ELSEVIER

International Journal of Pharmaceutics 199 (2000) 77–83

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Application of Carbopol® to controlled release preparations I. Carbopol® as a novel coating material

Mitsuo Muramatsu [a,*], Ken Kanada [a], Ayumu Nishida [a], Kiyohisa Ouchi [a], Noriyasu Saito [a], Minoru Yoshida [b], Akihiro Shimoaka [b], Tetsuya Ozeki [c], Hiroshi Yuasa [c], Yoshio Kanaya [c]

[a] *Pharmaceutical Laboratories, Kissei Pharmaceutical Company, Limited, 4365-1 Kashiwabara, Hotaka, Minamiazumi, Nagano 399-8304, Japan*

[b] *CBC Company Limited, 2-15-13 Tsukishima, Chuo-ku, Tokyo 104-0052, Japan*

[c] *Laboratory of Medical and Pharmaceutical Technology, School of Pharmacy, Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi Hachioji, Tokyo 192-0392, Japan*

Received 19 October 1999; received in revised form 2 February 2000; accepted 10 February 2000

Abstract

We investigated the application of Carbopol® (CP) as a novel coating material prepared with various grades of CP having different degrees of cross-linking and molecular weights. Viscosity and spray mist size of CP aqueous solutions at various concentrations of CP were measured. Core tablets containing theophylline (TP), as a model drug, were coated with CP at various coating ratios. The TP release profile from the CP-coated tablets was studied by the JP13 paddle method. CP tablets were prepared by compressing CP powder, and the swelling behavior of the CP tablets in JP 1st fluid, purified water, and JP 2nd fluid was observed. The spray mist size of all CP aqueous solutions was small at a concentration of 1% and below, and drastically increased over a concentration of 1%. This result suggests that the appropriate concentration of the CP solution for coating is 1% or below. Sustained release of TP from the CP-coated tablets at a coating ratio of only 3% was observed in the JP 1st fluid and purified water, although fast release was observed in the JP 2nd fluid. The fast release in the latter fluid may be due to the fact that CP is an acid material. These results suggest that it is feasible to control the drug release by use of an extremely small amount of CP coating and that CP is useful as a novel coating material.

Keywords: Carbopol®; Coating material; Controlled release; Cross-linking; Spray mist; Swelling

1. Introduction

Carbopol® (CP) is a polymer of acrylic acid and forms hydrogel in water or alkaline solution due to hydration of the carboxyl groups in its structure. Owing to this property CP has been used as

* Corresponding author. Tel.: +81-263-828820; fax: +81-263-828696.

0378-5173/00/$ - see front matter
PII: S0378-5173(00)00374-4

a gel matrix in suspensions and creams for external use or as a bioadhesive matrix for buccal, rectal, and nasal formulations (Morimoto et al., 1984, 1985, 1987; Nakajima et al., 1987; Wong et al., 1999). For the controlled release of drugs, CP has been studied as a matrix material directly compressed together with hydroxypropylcelluose (Machida et al., 1980; Ishida et al., 1981; Satoh et al., 1989; Mortazavi and Smart, 1994) or hydroxypropylmethylcellulose (Garcia-Gonzales et al., 1992; Perez-Marcos et al., 1996) in tablets and for a solid dispersion (Dangprasirt and Ritthidej, 1995; Ozeki et al., 1998a,b, 1999). However, there are few reports on the application of CP as a coating material (Hosoya et al., 1994).

In the present study we examined CP as a novel coating material and studied theophylline (TP) release from tablets coated with various grades of CP.

2. Material and methods

2.1. Material

TP (Shiratori Chiba), a bronchodilater, was used as the model medicine. Lactose (Lactochem®, Borculo Domo Ingredients, Zwolle, Netherland) used as a filler was supplied by CBC, Tokyo. Povidone (Kollidone® K-30, BASF Japan, Tokyo) was used as a binder, and magnesium stearate (Taihei Kagaku Sangyo, Osaka), as a lubricant. Various grades of CP (Carbopol® 907, 971P, 934P, 974P, 980, BF Goodrich, Brecksville, OH, USA) were supplied by CBC, Tokyo, and used as coating materials. The physical properties of CP are listed in Table 1. The particle diameter of CP was measured with a laser light-scattering particle sizer (LMS-24, Seishin Enterprise, Tokyo). The densities of CP were calculated from the volume measured with an air comparison pycnometer (model 930, Toshiba-Beckman, Tokyo).

