



## Mucoadhesive and Drug Release Properties of Benzocaine Gel

Mitra Jelvehgari<sup>a,\*</sup>, Mohammad-Reza Rashidi<sup>b</sup>, Hedayte Samadi<sup>a,b</sup>

<sup>a</sup>Department of Pharmaceutics, <sup>b</sup>Department of Medicinal Chemistry, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran

### Abstract

Gel dosage forms are successfully used as drug delivery systems considering their ability to control drug release and to protect medicaments from a hostile environment. The aim of this work was to investigate the properties of carbopol 934P polymeric system in water-miscible cosolvents such as glycerin and alcohol. Benzocaine is a local anesthetic and the mucosal gel formulation is applied in the treatment of dental pain. Samples were prepared by simply dispersing different amounts of Carbopols (0.5-3%) into the alcoholic solution at the room temperature and were kept at 4, 25 and 40 °C. All these systems were then characterized for distribution, bioadhesiveness on the mucosa, physical stability and drug release. The silastic membrane was employed. The membrane must not be a barrier for drug transport. Franz diffusion cell used to study *in vitro* drug release. The increase in carbopol concentration caused increased viscosity and bioadhesiveness. Neutralization of pH in various concentrations of carbopol gels showed resulted in increased viscosity. A relationship between the viscosity and bioadhesive strength was shown in the neutralized carbopol gels. On the other hand, the results indicated that increasing amount of alcohol and glycerin reduced drug release. In contrast, by increasing the amount of water, elasticity and release rate was increased. Vision-gel<sup>®</sup> was used as a reference for comparison with the oromucosal gel formulation. The results showed that diffusion of benzocaine from oromucosal gel and commercial sample followed Higuchi law.

**Keywords:** Benzocaine; Carbopol 934P; Drug release rate; Mucoadhesive.

**Received:** July 12, 2006; **Accepted:** September 28, 2006.

### 1. Introduction

Benzocaine, a para-aminobenzoic acid ester, is a local anesthetic used for surface anesthesia. It has low potency and systemic

toxicity. It is used, often in combination with other drugs such as analgesics, antiseptics, antibacterials, antifungals and antipruritics for the temporary local relief of pain associated with dental conditions, oropharyngeal disorders, hemorrhoids, anal pruritus and ear pain [1]. It is the active ingredient in many over-the-counter analgesic ointments.

\*Corresponding author: Mitra Jelvehgari, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz 51664, Iran.  
Tel (+98)411-3392617, Fax (+98)411-3344798  
E-mail: mitra\_jelvehgari@yahoo.com

Carbopols, which are very high molecular weight polymers of acrylic acid, have been used mainly in liquid or semi-solid pharmaceutical formulations, such as gels, suspensions and emulsions, as a thickening agent, in order to modify the flow characteristics. Recently, they are also used for their mucoadhesive properties [1] and a relevant amount of work has been done on the bioadhesive potential of carbopol polymers [1]. Carbopol 934P is a mucoadhesive polymer which has been investigated as a useful adjuvant for bioadhesive drug delivery system [1]. The main reasons for addition of mucoadhesive polymers in the system are the possibilities of prolongation of residence time in organ and increase of the contact time with absorbing mucosa, resulting in the enhancement of drug absorption. Carbopol 934P is a mucoadhesive polymer and has been investigated extensively by the pharmaceutical industry because of its high viscosity at low concentration as well as its low toxicity [1]. Carbopol 934P is a polyacrylic acid polymer, cross linked with allyl sucrose. This acidic carboxylic group partially dissociates in aqueous solution, producing a flexible coil structure. It is a fact that the carbopol gels are prepared by dispersing polymer in water, in which it swells up to 1000 times of the original volume [2] while neutralizing the system. It permits the ionization of carboxylic groups, and as a consequence, a strong gel is formed. The gel formation of carbopol 934P depends on the electrostatic repulsion between the anionic carboxyl groups [2]. The carbopol 934p gel has the following behavior in aqueous solution: 1) the gel consists of closely packed swollen particles; 2) the gel forms a thick layer that inhibits water penetration.

When a water-insoluble drug has to be added to this gel, it can only be dispersed, and a transparent aqueous phase can be obtained when the insoluble drugs are solubilized in hydrophilic water-miscible

cosolvents, e.g., PEG400 and glycerin [3].

The drug dissolved in the liquid phase of the gel under a non-ionized form may potentially penetrate more into a barrier like skin or a certain mucosa [3]. If the adhesion is on a mucosal surface, then the phenomenon is called mucoadhesion. This occurs by a process of wetting and interpenetration of the mucoadhesive polymer with the mucus gel [4, 5]. The recent development of mucoadhesive drug formulation permits the drug localization in a particular region, thereby increasing bioavailability and, at the same time, increasing the contact time between drug and mucosa.

