Available online at www.sciencedirect.com
SCIENCE DIRECT®
IL FARMACO 59 (2004) 155–161
IL FARMACO
www.elsevier.com/locate/farmac

# Development and evaluation of buccoadhesive propranolol hydrochloride tablet formulations: effect of fillers

Jafar Akbari [a], Ali Nokhodchi [b,c,*], Djavad Farid [b], Massoud Adrangui [b], Mohammad Reza Siahi-Shadbad [c], Majid Saeedi [a]

[a] Department of Pharmaceutics, Faculty of Pharmacy, Mazandaran(Sari) Medical Sciences University, Sari, Iran
[b] Department of Pharmacy, King's College London, Franklin-Wilkins Building, 150 Stamford Street, London SE1 9NN, UK
[c] Department of Pharmaceutics, School of Pharmacy, Tabriz Medical Sciences University, Tabriz 51664, Iran

Received 3 January 2003; accepted 23 November 2003

**Abstract**

The buccal mucosa has been investigated for local and systemic delivery of therapeutic peptides and other drugs that are subjected to first-pass metabolism or are unstable within the rest of the gastrointestinal tract. Propranolol hydrochloride (propranolol HCl) is subjected to first-pass effect, therefore formulation of buccal-adhesive dosage form can circumvent this effect. The effect of lactose (a soluble excipient) and dicalcium phosphate (DCP) (an insoluble excipient) on dissolution rate, kinetic of release and adhesion force of buccal-adhesive tablets of propranolol HCl were evaluated. Each tablet composed of 80 mg propranolol HCl, 80 mg hydroxypropylmethylcellulose (HPMC) K4M, polycarbophil AA1 and lactose or DCP with different ratios. The results showed that the presence of the fillers increased dissolution rate of the drug. The release data also showed that the effect of lactose on the dissolution rate was greater than the DCP. Kinetic release of propranolol HCl from buccal-adhesive matrices was affected by the different ratios of polymers and fillers. The fillers reduced the bioadhesion force and this effect was more considerable in formulation containing DCP. In order to determine the mode of release, the data were analyzed based on the equation $Q = kt^n$. The results showed that an increase in the concentration of HPMC K4M resulted in a reduction in the value of $n$. The value of $n$ was not significantly affected by an increase in the concentration of lactose or DCP. The values of $n$ in this study were calculated to be between 0.461 and 0.619, indicating both diffusional release and erosional mechanism.



*Keywords:* Buccoadhesive tablets; Propranolol; Fillers; Release rate; Polycarbophil; Kinetic of release

## 1. Introduction

The buccal mucosa has been investigated for local and systemic delivery of therapeutic peptides and other drugs that are subjected to first-pass metabolism or are unstable within the rest of the gastrointestinal tract [1–3].

One method of optimizing drug delivery is by the use of adhesive dosage forms. A bioadhesive has been defined as a synthetic or biological material, which is capable of adhering to a biological substrate or tissue [4]. When the biological substrate is mucus, the term "mucoadhesive" has been employed [5]. Mucosal-adhesive materials are hydrophilic macromolecules containing numerous hydrogen bond-forming groups [6]. Bioadhesive polymers not only cause the adhesion effects, but also control the release rate of drug [7].

Polycarbophil and hydroxypropylmethylcellulose (HPMC) are suitable polymers for the formulation of bioadhesive tablets. These polymers in addition of bioadhesion effects, decrease release rate and change kinetic of drug release from mucoadhesive tablets [8–10]. Propranolol is subjected to first-pass effect; therefore, formulation of buccal-adhesive dosage form can circumvent this effect [11]. In formulation of buccoadhesive tablets fillers were used for masking on unfavorite taste of drugs [12]. Most of the polymers and drugs used in mucoadhesive tablets are poorly compactible and also have poor flowability. In order to increase their compactibility or flowability of the mixture for tableting, fillers such as lactose or dicalcium phosphate (DCP) are usually added. Therefore, the objectives of this study were: (a) to examine the in vitro release characteristics of propranolol hydrochloride (propranolol HCl) from various controlled-release matrices; (b) to investigate the effects of different fillers on the bioadhesion

* Corresponding author.
*E-mail address:* ali.nokhodchi@kcl.ac.uk (A. Nokhodchi).


doi:10.1016/j.farmac.2003.11.011

property of compressed tablets containing polycarbophil and HPMC; (c) to study the effects of type of filler and polymer on the kinetic release of propranolol HCl from polymeric matrices.