2.2. Measurement of viscosity and spray mist size of CP solutions

The viscosity of CP solutions of various grades (CP concentrations: 0.1, 0.25, 0.5, 0.75, 1.0, 1.5 and 2.0%) was measured with a rotational viscometer (VISCONIC EMD, TOKIMEC, Tokyo). CP solutions were sprayed with the spray gun of the coating machine (HCT-MINI, Freund Industrial, Tokyo), and the spray mist size was measured with a laser light-scattering particle sizer (LMS-24, Seishin Enterprise, Tokyo).

2.3. Preparation of core tablets and CP coating

Formulation of the core tablets and the operating conditions for the CP coating are listed in Table 2. TP, lactose, and povidone (25/69/5) were granulated by a high-shear mixer (vertical-granulater®, FM-VG-25, Powrex, Osaka) after addition of water. The granules obtained were dried at an inlet temperature of 60°C with a fluidized bed dryer (FLO-5M, Freund Industrial, Tokyo) and then passed through the screen of a mill (speed

Table 1
Molecular weight, degree of cross-linking, particle diameter, and true density of CP

CP (grade)	Molecular weight[a]	Degree of cross-linking	Particle diameter (μm)		True density (g/cm^3)
			Mean diameter[b]	S.D.[b]	
907	450000	None	4.97	2.42	1.49
971P	1250000	Medium	3.37	1.62	1.44
934P	3000000	High	3.05	1.80	1.47
974P	3000000	Very high	4.21	1.77	1.43
980	4000000	Very high	4.02	1.93	1.51

[a] Nominal average molecular weight.
[b] Geometric.

Table 2
Formulation and operating conditions for CP coating

Core tablet		mg/tablet
Granule	TP	25
	Lactose	69
	Povidone	5
Lubricant	Mg stearate	1
Coated tablet		
	Core tablet	100
Coating material	CP	1–15
Operating conditions for coating		
Coating machine		HCT-MINI
Batch size (g)		300
Spray solution concentration (%)		1
Inlet air temperature (°C)		75–85
Outlet air temperature (°C)		42–46
Spray pressure (kgf/cm^2)		1
Flow rate (g/min)		1–1.5
Pan speed (rpm)		30–35

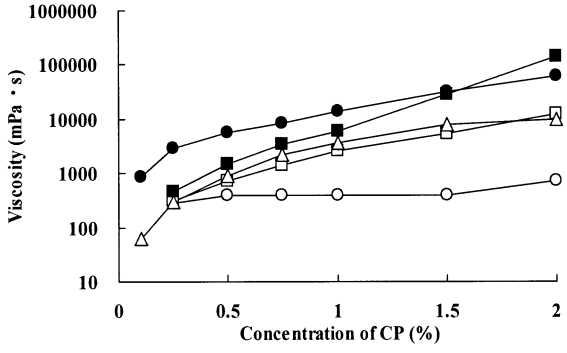

Fig. 1. Relationship between viscosity of CP aqueous solution and CP concentration. CP grade: ○, 907; ●, 971P; □, 934P; ■, 974P; and △, 980.

mill, ND-30, Okada Seiko, Tokyo). The milled granules were mixed with lubricant in a twin-shell mixer (V-30, Tokuju, Kanagawa) to make a powder mixture for tableting. The powder mixture was compressed into a core tablet with a rotary tableting machine (correct12HUK, Kikusui Seisakusho, Kyoto). The core tablets were coated with CP solutions of various grades by a coating-machine (HCT-MINI, Freund Industrial, Tokyo).

2.4. Dissolution test

The dissolution test of the CP-coated tablet was carried out according to the JP13 paddle method at 100 rpm in 900 ml of JP 1st fluid, purified water, and JP 2nd fluid at 37.0 ± 0.5°C with a flow cell system (dissolution tester: NTR-6100, Toyama Sangyou, Osaka; UV detector: UV-1600, Shimadzu Seisakusyo, Tokyo). The quantity of TP was determined spectrophotometrically by measuring the absorbance at 272 nm.