The purpose of the present investigation was to (a) prepare benzocaine gels using carbopol 934P, (b) study the mucoadhesion power of the formulations having better rheological properties, and (c) compare the release rate and flux of benzocaine between the gel formulations and the commercial sample (Vision-gel)<sup>®</sup>

## 2. Materials and methods

### 2.1. Materials

Benzocaine was from Ubichem, England and carbopol 934P was from B.F.G, USA. Ethanol, glycerin, phenol, camphor and triethanolamine were obtained from Merck, Darmstadt, Germany. Spearmint oil was purchased from Golriz Company, Iran. Vision-gel<sup>®</sup> was from Pharmaize, Germany. Silastic membrane was provided by Biogene (Mashad, Iran). All other chemicals and solvents were of analytical grade.

### 2.2. Gel preparation

Carbopol was dispersed in water and stirred magnetically, then stored in refrigerator or at 4 °C for 24 h. The dispersion was homogenized with paddle stirrer for 30 min. at 150-200 rpm and degassed under vacuum. Half of the amount of glycerin was added in carbopol mixture and stirred for 20 min. After that the hydroalcoholic solution was gradually

**Table 1.** Composition of benzocaine gels prepared in this study.

Constituent's	%Composition (w/w)					
	F <sub>1</sub>	F <sub>2</sub>	F <sub>3</sub>	F <sub>4</sub>	F <sub>5</sub>	F <sub>6</sub>
Benzocaine	6.3	6.3	6.3	6.3	6.3	6.3
Carbopol 934P	0.5	0.7	0.5	0.5	0.5	0.5
Glycerin	20	20	20	20	20	22
Camphor	2.5	2.5	2.5	2.5	0.5	0.5
Phenol	0.5	0.5	0.5	0.5	0.5	0.5
Ethanol (60°)	43.96	43.96	40.20	46.33	46.33	43.96

poured into the mixture for 60 min at 150-200 rpm. The resulting gel was neutralized to pH 6.5 by addition of triethanolamine and stirred at 100 rpm (Figure 2), until a homogeneous and transparent dispersion was formed, and then it was stored at 4, 25 and 40 °C.

In this method, the alcoholic solution consisted of ethanol, water, benzocaine, phenol, camphor and the remainder of the glycerin. The composition of benzocaine gels were used in this study is shown in Table 1.

### 2.3. Determination of pH

One g of gel was weighted and diluted 10 times with the hydroalcoholic solution (except benzocaine and carbopol). Then the pH was measured.

### 2.4. Measurement of viscosity of carbopol gels

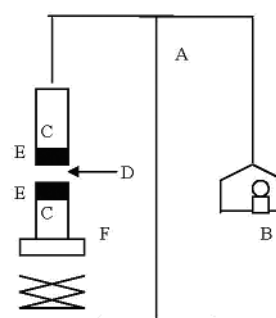
A Brookfield rotational digital viscometer DVLV-II was used to measure the viscosity (Pa.s) of gel formulations at 25 °C. Spindle number 1 was rotated at 100 rpm.

### 2.5. Adhesion strength measurement

The mucoadhesive forces of benzocaine gels were determined by means of the mucoadhesive force-measuring device shown in Figure 1, and according to the previously reported method [6], using tissue specimen obtained from the mucosal side of the abdominal area of the rat (hairless). The pieces of tissues were stored frozen in phosphate buffer at pH 7.4, and thawed to the room temperature before use [7]. At the time of testing, a section of rat skin (E) was secured

(keeping the mucosal side out) to the upper of a glass vial (C) using a cyanoacrylate adhesive. The diameter of each exposed mucosal membrane was 1.5 cm.

The vials were equilibrated and maintained at 37 °C for 10 min. After that, one vial with a section of tissue (E) was connected to the balance (A) and the other vial was fixed on a height-adjustable pan (F). To the exposed surface of the tissue attached on the vial, a constant amount of 0.1 g benzocaine gel (D) was applied. Before applying the gel, 150 µl of stimulated saliva solution (2.38 g NaHPO<sub>4</sub>, 0.19 g KH<sub>2</sub>PO<sub>4</sub> and 8 g NaCl in 1000 ml of distilled water adjusted to pH=6.75) was evenly spread on the surface of the test membrane. The height of the vial was adjusted so that of the gel could adhere to the mucosal surface of the both vials. Immediately, a constant force of 0.5 N was applied for 2 min. to ensure intimate contact between the tissues and the samples. The upper vial was then moved upwards at a constant speed, while it was connected to the balance. Weights were added at a constant rate



