ELSEVIER

International Journal of Pharmaceutics 180 (1999) 47–57

international journal of pharmaceutics

An in-vitro method for buccal adhesion studies: importance of instrument variables

Choy Fun Wong, Kah Hay Yuen *, Kok Khiang Peh

Department of Pharmaceutics, School of Pharmaceutical Sciences, University of Science Malaysia, 11800 Penang, Malaysia

Received 1 September 1998; received in revised form 10 November 1998; accepted 2 December 1998

Abstract

A method using a texture analyzer equipment and chicken pouch as the biological tissue was investigated for measuring the bioadhesive properties of polymers under simulated buccal conditions. The method was evaluated using two polymers, namely Carbopol 974P and Methocel K4M while the instrument variables studied included the contact force, contact time and speed of withdrawal of the probe from the tissue. The parameters measured were the work of adhesion and peak detachment force. Longer contact time and faster probe speed not only gave better reproducibility of results, but also better sensitivities for both parameters measured. On the other hand, a certain level of contact force was found essential for achieving good bioadhesion, above which there was no further contribution to the bioadhesion process. When the method was applied to determine the bioadhesiveness of several polymers, the values obtained for the work of adhesion and peak detachment force were quite consistent in the ranking of the polymers. The Carbopols were found to have the highest values, followed by gelatin, sodium carboxymethyl celluloses and hydroxypropylmethyl celluloses. On the other hand, Alginic acid, Eudragit RLPO and RSPO, and Chitosan appeared to have low bioadhesive values.

Keywords: Buccal; Bioadhesive; Texture analyzer; Chicken pouch

1. Introduction

Satisfactory bioadhesion is essential for the successful application of a buccal bioadhesive drug delivery system. It implied the strength of attachment of the dosage form to the biological tissue. Several techniques for in-vitro determination of bioadhesion have been reported, which included tensile testing (Park and Robinson, 1987), shear stress testing (Smart et al., 1984), adhesion weight method (Smart and Kellaway, 1982), fluorescent probe method (Park and Robinson, 1984), flow channel techniques (Mikos and Peppas, 1986), and colloidal gold staining method (Park, 1989). Presently, there is still no universal test method

* Corresponding author. Fax: +60-4-6596517.
E-mail address: khyuen@usm.my (K.H. Yuen)

0378-5173/99/$ - see front matter
PII: S0378-5173(98)00402-5

for bioadhesion measurement and some results of bioadhesion reported in the literature appeared to be contradictory. For instance, Lehr et al. (1992) reported that hydroxypropyl cellulose and carboxymethylcellulose showed almost no mucoadhesion, whereas other workers (Smart and Kellaway, 1982; Nagai and Machida, 1985; Rao and Buri, 1989; Sam et al., 1992) demonstrated good mucoadhesion with these two polymers.

Although reproducible adhesion measurements with small variability could be obtained with the Wilhelmy plates method (Sam et al., 1992), no biological tissue was employed and thus could not simulate the actual condition in the buccal cavity. More recently, Tobyn et al. (1995) reported the use of a texture analyzer equipment for mucoadhesive studies using porcine stomach tissue under simulated gastric conditions.

Here, a method to evaluate the adhesive properties of polymers using a TA.XT_2 texture analyzer equipment with chicken pouch as the model tissue under simulated buccal conditions is reported. The instrumental variables such as contact force, contact time and the speed of withdrawal of probe from the tissue, which can affect the bioadhesion were studied using two polymers, namely, Carbopol 974P, which has well characterized bioadhesive properties (Park and Robinson, 1984) and Methocel K4M, a weaker bioadhesive polymer. This method was then applied to evaluate the bioadhesive properties of some polymers.

2. Materials and methods

2.1. Materials

Hydroxypropylmethyl cellulose (Methocel K4M, K15M and K100M) were gifts from Colorcon, Kent, UK. Carbopol (CP 934P, 971P, 974P) and Polycarbophil were gifts from BF Goodrich, Cleveland, USA. Sodium carboxymethyl cellulose, SCMC 400 was obtained from Euro Chemo Pharma, Penang, Malaysia whereas Cekol 700 and Cekol 10000 were purchased from Metsa-Serla, Sweden. Xanthan gum was purchased from Rhone-Poulenc Chimie, Paris, France; polyvinylpyrolidone K-30, PVP K-30 from BASF, Parsippany, USA; alginic acid from BDH Chemical, Poole, England and Eudragit RSPO and RLPO from Rohm Gmbh, Darmstadt, Germany. Gelatin and Chitosan were purchased from Sigma, St. Louis, MO. All other chemicals and reagents used were AR grade, purchased from BDH Chemical, Poole, UK. All the materials were used as received.

2.2. Preparation of bioadhesive tablets

CP 974P and Methocel K4M tablets of 13 mm diameter were prepared by compressing 250 mg of the polymeric materials using IR hydraulic Press (Model P16, Beckman, UK) at a pressure of 4 tonnes for 30 s. In the bioadhesive evaluation of the other polymers, namely Methocel K15M and K100M, CP 934P, 971P and Polycarbophil, SCMC 400, Cekol 700, Cekol 10000, Xanthan gum, PVP K-30, Alginic acid, Eudragit RSPO and RLPO, Gelatin and Chitosan, tablets of each polymer were similarly prepared.