## 2. Materials and methods

### 2.1. Materials

Polycarbophil, Noveon AA1 (BF Goodrich Co.); HPMC (Methocel K4M, Colorcon Co.); lactose monohydrate, DCP and magnesium stearate (Merck); propranolol HCl (Rouz Darou Co.) were used.

### 2.2. Methods

#### 2.2.1. Preparation of tablets

Propranolol HCl buccoadhesive tablets were produced by mixing the drug with HPMC K4M or polycarbophil and their mixtures. The mixture was mixed with magnesium stearate for 2 min and then compressed on a 9-mm punch and die using a single-punch machine (Korsch, model 9219-77). Formulations F1–F5 composed of 80 mg propranolol HCl, 80 mg of different ratios of HPMC K4M/polycarbophil and 1% of magnesium stearate as the lubricant.

To determine the effect of lactose on the release rate of propranolol from the tablets formulations F6–F10 containing 5% w/w polycarbophil and different ratios of HPMC K4M to lactose were formulated.

Formulations F11–F15 were prepared in a similar manner to formulations F6–F10, and lactose was replaced by DCP as the insoluble filler (see Table 1). List of the ingredients for each formulation is represented in Table 1.

#### 2.2.2. Dissolution studies

The USP paddle method was employed for all the in vitro dissolution studies. To study the drug release from only one side of tablets, the glass dies were used. For this purpose, each die was filled with the molted wax, and before solidification, the tablet was placed in the semisolid wax. In this case, only one side of tablet was in contact with the dissolution medium.

Table 1
The different formulations of propranolol HCl matrices and their composition (mg)

| Formulation code | Formulation composition | | | | |
|---|---|---|---|---|---|
| | Propranolol HCl | HPMC K4M | Polycarbophil | Lactose | DCP |
| F1 | 80 | 72 | 8 | – | – |
| F2 | 80 | 68 | 12 | – | – |
| F3 | 80 | 64 | 16 | – | – |
| F4 | 80 | 60 | 20 | – | – |
| F5 | 80 | 56 | 24 | – | – |
| F6 | 80 | 72 | 4 | 4 | – |
| F7 | 80 | 68 | 4 | 8 | – |
| F8 | 80 | 64 | 4 | 12 | – |
| F9 | 80 | 60 | 4 | 16 | – |
| F10 | 80 | 56 | 4 | 20 | – |
| F11 | 80 | 72 | 4 | – | 4 |
| F12 | 80 | 68 | 4 | – | 8 |
| F13 | 80 | 64 | 4 | – | 12 |
| F14 | 80 | 60 | 4 | – | 16 |
| F15 | 80 | 56 | 4 | – | 20 |

In this method, 500 ml of USP phosphate buffer with pH 6.8 was used as the dissolution media. The rate of stirring was 50 rpm. The tablets along with the glass die were placed in phosphate buffer and maintained at 37 °C for a period of 8 h. At appropriate intervals (0.5, 1, 1.5, 2, 3, 4, 5, 6, 7 and 8 h), 10 ml of each sample was taken and filtered. The dissolution media was then replaced by 10 ml of fresh dissolution fluid to maintain a constant volume. The samples were assayed at 288.8 nm by UV–visible spectrophotometer (Shimadzu 60A). The mean of three determinations was used to calculate the drug release from each of the formulation.

#### 2.2.3. Kinetic models

In order to investigate the mode of release from the tablets the release data were analyzed with the following mathematical models: zero-order kinetic (Eq. (1)); first-order kinetic (Eq. (2)); square root of time equation (Higuchi equation, Eq. (3)) and Peppas equation (Eq. (4)).

(1) $Q = k_0 t$

(2) $\ln(100 - Q) = \ln Q_0 - k_1 t$

(3) $Q = k_H t^{1/2}$

(4) $Q = k_P t^n$

In equations $Q$ is the percent of drug released at time $t$ and $k_0$, $k_1$ and $k_H$ are the coefficients of the equations. $k_P$ is constant incorporating structural and geometric characteristics of the release device and $n$ is the release exponent indicative of the mechanism of release. When $n$ approximates to 0.5, a Fickian/diffusion-controlled release is implied, where $0.5 < n < 1.0$ non-Fickian transport and $n = 1$ for zero order (case II transport). When the value of $n$ approaches 1.0, phenomenologically one may conclude that the release is approaching zero order.