**Figure 1.** Bioadhesive force-measuring device: (A) modified balance; (B) weights; (C) glass vial; (D) benzocaine gel; (E) rat tissue; (F) height-adjustable pan.

to the pan on the other side of the modified balance until the two vials were separated. The bioadhesive force, expressed as the detachment stress in  $\text{dyne/cm}^2$ , was determined from the minimal weights needed to detach the tissues from the surface of each formulation, using the following equation [6].

$$\text{Detachment Stress (dyne/cm}^2\text{)} = \frac{m \cdot g}{A}$$

Where  $m$  is the weight added to the balance in grams;  $g$  is the acceleration due to gravity taken as  $980 \text{ cm/s}^2$ ; and  $A$  is the area of tissue exposed. Measurements were repeated three times for each of the gel preparations, while before each measurement a fresh smooth gel surface was created. Effect of varying contact time (1, 2, 3, 5 and 10 min.) was investigated for some of the gel preparations to optimize initial contact time. In brief, formulations were allowed to be in contact with mucosa for carrying contact times (1, 2, 3, 5, and 10 min.), and the bioadhesive force was determined as discussed above. Contact time that resulted in maximum bioadhesive strength was selected as optimum contact time required for adequate adhesion. All of the above-mentioned experiments were conducted in

triplicates.

## 2.6. Assay procedures

### 2.6.1. Analytical method for the assay of benzocaine

In order to determine the standard calibration curve of benzocaine, a stock of  $1 \text{ mg/ml}$  was prepared. Then, dilutions were made to prepare a series of solutions containing benzocaine in different concentrations. In these solutions, absorbance values at  $291 \text{ nm}$  ( $\lambda_{\text{max}}$ ) were determined spectrophotometrically. The calibration curve of benzocaine was prepared by plotting the concentration values ( $x$ ) versus absorbance values ( $y$ ). Analytical parameters for the assay of benzocaine were calculated using ANOVA test.

### 2.6.2. Recovery studies

To study the accuracy, reproducibility, precision and to check the interference with the excipients used in the formulation, recovery experiments were carried out. In order to know whether the excipients show any interference with the analysis, known amounts of the pure drug were added to the gels and the mixtures were analyzed spectrophotometrically. Percentage of recovery

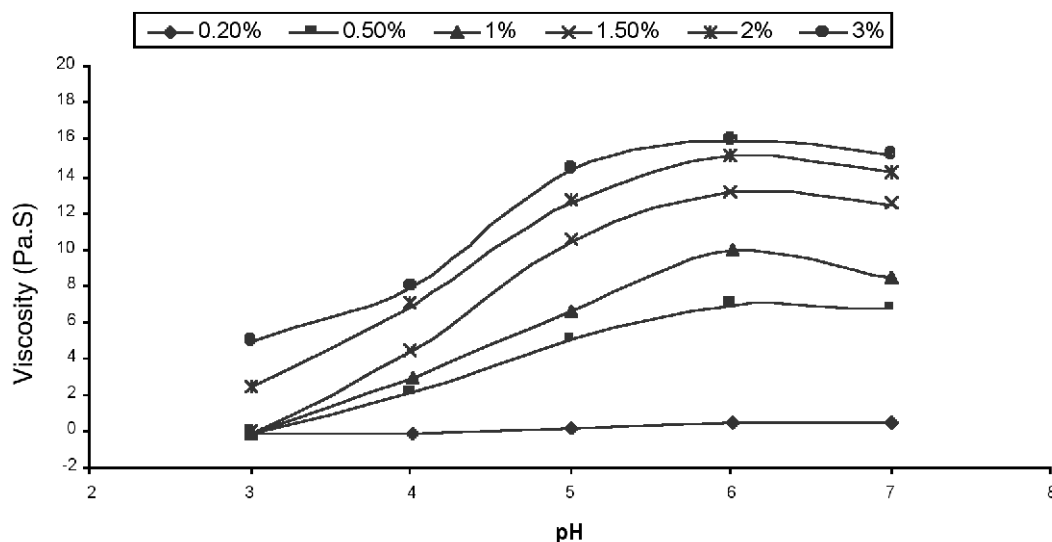


Figure 2. Viscosity of various carbopol gels at various pH at a shear rate 40.

**Table 2.** Effect of different concentrations of carbopol 934p in formulations on the mucoadhesive force of benzocaine gel (n=6).

Concentration (%w/w)	Mean mucoadhesive force (dyne/cm <sup>2</sup> ) $\times 10^3 \pm SD$
0.5	6.347 $\pm$ 0.587
1.0	17.563 $\pm$ 0.235
1.5	25.872 $\pm$ 0.916
2.0	32.296 $\pm$ 0.803
2.5	33.102 $\pm$ 0.596
3.0	33.852 $\pm$ 0.428

was calculated after three experiments.