2.3. Influence of contact force, contact time and speed of probe withdrawal on the bioadhesion measurements

A TA.XT_2 texture analyzer (Stable Micro Systems, Haslemere, Surrey, UK), equipped with a 5 kg load cell was employed to determine the bioadhesion using inverted surface of chicken pouch (removed of its contents and surface fats) as the model tissue. The chicken pouch was stored frozen in a simulated saliva solution (2.38 g Na_2HPO_4, 0.19 g KH_2PO_4 and 8.00 g NaCl in 1000 ml of distilled water at pH 6.75) and thawed to room temperature before used. The chicken pouch was mounted onto a cylindrical perspex support of 2 cm diameter and 4 cm length and secured with a string. A foam tape was placed underneath the chicken pouch on the perspex support at the cross-sectional end to provide cushioning effect. The chicken pouch was further secured by placing an aluminium cap over this perspex support. A circular hole of 17 mm diameter was made on the top of the cap to expose the chicken pouch for contact with the tablet during measurements. The whole perspex support was

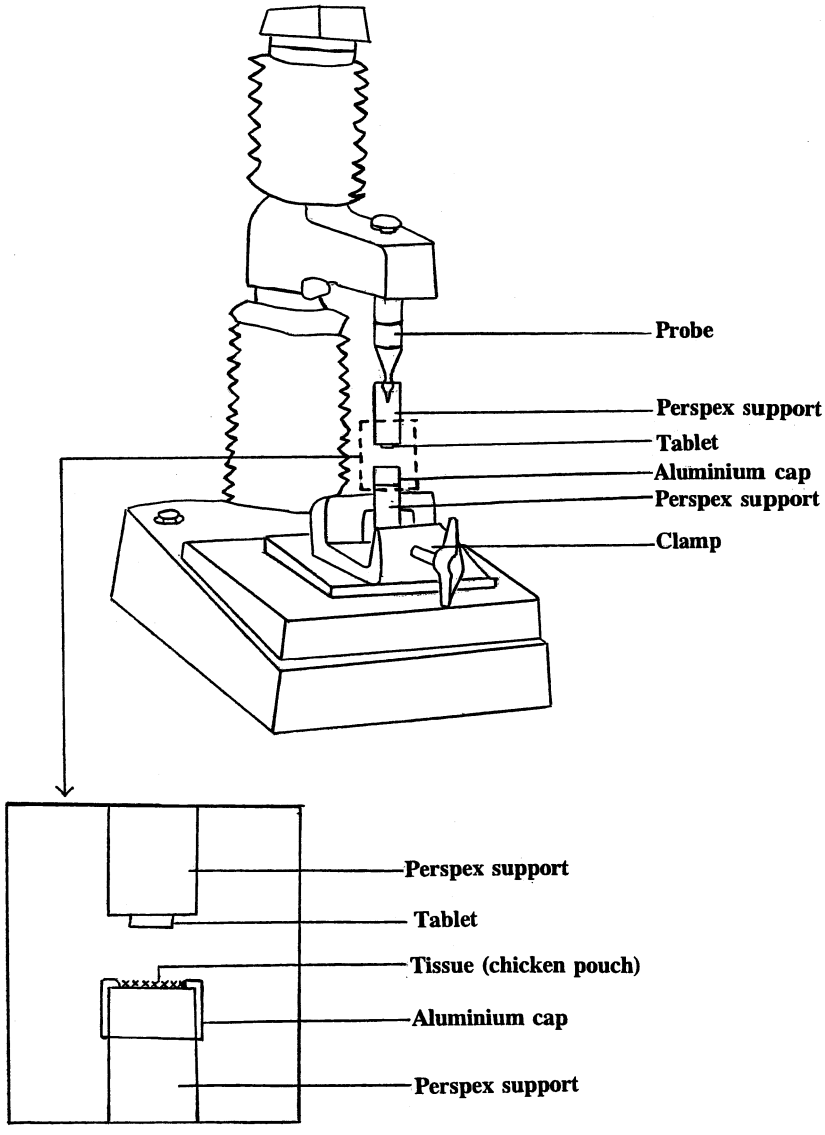

Fig. 1. Bioadhesive testing system utilizing the texture analyzer equipment.

then positioned at the bottom of the measuring system and held in place by a clamp. Tablet was affixed to another perspex support of similar dimension using a double sided tape and the support was then screwed onto the upper probe of the instrument. These two perspex supports were aligned to ensure that the tablet would come into direct contact with the exposed surface of the chicken pouch when the upper tablet support was lowered. The whole assembly is as shown in Fig. 1. All measurements were conducted at a room temperature of 21°C and relative humidity of 50–60%.

During measurement, 200 μl of simulated saliva solution was evenly spread on the surface of the tissues. The upper perspex support was lowered at a speed of 0.5 mm/s until contact was made with the tissue at a predetermined force for a certain duration of contact time. At the end of the contact time, it was then with-

drawn at a speed of 0.5 mm/s to a distance of 20 mm. Four contact forces were chosen to investigate the work of adhesion and peak detachment force at this speed of withdrawal using CP 974P and Methocel K4M tablets. For the former tablets, contact forces used were 0.05, 0.1, 0.5 and 1.0 N, whereas for the latter, the contact forces employed were 0.1, 0.5, 1.0 and 2.0 N. In the study using CP 974P tablets, four contact times, namely 10, 30, 60, and 180 s were used for each contact force employed. As for the Methocel K4M tablets, six contact times of 10, 30, 60, 180, 300, and 600 s were used at each contact force. The effect of the speed of withdrawal of the probe was further studied using a contact force of 0.5 N and a contact time of 180 s. These values were chosen based on the results obtained from the earlier experiments. The probe speeds studied were 0.1, 0.3, 0.5 and 1.0 mm/s. An acquisition rate of 25 points/s was chosen for all the measurements. Also, all the above studies were conducted in ten replicates.