Two factors diminish the applicability of Higuchi's equation to all hydrophilic matrix systems. The model fails to allow for influence of swelling of the matrix (upon hydration) and gradual erosion of the matrix. Eq. (4) is a simple empirical equation to describe general solute behavior from controlled-release polymeric matrices and assumes that release occurs as soon as the matrix is placed in contact with fluid and thus predicts an intercept at the origin.

#### 2.2.4. Turbidity measurement

HPMC solution was mixed with polycarbophil AA1 (PAA) solution at 37 °C for 1 h to prepare the sample solution. Buffer solutions (pH 3.5 and 6.8) were used to dissolve samples. The total polymer concentration was fixed at 0.02% in all samples. The turbidity of each sample solution was determined at 600 nm, where there was no absorption

due to polymers in solution, using a UV-160A Shimadzu spectrophotometer.

*2.2.5. Determination of bioadhesive strength*

To evaluate the bioadhesion strength, a tensile tester apparatus was designed similar to a tensile tester apparatus (Instron model 4301) and the bioadhesive strength of the tablets was measured according to previously published method [13] by a tensile tester apparatus. After isolation of hairless abdominal skin of the rat, the dorsal section of abdominal skin of rat (mucosa part) was fixed on the head of diffusion cell and filled with phosphate buffer with pH 6.8. The same conditions were exactly used according to previously published method [14].

*2.2.6. Statistical analysis*

All the data were statistically analyzed by analysis of variance (ANOVA) or Turkey's multiple comparison test. Results are quoted as significant where $P < 0.05$.

## 3. Results and discussion

### *3.1. Effect of polycarbophil/HPMC K4M ratio on dissolution rate*

Fig. 1 shows the effect of polycarbophil/HPMC K4M ratio on the release of propranolol HCl. The results showed that as the concentration of polycarbophil increased, the release rate decreased. The lowest release rate was observed with formulation F5 containing 30% w/w of polycarbophil and 70% w/w of HPMC K4M, and the highest release rate was observed with formulation F1 containing 10% of polycarbophil and 90% of HPMC K4M (see the values of $k_H$ in Table 2).

It is well known that cationic drugs form complexes with anionic polymers and that the complex influences the release of the drug from the matrix [8]. When propranolol HCl was added to solutions containing polycarbophil, an insoluble precipitate was formed. This interaction was shown by the turbidometry results (Fig. 2). The figure shows that the maximum interaction of propranolol HCl with polycarbophil occurs when the concentration of polycarbophil is 60% w/w. Taylan et al. [11] also confirmed the complex formation between propranolol HCl and polycarbophil using FT-IR technique. Polycarbophil, at pH 6.8, showed a great degree of swelling (the viscosity of the solution containing 0.5% polycarbophil was increased about 45% as pH of the solution increased from 3.5 to 6.8 indicating a great degree of swelling at pH 6.8) and would be ionized. It should, thus, be the major contributor to the gel layer. Furthermore, about 99% of propranolol HCl would be ionized and hence would be able to complex with the polymer, giving a further retardation in drug release. The interaction is possibly the reason for the observed reduction in the total release of the drug, as the percentage drug released from one side of buccoadhesive tablet after 8 h was 17.92% with formulation F5 (the highest concentration of polycarbophil in the matrix).

Dissolution rate data were analyzed based on Eqs. (1–4) and their results are listed in Table 2. The results showed that a reduction in HPMC/polycarbophil ratio had no effect on the release kinetic of propranolol HCl from buccoadhesive tablets and the highest correlation coefficients were achieved with the Higuchi square root of time model. As the percent of polycarbophil increased, the release exponent ($n$) decreased. The highest value ($n = 0.53$) was obtained for formulation F1 containing the lowest percent of polycarbophil (10% w/w), and the lowest value ($n = 0.44$) was obtained for formulation F5 containing the highest percent of polycarbophil (30% w/w). These results indicated that the value of $n$ was slightly