2.5. Observation of swelling behavior of CP tablets

CP powder (200 mg) of various grades was compressed at 500 kg/cm^2 with an IR tableting machine. The CP tablets were soaked in JP 1st fluid, purified water, and JP 2nd fluid, and the swelling behavior of the CP tablets was observed.

3. Results and discussion

3.1. Evaluation of physical properties of CP solutions

Fig. 1 shows the viscosity of CP aqueous solutions at CP concentrations of 0.1–2.0%. With the non cross-linked CP grades, CP907, an increase in the viscosity dependent on the CP concentration was hardly observed. However, with other cross-linked CPs, the viscosity increased with increasing CP concentration, and the highest viscosity was observed with CP 971P, which had a medium degree of cross-linking. CP is different from the usual linear polymers, and each grade of CP has not only a different molecular weight but also a different degree of cross-linking. In the case of different degrees of cross-linking we considered that the fluid unit of CP changed in solvent. Therefore, we concluded that the change in viscosity of the cross-linked CP solution did not depend only on the molecular weight of the CP; in fact, the viscosity of the CP solution was highest for CP 971P, a grade with a medium degree of cross-linking.

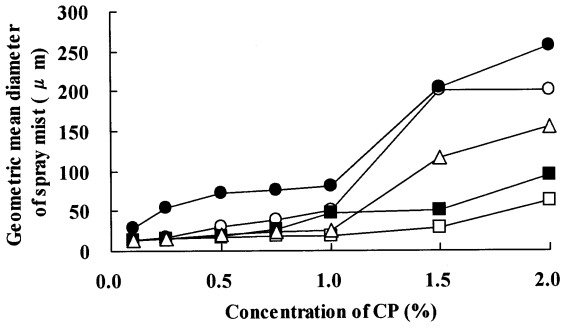

Fig. 2. Relationship between geometric mean diameter of spray mist and CP concentration of CP aqueous solutions. CP grade: ○, 907; ●, 971P; □, 934P; ■, 974P; and △, 980.

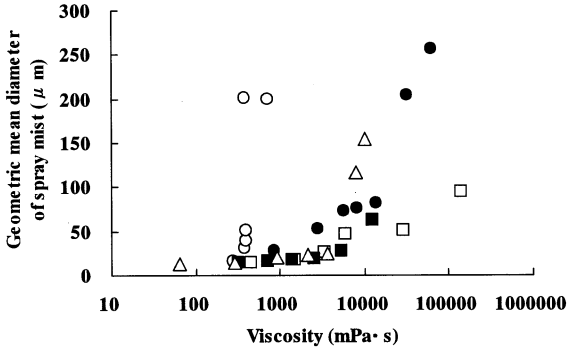

Fig. 3. Relationship between geometric mean diameter of spray mist and viscosity of CP aqueous solution. CP grade: ○, 907; ●, 971P; □, 934P; ■, 974P; and △, 980.

The mist size obtained by the spray gun that was used for the actual coating was measured, and the relationship between the geometric mean diameter of the spray mist and the CP concentration is shown in Fig. 2. In all grades of CP the geometric mean diameter of the spray mist tended to abruptly increase over a concentration of 1%. These results suggest that the appropriate concentration of solution for coating is 1% and below.

Fig. 3 shows the relationship between the geometric mean diameter of the spray mist and the viscosity of the CP aqueous solution. With non cross-linked CP 907 the diameter of the spray mist was drastically increased when the viscosity was over about 400 mPa · s. For the cross-linked CPs, the mist diameter was small until the viscosity reached about 3000–6000 mPa · s and then abruptly increased over this approximate viscosity.

3.2. Profile of TP release from CP-coated tablets and swelling behavior of CP tablets

Fig. 4 shows the profiles of TP release from the core tablet and the CP-coated core tablets with various CP grades at a coating ratio of 3%. CP974P is not shown because it was difficult to coat with more than 1%. The release rate of TP was large from all tablets in JP 2nd fluid and sustained release was not observed. Conversely, in JP 1st fluid the sustained release was observed for CP-coated tablets having only a 3% coating, compared with the rapid release from the core tablet.