2.4. Bioadhesive evaluation of some polymers

The evaluation of bioadhesion performance of the various polymers was conducted using a contact force of 0.5 N, contact time of 180 s and a probe speed of 1 mm/s. These values were chosen based on the results obtained from the above studies. For each polymer, the measurements were conducted in ten replicates.

2.5. Data analysis

Two parameters, namely the work of adhesion and peak detachment force were used to study the buccal adhesiveness of the polymers. The work of adhesion was determined from the area under force–distance curve while the peak detachment force was the maximum force required to detach the tablet from tissue. An analysis of variance (ANOVA) procedure appropriate for a completely randomized 2 factorial design (Kirk, 1968) was used to analyze the results obtained from the effect of contact force and contact time. On the other hand, a one way ANOVA was performed to evaluate the effect of probe speed as well as in the evaluation of bioadhesive strength of the different polymers. A statistically significant difference was considered when $p < 0.05$. Pair-wise posteriori analysis was carried out using Tukey's test (Kirk, 1968) when a statistically significant difference was obtained.

3. Results and discussion

3.1. Selection of model mucosa

Several types of mucosa have been used as model biological tissues for the evaluation of bioadhesion which included mouse peritoneum (Ishida et al., 1981), rat intestine (Smart, 1991), rabbit stomach (Ch'ng et al., 1985), bovine sublingual mucosa (Ponchel et al., 1987; Lejoyeux et al., 1989), porcine buccal mucosa (Chen and Hwang, 1992), and porcine gastric mucosa (Tobyn et al., 1995). However, it is rather difficult to obtain mucosa with uniform surfaces and consistencies that will yield for reproducible results. Smart (1991) found a visibly non uniform surface with pig oral mucosa. Moreover, Tobyn et al. (1995) found that different parts of the pig stomach gave different results. Although a relatively flat uniform surface may be obtained with intestinal tissue, different parts of the intestine may have different surface characteristics. Although the rabbit or dog buccal mucosa were reported to be rather similar to human buccal mucosa (Harris and Robinson, 1992), their use may involve sacrificing a lot of animals since in our study each mucosa can only be used once for each measurement. In the present study, chicken pouch was used as the model mucosa. It is easily available and has uniform surface, thus giving reproducible results with relatively small coefficient of variation (CV) values.

3.2. Effect of contact time and contact force on bioadhesion

Figs. 2 and 3 show the effect of contact time on the work of adhesion and peak detachment force respectively, under different contact forces for CP 974P tablets. It can be inferred from the two figures that, at all four contact forces employed,

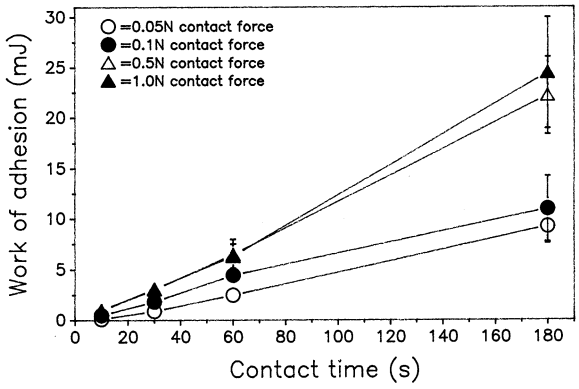

Fig. 2. Influence of contact time on the work of adhesion of Carbopol 974P tablets under different contact forces; error bar = ± S.D. ($n = 10$).

both the work of adhesion and peak detachment force were correspondingly increased with an increase in the contact time. Moreover, all the increases were statistically significant except for the work of adhesion when the contact time was increased from 10 to 30 s. This is in good agreement with the results obtained by Tobyn et al. (1995). In comparison, the bioadhesion appeared to be less influenced by the change in contact force. Increasing the contact force from 0.05 to 0.1 N, or 0.5 to 1.0 N, did not cause any statistically significant increase in the work of adhesion at all contact times studied. A statistically significant increase was observed only with a larger

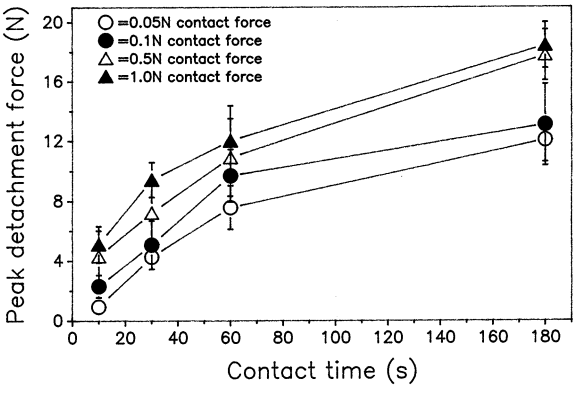

Fig. 3. Influence of contact time on the peak detachment force of Carbopol 974P tablets under different contact forces; error bar = ± S.D. ($n = 10$).

percentage increase in the contact force from 0.05 to 0.5 N and greater, or from 0.1 to 0.5 N and greater, but only when the respective contact times used were 60 s or more and 180 s or more. Almost similar observations were obtained when the bioadhesion was quantified using the peak detachment force. No statistically significant increase in the peak detachment force was seen when the contact force was increased from 0.05 to 0.1 N (except at a contact time of 60 s) and from 0.5 to 1.0 N (except at a contact time of 30 s).