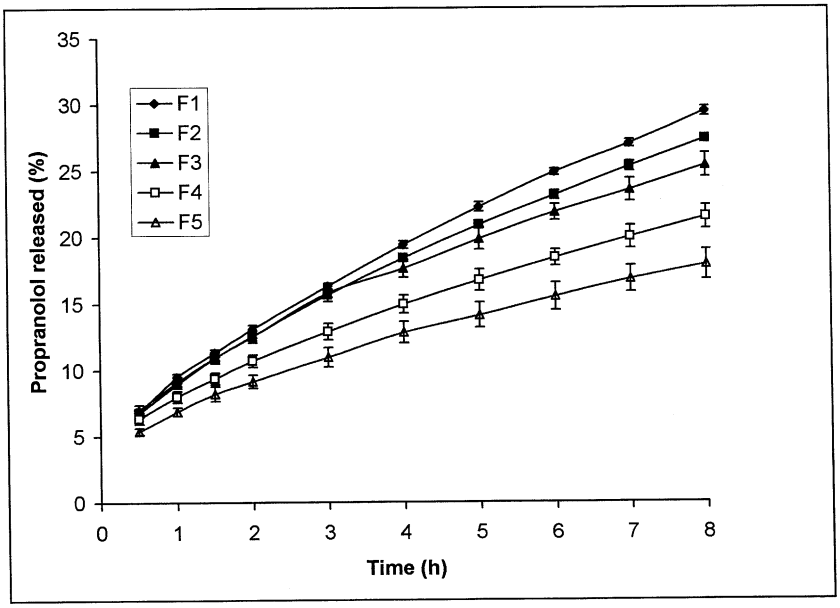


Fig. 1. The effect of polycarbophil on the release profile of propranolol HCl from HPMC matrices ($n = 3$).

Table 2
The kinetic of release of different formulations of propranolol HCl

| Formulation code | Zero-order model | | | First-order model | | | Higuchi model | | | Peppas model | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $k_0$ | $r^2$ (%) | *ss* | $k_1$ | $r^2$ (%) | *ss* | $k_H$ | $r^2$ (%) | *ss* | $k_P$ | *n* | $r^2$ (%) | *ss* |
| F1 | 0.05 | 99.0 | 5.27 | 0.06 | 99.6 | 0.61 | 1.39 | 99.6 | 2.29 | 1.07 | 0.53 | 99.6 | 14.7 |
| F2 | 0.04 | 98.9 | 5.28 | 0.05 | 99.5 | 0.70 | 1.27 | 99.7 | 1.32 | 1.10 | 0.52 | 99.6 | 14.5 |
| F3 | 0.04 | 98.5 | 5.45 | 0.05 | 99.1 | 0.86 | 1.13 | 99.8 | 0.56 | 1.35 | 0.47 | 99.6 | 12.0 |
| F4 | 0.03 | 98.8 | 2.90 | 0.04 | 99.3 | 0.46 | 0.93 | 99.7 | 0.69 | 1.29 | 0.45 | 99.3 | 20.6 |
| F5 | 0.03 | 98.4 | 2.73 | 0.03 | 98.8 | 0.48 | 0.77 | 99.9 | 0.24 | 1.15 | 0.44 | 99.6 | 11.9 |
| F6 | 0.06 | 99.4 | 4.47 | 0.08 | 99.9 | 0.36 | 1.67 | 99.2 | 6.47 | 0.95 | 0.57 | 99.5 | 22.7 |
| F7 | 0.06 | 99.1 | 7.63 | 0.08 | 99.7 | 0.71 | 1.74 | 99.5 | 4.54 | 1.02 | 0.57 | 99.8 | 11.2 |
| F8 | 0.06 | 99.4 | 5.59 | 0.08 | 99.8 | 0.46 | 1.73 | 99.3 | 6.25 | 0.95 | 0.58 | 99.6 | 17.5 |
| F9 | 0.07 | 99.2 | 7.24 | 0.09 | 99.8 | 0.45 | 1.87 | 99.4 | 5.2 | 1.48 | 0.61 | 99.7 | 13.3 |
| F10 | 0.07 | 98.9 | 11.1 | 0.09 | 99.7 | 0.92 | 1.91 | 99.6 | 4.1 | 0.98 | 0.59 | 99.8 | 8.7 |
| F11 | 0.06 | 99.1 | 6.86 | 0.07 | 99.7 | 0.61 | 1.63 | 99.6 | 3.36 | 0.85 | 0.59 | 99.8 | 11.3 |
| F12 | 0.06 | 98.9 | 8.71 | 0.08 | 99.6 | 0.87 | 1.68 | 99.6 | 2.85 | 1.05 | 0.56 | 99.8 | 9.8 |
| F13 | 0.06 | 98.9 | 8.49 | 0.07 | 99.6 | 0.86 | 1.64 | 99.7 | 2.47 | 0.78 | 0.61 | 99.9 | 4.5 |
| F14 | 0.06 | 98.9 | 8.62 | 0.07 | 99.6 | 0.87 | 1.66 | 99.7 | 2.57 | 1.00 | 0.57 | 99.8 | 10.2 |
| F15 | 0.07 | 98.8 | 11.1 | 0.08 | 99.2 | 1.03 | 1.82 | 99.7 | 2.67 | 1.05 | 0.58 | 99.9 | 6.1 |

