhesive polymer (s), one should also critically evaluate the effect of the nature and amount of the excipients added to the formulation on its' adhesive properties and in particular durability.

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