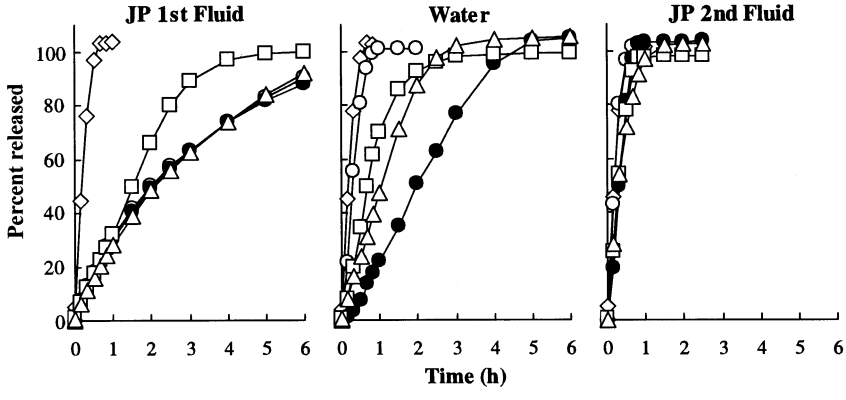

Fig. 4. Profiles of TP release from core tablet and CP-coated core tablets with various CP grades at a coating ratio of 3%. Core tablet, ◇. CP-coated core tablets, CP grades 907, ○; 971P, ●; 934P, □; and 980, △.

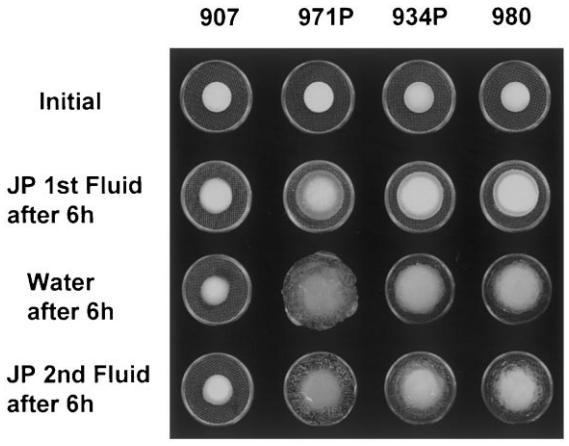

Fig. 5. Photographs of CP tablets before and after soaking in various test fluids.

In purified water the sustained release was also observed except for CP907. The coating to obtain the controlled release generally requires a coating ratio of 5–15% (Ludden et al., 1988; Heinämäki et al., 1988, 1994; Béchard et al., 1995). Therefore, controlled release could be achieved with a smaller amount of coating by using CP as a coating material.

CP tablets were prepared by compressing CP powder of CP907, 971P, 934P, and 980 used in the release test. Fig. 5 shows photographs of the CP tablets before and after soaking in JP 1st fluid, purified water, or JP 2nd fluid for 6 h. In JP 1st fluid the degree of swelling of the CP tablet was small for all grades of CP. In purified water and JP 2nd fluid, the CP tablets except for CP907 were remarkably swollen. The difference in the swelling property of the coating layer of the CP-coated tablets can not be directly explained through these phenomena because the CP tablets were compacted powder. However, we propose the following explanation for the release profiles shown in Fig. 4. The coating layer of CP was held on the tablet in acidic JP 1st fluid because CP is a kind of polycarboxylic acid and its pK_a is about 6.0, causing the suppression of the release rate for any CP grade. In JP 2nd fluid, which has a pH of 6.8, it was easier for the coating layer of CP to swell and erode or fall off than in purified water. Therefore, the fastest release was observed in JP 2nd fluid.

Fig. 6 shows the relationship between the time required to release 75% of the amount of the drug ($T_{75\%}$) and the CP coating ratio (1, 3, and 5%). In JP 1st fluid, in which the swelling of CP is very small, $T_{75\%}$ increase depended on the CP coating ratio (reflecting the thickness of the coat) at all grades of CP. On the other hand, small $T_{75\%}$ was observed in JP 2nd fluid. Particularly, in the case of CP907, $T_{75\%}$ was small at all coating ratios. This may be due to dissolution of the coating layer by erosion, because CP907 is a non cross-linking grade.