*ss*: sun of square

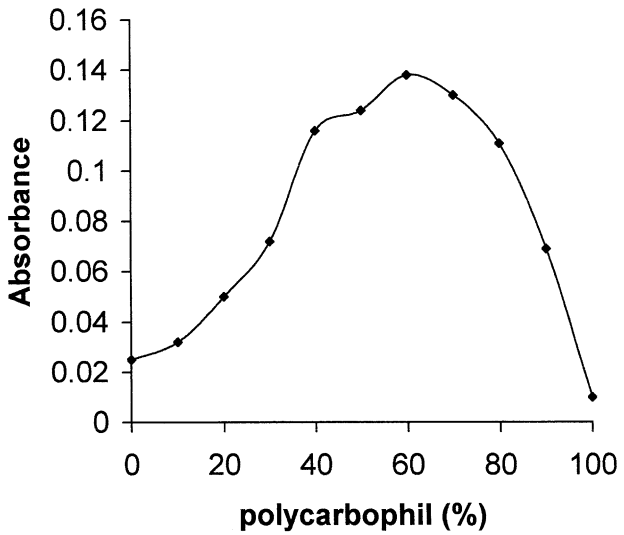


Fig. 2. Turbidity of the polycarbophil/HPMC system containing propranolol HCl as a function of polycarbophil concentration.

reduced with increasing the amount of polycarbophil in the tablets. The values of *n* showed that up to 15% of polycarbophil, the release of propranolol was only controlled by diffusion, whereas above 15% w/w of polycarbophil, the mechanism of release was slightly complex.

### *3.2. Effect of type and amount of diluents on dissolution rate*

Formulation of buccoadhesive tablets may require the addition of excipients to alter the size of the tablets, for masking the unfavorite taste of drugs and/or to replace the portion of polymer by various types of diluents. Therefore, the assessment of the effects of partial replacement of polymer by lactose and DCP will be important.

Figs. 3 and 4 show the effect of replacement of HPMC and polycarbophil by lactose and DCP on the release profile of propranolol, respectively. The figures show that an increase in the percent of lactose or DCP resulted in a slightly increase in the release rate of the drug from buccoadhesive tablets. Difference between the drug released from formulations containing 5% lactose (F6) or DCP (F11) and 25% lactose (F10) or DCP (F15) was significant ($P < 0.05$).

Changing the polymer/filler ratio increases the release rate by altering the diffusivity of drug in gel layer. Water diffusivity depends only on the total concentration of viscosity-inducing agents in the system irrespective of their nature or polymerization degree [15]. Replacement of polymer by lactose or DCP decreases the concentration of polymer in gel layer and therefore diffusion of water into the tablet is facilitated. Lactose also decreases the tourtosity of the path of diffusion [16]. The results confirmed the finding of Lapidus and Lordi [16] that replacement polymer by either a soluble or an insoluble diluents increased dissolution rate. Additionally the results contradict the statement of Alderman [17] that as little as 10% insoluble solids, such as DCP, may destroy the tablet by producing non-uniformity of the gel, since in the tablets containing 25% DCP, controlled release was still maintained [17].

The results of kinetic release obtained from the matrices containing the fillers are listed in Table 2. Results showed that amount of diluents had no effect on the kinetic of release, and the type of diluents could influence the release kinetic. The highest correlation coefficient was achieved with the first-order release for matrices containing lactose. The kinetic release of the drug from matrices containing DCP followed Higuchi model. The values of exponent (*n*) indicated that both diffusion and erosion are involved in the release of drug in the formulations containing lactose and/or DCP (the *n* value is 0.56–0.61).