The above findings indicated that the contact time is more critical in affecting the bioadhesion process than the contact force used. The contact time may affect the degree of hydration and swelling which in turn will influence the mucoadhesion as suggested by Ponchel et al. (1987). Our results showed an almost linear relationship between the work of adhesion and contact time for all the contact forces employed, as indicated by the r^2 values which ranged from 0.992 to 0.999. This is consistent with those obtained by Tobyn et al. (1995). Although Tobyn et al. (1995) reported that increasing the applied force (apart from 0.05 to 0.1 N) would cause a significant increase in the work of adhesion, they conducted the experiments using only one contact time of 10 min. On the other hand, when studying the effect of contact time on the mucoadhesion, they used only one contact force. However, in our present study, we investigated the effects of different contact times on the bioadhesion using different contact forces. It was found that under different contact forces, certain contact times were required to show significant differences on the bioadhesiveness. In addition, the bioadhesiveness was evaluated using two parameters, work of adhesion and peak detachment force, whereas only the former was used by Tobyn et al. (1995) for evaluation.

From an interfacial point of view, certain contact force is required to develop a satisfactory intimate molecular contact between the bioadhesive system and tissue, so that interaction could be achieved to allow strong adhesion. In the present study, it was interesting to observe that at a contact force above 0.5 N, no significant increase in the work of adhesion was seen, suggesting that there was a 'ceiling' contact force for maximum

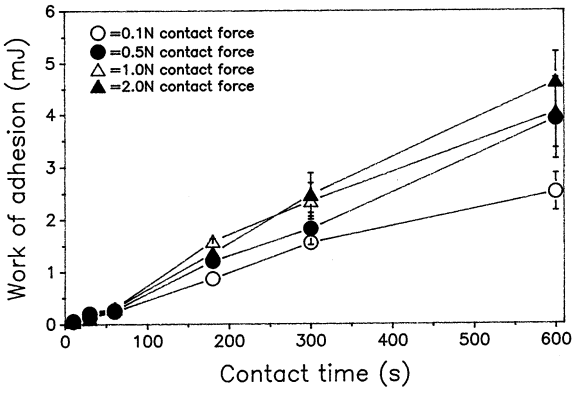

Fig. 4. Influence of contact time on the work of adhesion of Methocel K4M tablets under different contact forces; error bar = ± S.D. ($n = 10$).

intimate contact, above which there was no further contribution to the adhesion process. Hence, too high a contact force may not be advantageous, and may damage the mucosa without achieving better contact. On the other hand, contact time is very critical in affecting the bioadhesion results. The process of mucoadhesion has been proposed to begin with the establishment of an intimate contact between the polymer and the mucosal surface followed by penetration of the polymer into the mucosal surface to form secondary chemical bonds (Duchene et al., 1988). As such, contact time is important to permit sufficient hydration, swelling, interpenetration and formation of non-covalent interactions for bioadhesion.

Figs. 4 and 5 show the influence of increasing contact time at different contact forces on the work of adhesion and peak detachment force for Methocel K4M tablets. A statistically significant increase in the work of adhesion as well as the peak detachment force was observed as the contact time was increased (except from 10 to 30 s and from 30 to 60 s) for all the contact forces employed. On the other hand, the effect of contact force on the work of adhesion and peak detachment force was not that apparent, as no statistically significant difference was observed when the contact time employed was below 180 s. A statistically significant increase in the work of adhesion was seen only after being subjected to 600 s of contact time when contact forces were increased from 0.1 to 0.5 N and from 1.0 to 2.0 N. There was no statistically significant difference in the peak detachment force between contact forces of 0.5 and 2.0 N at all contact times employed. Hence, the results obtained are in accord with those using CP 974P tablets, in which the contact time was shown to be a critical factor in affecting the bioadhesion.

3.3. Effect of speed of probe withdrawal

A contact force of 0.5 N and a contact time of 180 s were employed to study the effect of probe speed on the work of adhesion and peak detachment force. This setting was chosen since it was found optimum for both CP 974P and Methocel K4M tablets.

Figs. 6 and 7 show the influence of probe speed on the work of adhesion and peak detachment force for CP 974P tablets. At each increment in the probe speed (except from 0.1 to 0.3 mm/s), there was a statistically significant increase in the work of adhesion. A statistically significant increase in the peak detachment force was also seen as the probe speed was increased (except from 0.1 to 0.3 mm/s, and from 0.5 to 1.0 mm/s). Thus, it appeared that the probe speed can also influence the values of work of adhesion and peak detachment force.