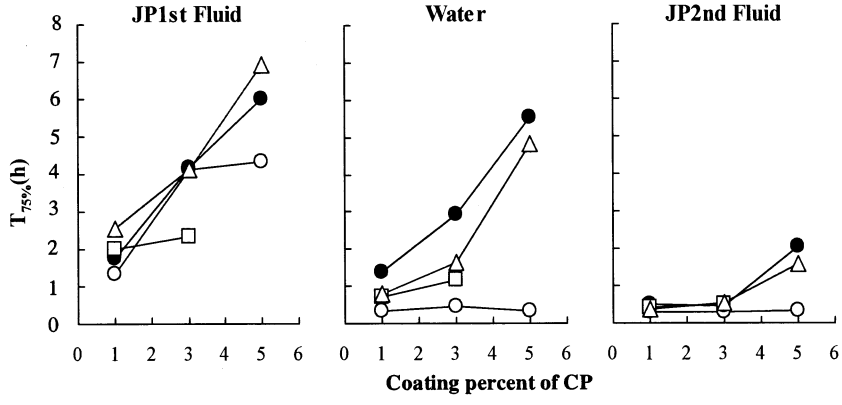

Fig. 6. $T_{75\%}$ for TP release from CP-coated tablets at various coating ratios and grades of CP. CP grade: ○, 907; ●, 971P; □, 934P; and △, 980.

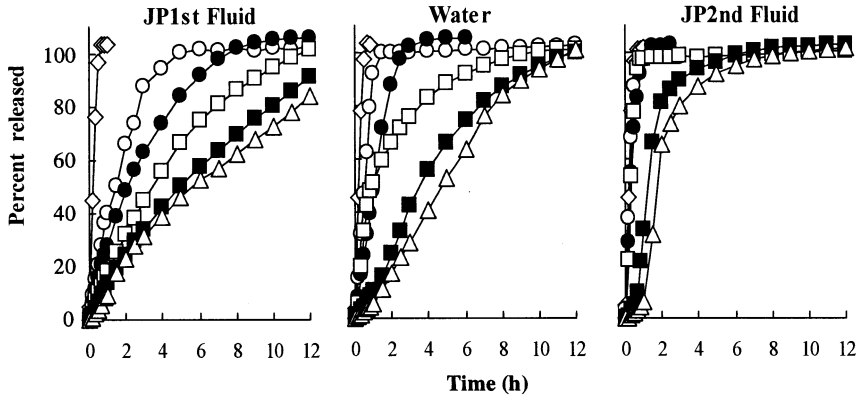

Fig. 7. Profiles of TP release from core tablet and CP-coated tablets at various CP980 coating ratios. Core tablet, ◇. CP-coated tablets having coating ratios of 1%, ○; 3%, ●; 5%, □; 10%, ■; and 15%, △.

Fig. 7 shows the release profiles of TP from the core tablet and the CP-coated tablets having CP980 at various coating ratios from 1 to 15%. In all test fluids the release rate decreased with an increase in CP coating ratio, and the order of decrease in the release rate was JP 1st fluid > purified water > JP 2nd fluid. Furthermore, almost zero-order release was observed in JP 1st fluid.

4. Conclusion

The spray mist size of all CP aqueous solutions was small at a concentration of 1% and below and increased remarkably for concentrations over 1%, suggesting that the appropriate concentration of CP solution for coating is 1% or below in an aqueous solution. Although TP release from the CP-coated tablets in JP 2nd fluid was fast, sustained release was observed in JP 1st fluid and purified water at a coating ratio of only 3%. The dependence of the release behavior on the pH of the test fluid may be attributed to the fact that CP is an acidic material. Furthermore, it is feasible to control the release rate by varying the CP coating ratio. Our results suggest that it is feasible to control drug release with an extremely small amount of CP coating and that CP is useful as a novel coating material.

References

Béchard, S.R., Levy, L., Clas, S.-D., 1995. Thermal, mechanical and functional properties of cellulose acetate phthalate (CAP) coatings obtained from neutralized aqueous solutions. Int. J. Pharm. 114, 206–213.

Dangprasirt, P., Ritthidej, G.C., 1995. Development of diclofenac sodium controlled-release solid dispersions by spray drying using optimization strategy I. Powder formulation. Drug Dev. Ind. Pharm. 21, 2323–2337.

Garcia-Gonzales, N., Blanco-Fuente, H., Anguiano-Igea, S., Delgado-Charro, B., Otero-Espinar, F.J., Blanco-Mendez, J., 1992. In vitro characterization of bio adhesive metoclopramide tablets for buccal application prepared with polyacrylic acid and hydroxypropylmethylcellulose. STP Pharm. Sci. 2, 494–499.