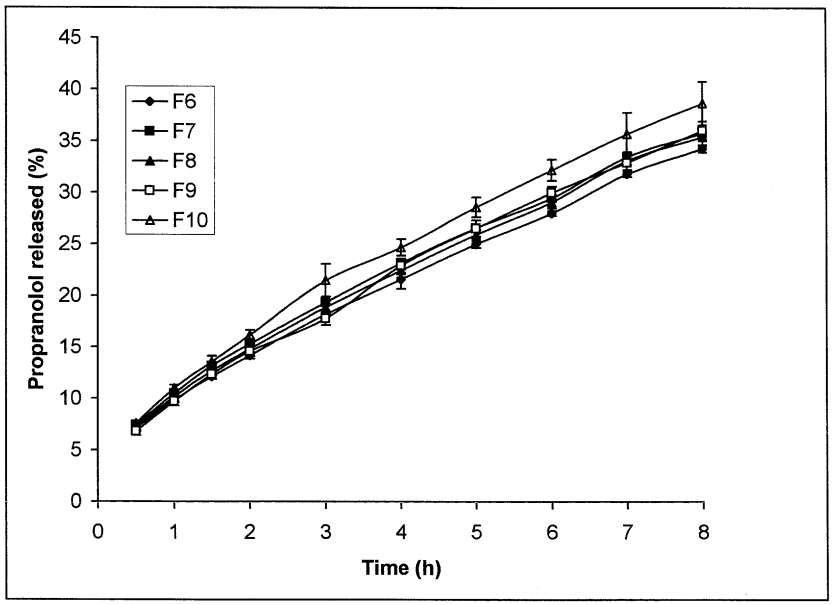


Fig. 3. The effect of lactose on the release profile of propranolol HCl from HPMC matrices ($n = 3$).

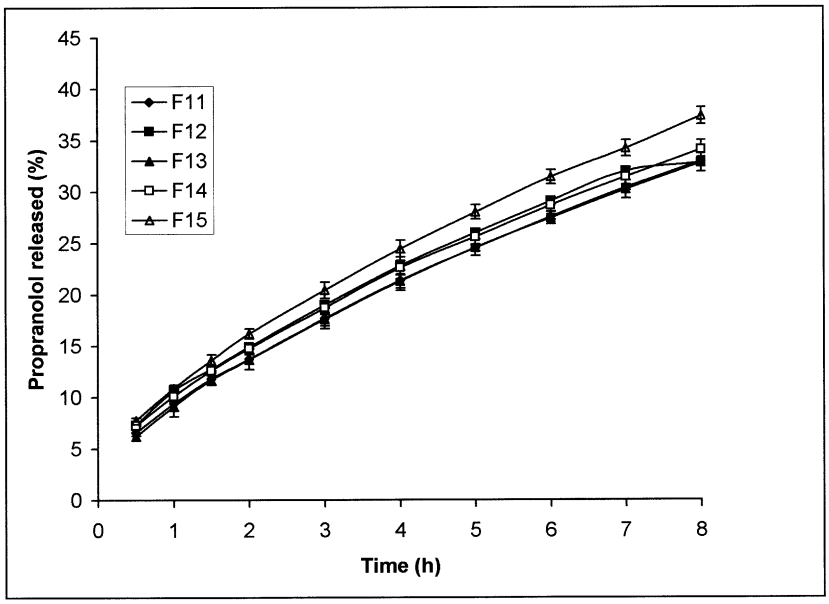


Fig. 4. The effect of DCP on the release profile of propranolol HCl from HPMC matrices ($n = 3$).

### *3.3. Effect of HPMC/polycarbophil ratio on bioadhesion strength*

Fig. 5 shows the effect of HPMC/polycarbophil ratio on bioadhesion strength (formulations F1–F5). In these buccoadhesive tablets the bioadhesion force increased with increasing the concentration of polycarbophil. It is clear that the formation of very thin and strong gel layer at the boundary might be necessary for adhesion. The viscosity of this layer is increased by adding polycarbophil and therefore the bioadhesion strength increases. To interpret the results, the possibility of the formation of interpolymer complex between the HPMC K4M and polycarbophil was evaluated. Fig. 6 confirmed the interpolymer complex formation employing turbidity measurements at various pH values (pH 3.5 and 6.8). The figure shows the turbidity of PAA/HPMC solution as a function of the weight ratio of PAA/HPMC. Maximum turbidity was observed for the solution containing 60% HPMC and 40% PAA in the acidic medium (pH 3.5). This result suggested that the interpolymer complex of HPMC and PAA could be formed at pH 3.5. Therefore, it is expected that the bioadhesion force decreases with increasing the concentration of polycarbophil in matrices. No interpolymer complex formation was observed in the higher pH (pH 6.8) since the pKa value of acrylic acid, the main monomer of PAA, was reported to be 4.25 at 25 °C [18]. Fig. 5 shows that an increase in the concentration of polycarbophil resulted in an increase in the bioadhesion force. This could be