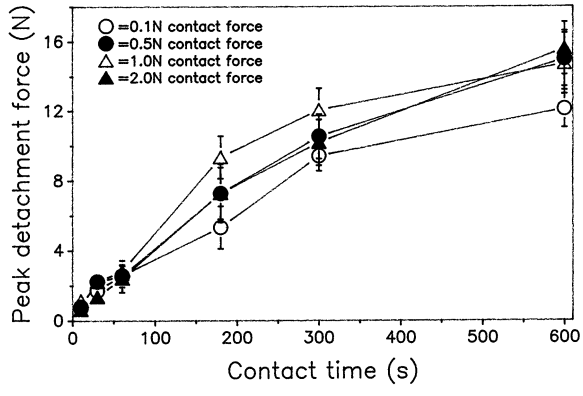

Fig. 5. Influence of contact time on the peak detachment force of Methocel K4M tablets under different contact forces; error bar = ± S.D. ($n = 10$).

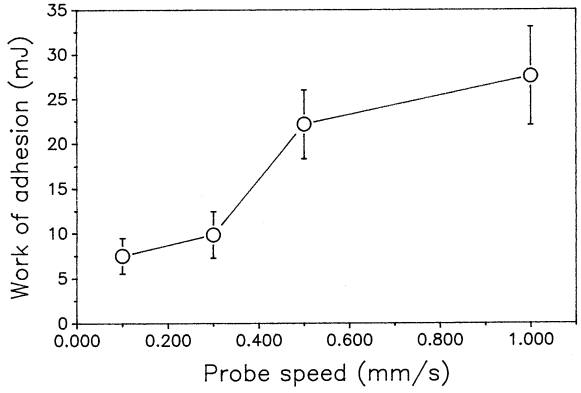

Fig. 6. Influence of probe withdrawal speed on the work of adhesion of Carbopol 974P tablets; error bar = ± S.D. (n = 10).

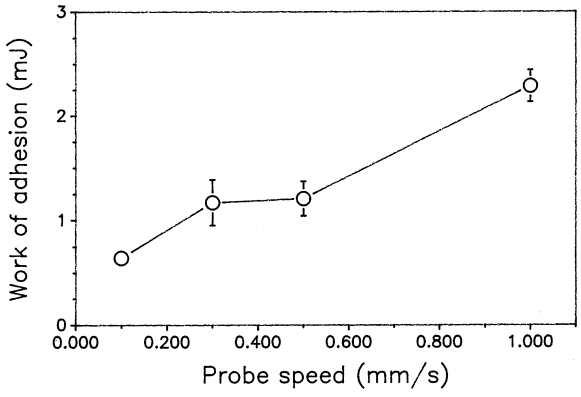

Fig. 8. Influence of probe withdrawal speed on the work of adhesion of Methocel K4M tablets; error bar = ± S.D. (n = 10).

Figs. 8 and 9 show the effect of probe speed on the work of adhesion and peak detachment force measured using Methocel K4M tablets. Again, increasing the probe speed was found to cause a statistically significant increase in both parameters measured, except for the increment from 0.3 to 0.5 mm/s in both cases.

A log-linear relationship between the work of adhesion and crosshead speed was observed by Tobyn et al. (1995) but not in our study. This may be due to the different experimental conditions employed. Although Tobyn et al. (1995) have reported that high probe speeds tend to give rise to large variations in the measurements, this was not observed in our study. Instead, it was observed in our study that low probe speeds such as 0.1 and 0.3 mm/s produced larger CVs as compared to higher probe speeds such as 0.5 and 1.0 mm/s. Furthermore, higher probe speeds were shown to produce larger values for both the work of adhesion and peak detachment force, thus giving higher sensitivities in measuring the bioadhesion. As such, a high probe speed of 1.0 mm/s was employed for the subsequent bioadhesion studies of some polymers.

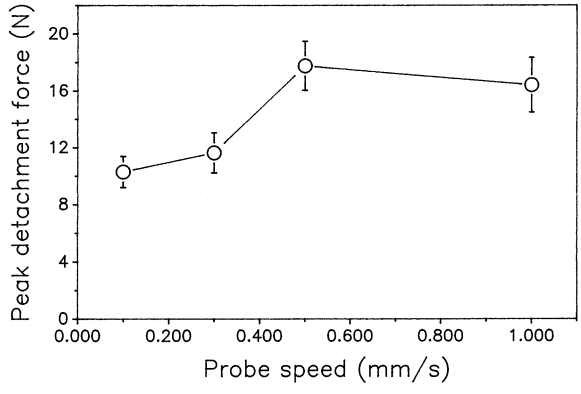

Fig. 7. Influence of probe withdrawal speed on the peak detachment force of Carbopol 974P tablets; error bar = ± S.D. (n = 10).

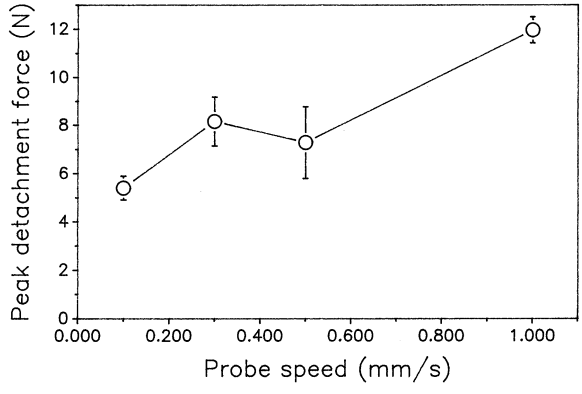

Fig. 9. Influence of probe withdrawal speed on the peak detachment force of Methocel K4M tablets; error bar = ± S.D. (n = 10).