Heinämäki, J., Marvola, M., Happonen, I., Westermarck, E., 1988. Formulations releasing the drug proximal to the pylorus in the dog. Int. J. Pharm. 48, 51–61.

Heinämäki, J.T., Colarte, A.I., Nordstrom, A.J., Yliruusi, J.K., 1994. Comparative evaluation of ammoniated aqueous and organic-solvent-based cellulose ester enteric coating systems: a study on free films. Int. J. Pharm. 109, 9–16.

Hosoya, K., Ukigaya, T., Niwa, H., Ochiai, M., 1994. Design and evaluation of sustained-release granules of sodium valproate. Yakuzaigaku 54, 49–54.

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

Ludden, T.M., Rotenberg, K.S., Ludden, L.K., Shepherd, M.M., Woodworth, J.R., 1988. Relative bioavailability of immediate- and sustained-release hydralazine formulations. J. Pharm. Sci. 77, 1032–1062.

Machida, Y., Masuda, H., Fujiyama, N., Iwata, M., Nagai, T., 1980. Preparation and phase II clinical examination of topical dosage forms for the treatment of *Carcinoma colli* containing bleomycin, carboquone, or 5-fluoruracil with hydroxypropyl cellulose. Chem. Pharm. Bull. 28, 1125–1130.

Morimoto, K., Akatsuchi, H., Aikawa, R., Morishita, M., Morisaka, K., 1984. Enhanced rectal absorption of [Asu^{1,7}]-eel calcitonin in rats using polyacrylic acid aqueous gel base. J. Pharm. Sci. 73, 1366–1368.

Morimoto, K., Morisaka, K., Kamada, A., 1985. Enhancement of nasal absorption of insulin and calcitonin using polyacrylic acid gel. J. Pharm. Pharmacol. 37, 134–136.

Morimoto, K., Iwamoto, T., Morisaka, K., 1987. Possible mechanisms for the enhancement of rectal absorption of hydrophilic drugs and polypeptides by aqueous polyacrylic acid gel. J. Pharmcobio.-Dyn. 10, 85–91.

Mortazavi, A.S., Smart, J.D., 1994. Factors influencing gel-strengthening at the mucoadhesive-mucus interface. J. Pharm. Pharmacol. 46, 86–90.

Nakajima, T., Takashima, Y., Iida, K., Mitsuta, H., Furuya, A., Koishi, M., 1987. Preparation of sustained-release suppositories containing microencapsulated indomethacin and bioavailability of indomethacin in rabbits. Chem. Pharm. Bull. 35, 4249–4254.

Ozeki, T., Yuasa, H., Kanaya, Y., 1998a. Control of medicine release from solid dispersion through poly(ethylene oxide)-carboxyvinylpolymer interaction. Int. J. Pharm. 165, 239–244.

Ozeki, T., Yuasa, H., Kanaya, Y., 1998b. Mechanism of medicine release from solid dispersion composed of poly(ethylene oxide)-carboxyvinylpolymer interpolymer complex and pH effect on medicine release. Int. J. Pharm. 171, 123–132.

Ozeki, T., Yuasa, H., Kanaya, Y., 1999. Control of medicine release from solid dispersion composed of the poly(ethylene oxide)-carboxyvinylpolymer interpolymer complex by varying molecular weight of poly(ethylene oxide). J. Control. Release 58, 87–95.

Perez-Marcos, B., Ford, J.L., Armstrong, D.J., Elliott, P.N.C., Rostron, C., Hogan, J.E., 1996. Influence of pH on the release of propranolol hydrochloride from matrices containing hydroxypropylmethylcellulose K4M and carbopol 974. J. Pharm. Sci. 85, 330–334.

Satoh, K., Takayama, K., Machida, Y., Suzuki, Y., Nagai, T., 1989. Disintegration and dissolution characteristics of compressed tablets consisting of hydroxypropyl cellulose and carboxyvinyl polymer. Chem. Pharm. Bull. 37, 1642–1644.

Wong, C.F., Yuen, K.H., Peh, K.K., 1999. An in-vitro method for buccal adhesion studies: importance of instrument variables. Int. J. Pharm. 180, 47–57.