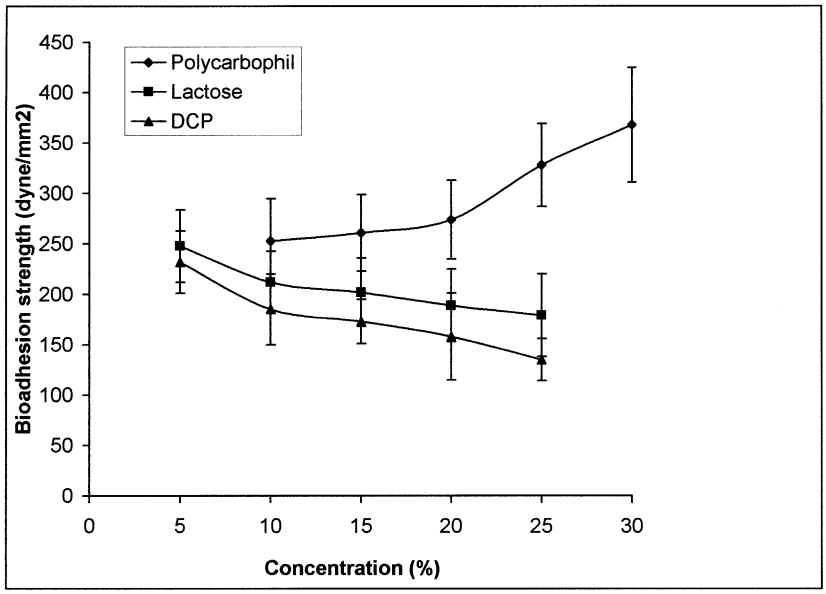


Fig. 5. The effect of polycarbophil, lactose and DCP on the bioadhesion force of HPMC matrices ($n = 3$).

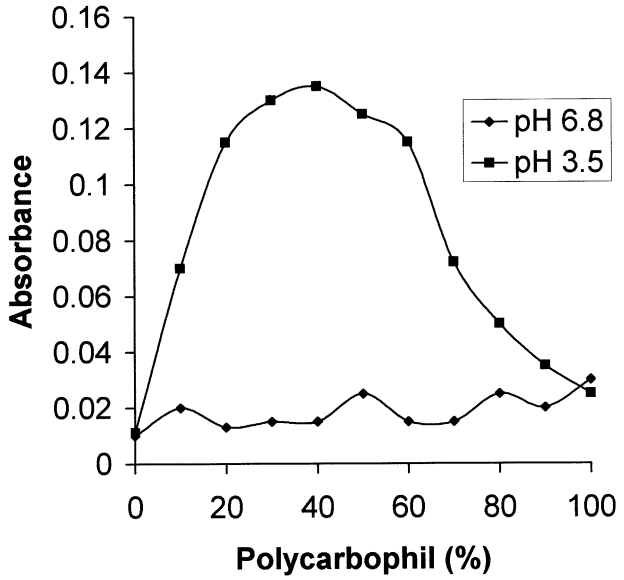


Fig. 6. Turbidity of the PAA/HPMC system as a function of polycarbophil concentration in media of various pH values.

attributed to an inhibitory effect of propranolol HCl on interpolymer complex formation in the matrices that causes an increase in bioadhesion strength.

### *3.4. Effect of type and amount of diluents on bioadhesion strength*

Fig. 5 also shows the effect of fillers (lactose and DCP) on the bioadhesion strength of the buccoadhesive tablets. The results showed that the bioadhesion strength decreased with increasing the concentrations of the fillers. The statistical test (ANOVA) showed that the mean adhesion force values of the tablets containing DCP were significantly less than that of the tablet containing lactose ($P < 0.05$). Since DCP can provide calcium cations, therefore there would be a complex between carboxylic groups of carbophil and calcium cations. Thus, the reduction in bioadhesion force for the tablets containing DCP is more considerable than that of the tablets containing lactose. The complex formation was confirmed between polycarbophil and DCP by turbidometry results. The results showed that an increase in the concentration of polycarbophil the absorbance of the sample containing DCP was increased. For example, when the concentration of polycarbophil in the sample containing DCP was increased from 10% to 90% the absorbance measured at 600 nm was increased from 0.021 to 0.33 indicating complex formation between calcium ions and polycarbophil, whereas no significant changes were observed in the sample containing lactose.