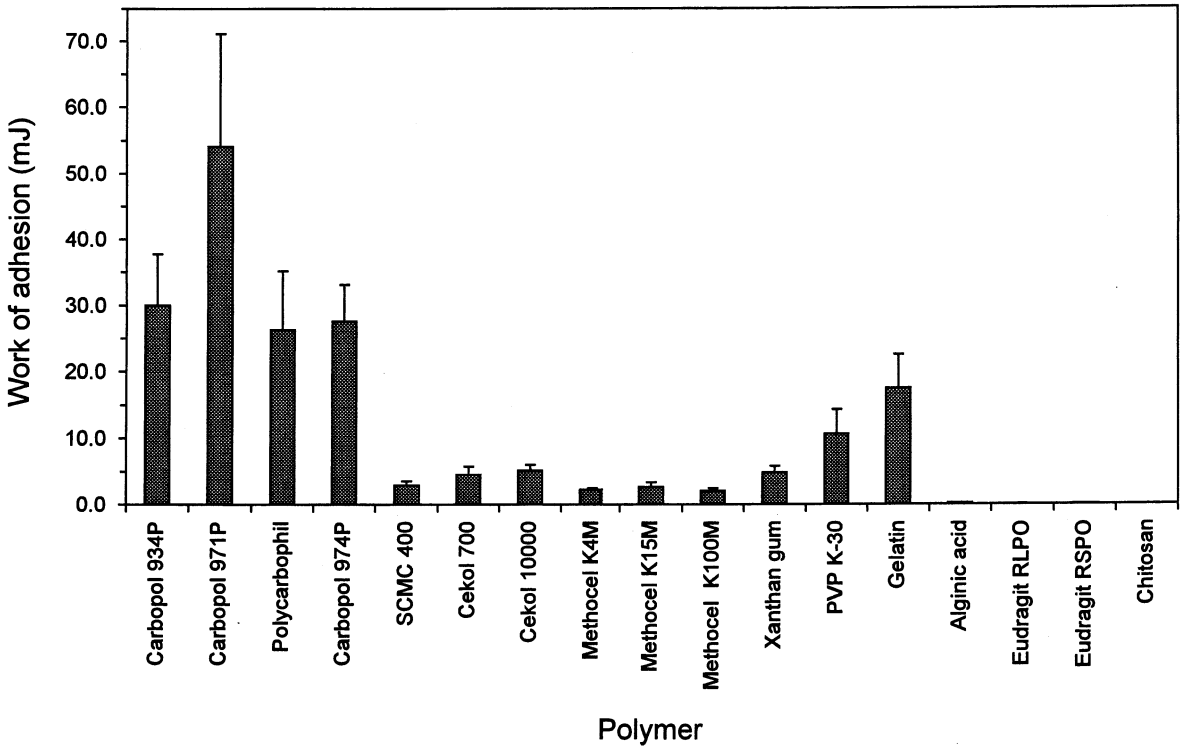

Fig. 10. Evaluation of work of adhesion of various polymers; error bar = ± S.D. ($n = 10$).

3.4. Evaluation of bioadhesion of some polymers

A contact force of 0.5 N, contact time of 180 s and probe speed of 1.0 mm/s was used in this part of the study. The results obtained from the measurements of the various polymers are shown in Figs. 10 and 11. It can be inferred from the two figures that the polymers varied considerably when measured using both the work of adhesion and peak detachment force. Some consistencies can also be observed between the two sets of values in terms of the ranking of the polymers. The poly(acrylic acid) (Carbopol 934P, 971P, 974P, and Polycarbophil) were found to have the highest values, followed by gelatin, PVP K-30, Xanthan gum, sodium carboxymethyl cellulose (SCMC 400, Cekol 700, and Cekol 10000) and hydroxypropylmethyl cellulose (Methocel K4M, K15M, and K100M). Tobyn et al. (1996) reported that the molecular weight of a polyacrylic acid can crucially influenced the observed work of detachment between the polymer and pig gastric tissue. However, they found no significant differences in the mucoadhesion for Carbopol 934P, 974P and Polycarbophil, which correlated well with our results. The rank order of mucoadhesion using the test system employed by Tobyn et al. (1996) indicated that the low, medium and high viscosity grades of SCMC were slightly more mucoadhesive than Xanthan gum, followed by the Carbopols. However, the differences in the mucoadhesion values for these polymers were not significant. This is in contrast with our results which showed that Carbopols are broadly more bioadhesive compared to Xanthan gum and SCMC. Carbopols contain large numbers of carboxylic acid groups which provide the ability to form hydrogen bonds. Moreover, they swelled readily in water thus providing a large adhesive surface for maximum contact (Pharmaceutical Bulletin BF Goodrich, 1995). The SCMCs were slightly more bioadhesive compared to HPMCs,