## Acknowledgements

The authors thank Colorcon Ltd. UK, specially Dr S. Khorami (Targol Chemiae Noor, Tehran, Iran) for providing the gift sample of HPMC K4M.

## References

[1] A. Ahuja, R.K. Khar, J. Ali, Mucoadhesive drug delivery, Drug Dev. Ind. Pharm. 23 (1997) 489–515.
[2] N. Chidambaram, I.K. Srivatsava, Buccal drug delivery systems, Drug Dev. Ind. Pharm. 21 (1995) 1009–1036.
[3] J.D. Smart, Drug delivery using buccal-adhesive systems, Adv. Drug Del. Rev. 11 (1993) 253–270.
[4] M. Helliwell, Use of bioadhesives in targeted delivery within the gastrointestinal tracts, Adv. Drug Del. Rev. 11 (1993) 221–251.
[5] K. Park, New approach to study mucoadhesion: colloidal gold staining, Int. J. Pharm. 53 (1989) 209–217.
[6] A.G. Mikos, N.A. Peppas, Systems for controlled release of drugs. Part 5, Bioadhesive systems, S.T.P. Pharm. 2 (1986) 705–716.

[7] D. Duchene, F. Touchard, N.A. Peppas, Pharmaceutical and medical aspects of bioadhesive systems for drug administration, Drug Dev. Ind. Pharm. 14 (1988) 283–318.

[8] B. Perez-Marcos, J.L. Ford, D.J. Armstrong, P.N.C. Elliot, C. Rostron, J.E. Hogan, Release of propranolol hydroxide from matrix tablets containing hydroxypropylmethylcellulose and carbopol 974, Int. J. Pharm. 111 (1997) 251–259.

[9] H.L. Lueben, C.M. Lehr, C.O. Rentel, A.B.J. Noach, A.G. De Boer, J.C. Verhoef, et al., Bioadhesive polymers for the peroral delivery of peptide drugs, J. Contr. Rel. 29 (1994) 329–338.

[10] M.A. Longer, H.S. Chng, J.R. Robinson, Bioadhesive polymers as platforms for oral controlled drug delivery. Part 3. Oral delivery of chlorothiazide using a bioadhesive polymer, J. Pharm. Sci. 74 (1985) 406–411.

[11] B. Taylan, Y. Capan, O. Guven, S. Kes, A.A. Hincall, Design and evaluation of sustained release and buccal adhesive propranolol hydrochloride tablets, J. Contr. Rel. 37 (1996) 11–20.

[12] R. Khanna, S.P. Agrawal, A. Ahuja, Mucoadhesive buccal tablets of clotrimazol for oral candidiasis, Drug Dev. Ind. Pharm. 23 (1997) 831–837.

[13] G. Pounchel, F. Touchard, D. Duchene, N.A. Peppas, Bioadhesive analysis of controlled release systems. Part 1. Fracture and interpretation analysis in poly (acrylic)-containing systems, J. Contr. Rel. 5 (1987) 129–141.

[14] N. Celebi, O. Kisal, Development and evaluation of a buccoadhesive propranolol tablet formulation, Pharmazie 50 (1995) 470–472.

[15] P. Gao, P.E. Fagerness, Diffusion in hydroxypropylmethylcellulose gels. Part 1. Determination of drug and water diffusivity by pulsed field gradient spin echo NMR, Pharm. Res. 12 (1995) 955–964.

[16] H. Lapidus, N.G. Lordi, Some factors affecting the release of water soluble drug form a compressed hydrophilic matrix, J. Pharm. Sci. 55 (1988) 840–843.

[17] D.A. Alderman, Review of cellulose ethers in hydrophilic matrices for oral controlled release dosage forms, Int. J. Pharm. Technol. Prod. Mfr. 5 (1984) 1–9.

[18] Budvari (Ed.), The Merck Index, eleventh ed., Merck Co. Inc., Rahway, NJ.