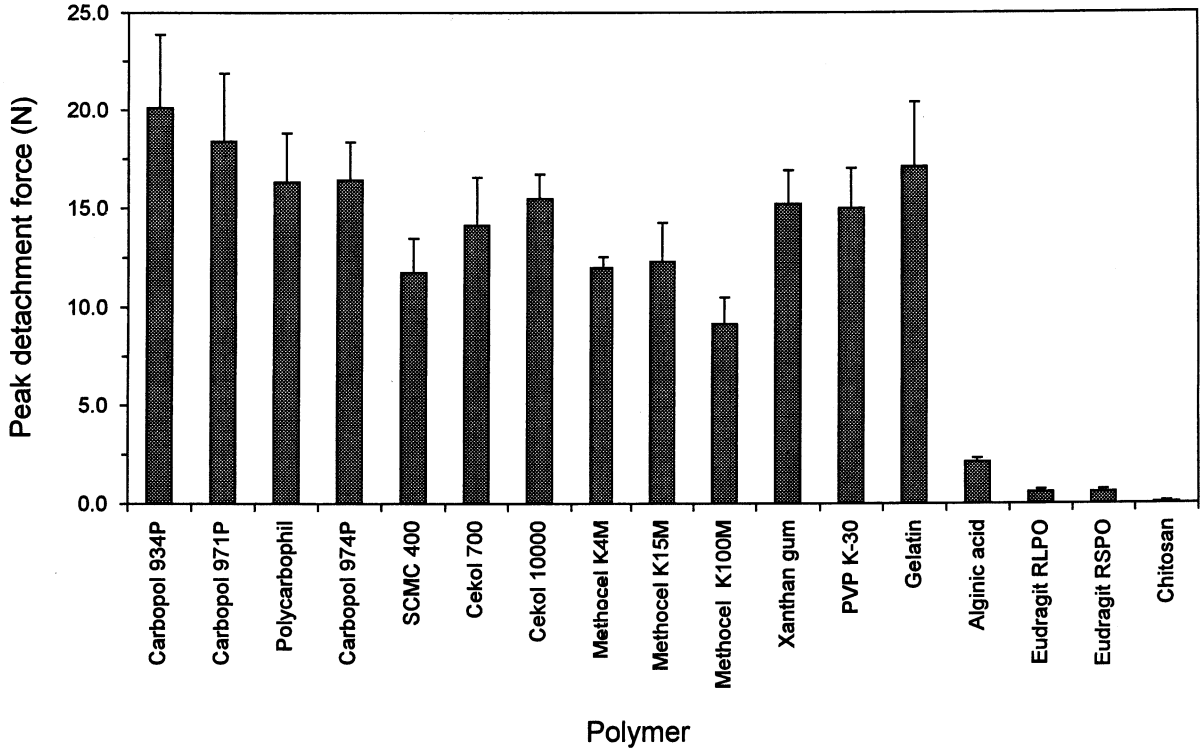

Fig. 11. Evaluation of peak detachment force of various polymers; error bar = ± S.D. ($n = 10$).

in accord with the findings of other workers (Smart et al., 1984; Ch'ng et al., 1985; Rao and Buri, 1989; Sam et al., 1992). On the other hand, Alginic acid, Eudragit RLPO and RSPO, and Chitosan appeared to have low bioadhesive values. The less mucoadhesive properties of Eudragit and Chitosan may be explained by the poor wetting properties of the polymers. In general, the results obtained were in good agreement of those reported by other workers (Ch'ng et al., 1985; Rao and Buri, 1989).

3.5. Reproducibility

The CV values obtained from the measurements of the peak detachment force and the work of adhesion are shown in Tables 1–3. In general, the CV values were relatively small. For most measurements, the values were less than 25%. Higher CV values were observed when the contact time employed was less than 30 s. Thus, a longer contact time appeared to be more suitable for conducting the measurements. Another consideration is the speed of probe withdrawal. Low

Table 1
The CV values (%) for the work of adhesion and peak detachment force of CP 974P tablets under different contact forces and contact times at a probe withdrawal speed of 0.5 mm/s ($n = 10$)

Contact force (N)	Contact time (s)			
	10	30	60	180
Work of adhesion				
0.05	19.64	20.93	14.82	17.80
0.1	22.46	26.30	19.03	29.51
0.5	22.30	18.47	23.07	17.30
1.0	17.71	26.02	18.56	22.62
Peak detachment force				
0.05	24.09	15.01	19.25	12.02
0.1	32.27	32.03	18.02	20.79
0.5	40.07	27.65	23.64	9.66
1.0	23.86	12.29	19.47	8.36

Table 2
The CV values (%) for the work of adhesion and peak detachment force of Methocel K4M tablets under different contact forces and contact times at a probe withdrawal speed of 0.5 mm/s ($n = 10$)

Contact force (N)	Contact time (s)					
	10	30	60	180	300	600
Work of adhesion						
0.1	20.75	23.53	19.17	18.37	11.68	14.20
0.5	26.23	20.98	24.33	13.66	16.81	19.51
1.0	13.58	19.46	19.00	12.03	14.74	16.89
2.0	20.69	20.56	20.13	20.04	16.72	12.52
Peak detachment force						
0.1	32.54	23.89	18.56	23.01	9.07	8.90
0.5	28.57	23.76	24.28	20.34	12.02	10.60
1.0	25.04	23.70	21.77	12.94	10.34	11.88
2.0	35.50	26.06	32.91	22.93	12.78	9.64

Table 3
The CV values (%) for the work of adhesion and peak detachment force of CP 974P and Methocel K4M tablets under different probe speeds using a contact force of 0.5 N and a contact time of 180 s ($n = 10$)

Probe speed (mm/s)PRIVATE	Carbopol 974P		Methocel K4M	
	Work of adhesion	Peak detachment force	Work of adhesion	Peak detachment force
0.1	26.25	10.60	12.29	9.11
0.3	26.34	12.08	18.63	12.45
0.5	17.30	9.66	13.66	20.33
1.0	20.02	11.81	6.69	4.48

probe speeds tended to produce bigger variations in the measurements.

4. Conclusion

The bioadhesive measurements of polymers could be influenced by instrumental variables such as contact force, contact time and speed of probe removal from the tissue. Therefore, a test system should be adequately assessed to optimize the conditions for conducting the measurements. In the present study, it was found that longer contact time and higher probe speed, not only gave better reproducibility of results, but also produced higher measurement values, thus giving better sensitivity. On the other hand, a certain level of contact force was also required for affecting the bioadhesion, but beyond which did not contribute further to the process. Also, both the work of adhesion and peak detachment force appeared suitable for evaluating the bioadhesiveness of the polymers.

References

Chen, W.G., Hwang, G., 1992. Adhesive and in vitro release characteristics of propanolol bioadhesive disc system. Int. J. Pharm. 82, 61–66.

Ch'ng, H.S., Park, H., Kelly, P., Robinson, J.R., 1985. Bioadhesive polymers as platforms for oral controlled drug delivery. II. Synthesis and evaluation of some swelling, water-insoluble bioadhesive polymers. J. Pharm. Sci. 74, 399–405.

Duchene, D., Touchard, F., Peppas, N.A., 1988. Pharmaceutical and medicinal aspects of bioadhesive systems for drug administration. Drug Dev. Ind. Pharm. 14, 283–318.

Harris, D., Robinson, J.R., 1992. Drug delivery via the mucous membranes of the oral cavity. J. Pharm. Sc. 81 (1), 1–10.

Ishida, M., Machida, Y., Nambu, N., Nagai, T., 1981. New mucosal dosage form of insulin. Chem. Pharm. Bull. 29, 810–816.

Kirk, R.E., 1968. Experimental design: procedures for the behavioral sciences. Wadsworth Publishing Co., USA, pp. 171–244.

Lehr, C-M., Bouwstra, J.A., Schacht, E.H., Junginger, H.E., 1992. In vitro evaluation of mucoadhesive properties of chitosan and some other natural polymers. Int. J. Pharm. 78, 43–48.

Lejoyeux, F., Ponchel, G., Wouessidjewe, D., Peppas, N.A., Duchene, D., 1989. Bioadhesive tablets influence of the testing medium composition on bioadhesion. Drug Dev. Ind. Pharm. 15, 2037–2048.

Mikos, A.G., Peppas, N.A., 1986. Comparison of experimental technique for measurement of the bioadhesive forces of polymeric materials with soft tissues. Proc. Int. Symp. Controlled Release Bioact. Mater. 13, 97.

Nagai, T., Machida, Y., 1985. Mucosal adhesive dosage forms. Pharm. Int., August, 196–200.

Park, K., 1989. A new approach to study mucoadhesion: colloidal gold staining. Int. J. Pharm. 53, 209–217.

Park, K., Robinson, J.R., 1984. Bioadhesive polymers as platforms for oral-controlled drug delivery: method to study bioadhesion. Int. J. Pharm. 19, 107–127.

Park, H., Robinson, J.R., 1987. Mechanisms of mucoadhesion of poly(carboxylic acid) hydrogels. Pharm. Res. 4, 457–464.

Pharmaceutical Bulletin BF Goodrich, 1995. Carbopol, Noveon, Pemulen—the proven polymers in pharmaceuticals.

Ponchel, G., Touchard, F., Duchene, D., Peppas, N.A., 1987. Bioadhesive analysis of controlled-release systems. I. Fracture and interpenetration analysis in poly(acrylic acid) containing systems. J. Control. Release 5, 129–141.

Rao, K.V.R., Buri, P., 1989. A novel in situ method to test polymers and coated microparticles for bioadhesion. Int. J. Pharm. 52, 265–270.

Sam, A.P., Van den Heuij, J.T.M, Tukker, J.J., 1992. Mucoadhesion of both film-forming and non-film-forming polymeric materials as evaluated with Wilhemy plate method. Int. J. Pharm. 79, 97–105.

Smart, J.D., 1991. An in vitro assessment of some mucosa-adhesive dosage forms. Int. J. Pharm. 73, 69–74.

Smart, J.D., Kellaway, I.W., 1982. In vitro techniques for measuring mucoadhesion. J. Pharm. Pharmacol. 34 (Suppl.), 70P.

Smart, J.D., Kellaway, I.W., Worthington, H.E.C., 1984. An in-vitro investigation of mucosa-adhesive materials for use in controlled drug delivery. J. Pharm. Pharmacol. 36, 295–299.

Tobyn, M.J., Johnson, J.R., Dettmar, P.W., 1995. Factors affecting in vitro gastric mucosa adhesion. I. Test conditions and instrumental parameters. Eur. J. Pharm. Biopharm. 41 (4), 235–241.

Tobyn, M.J., Johnson, J.R., Dettmar, P.W., 1996. Factors affecting in vitro gastric mucosadhesion. II. Physical properties of polymers. Eur. J. Pharm. Biopharm. 42 (1), 56–61.