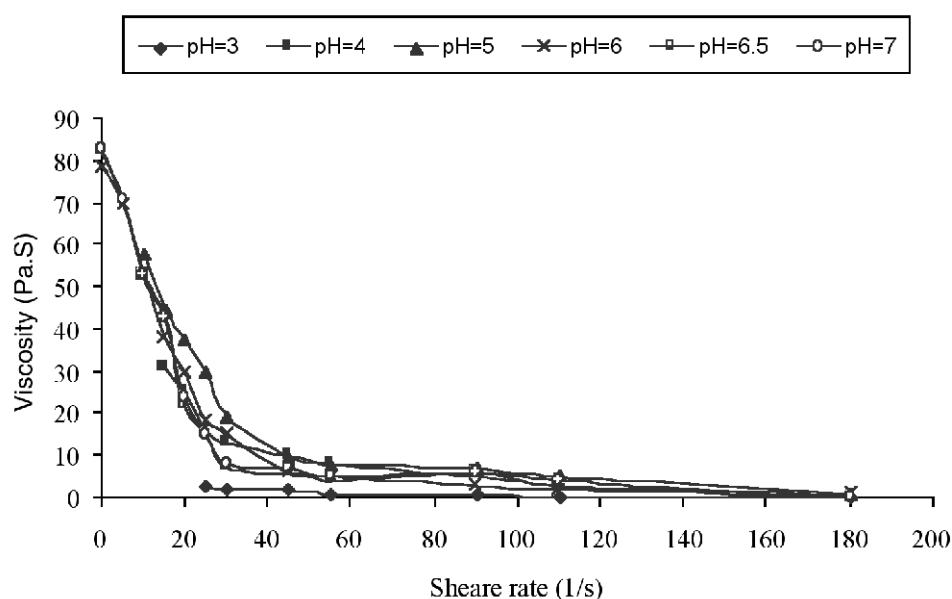
### 2.7. Drug release studies

The release studies were conducted using Franz diffusion cells (ERWEKA®HDT6, Germany). Silastic membrane (surface area = 5.3  $\pm$  0.082 cm<sup>2</sup> and thickness of membrane = 30  $\pm$   $\mu$ ) was fitted into the place between the chambers of cells. The receptor phase (30 ml) composed of alcohol 60° and the temperature was maintained at 37 °C. Preliminary experiments showed no interactions of the receptor phase with either the membrane or the formulations placed on the donor side. The receptor phase was stirred at 700 rpm during the study. A pre-determined amount of gel (2 g contained 126 mg benzocaine) was mounted on the donor side of Franz cell. One ml of the receptor phase

was withdrawn and the volume was replaced by the fresh solution. The sample was diluted by 3 ml of receptor medium. Samples were assayed spectrophotometrically at 291 nm. Each test was carried out in triplicate and the mean of three observations was reported.

### 2.8. Statistical analysis

The results obtained from the experiments of mucoadhesive strength and release studies were analyzed statistically using multivariate tests. When a statistically significance difference was found, Tukey HSD (honestly significant difference) test was then conducted (using SPSS version 13). A statistically significant difference was considered when  $p < 0.05$  [8].

**Figure 3.** Viscosity of various carbopol .05% gels of various pH.

**Table 3.** Analytical parameters for the assay of benzocaine.

Parameter	Result
Linearity range ( µg/ml)	0.25-8
Slope	9.594
Intercept	0.03
Determination coefficient (r <sup>2</sup> )	0.9998
LOD <sup>a</sup> (µg/ml)	0.055
LOQ <sup>b</sup> (µg/ml)	0.25

<sup>a</sup>LOD= limit of detection<sup>b</sup>LOQ= limit of quantitation

### 3. Results and discussion

#### 3.1. The effect of pH

Aqueous dispersions of carbopol (0-3%) exhibited pH values between 2.8 to 6.5, at 25 °C. In general, increasing the carbopol concentration (higher carboxyl concentration) caused increase of the gel viscosity (Figure 2) because of the ionization of carboxylic groups, and as a consequence a strong gel then formed. The pH of all of the formulations was adjusted to 6.5 with triethanolamine. The pH of the gel was measured and adjusted to pH between 3-7, because benzocaine is hydrolyzed in strong acidic and alkaline conditions, and may also damage the mucosa.

#### 3.2. The effect of viscosity

The viscosity of 0.5% carbopol gels of various pH was determined at various shear rates (Figure 3). As the shear rate increased the viscosity of carbopol gel decreased. Results show the viscosity of carbopol gel of various concentrations and various pH (Figure 3). Also, the increase in carbopol concentration to about (3%) caused increase of viscosity and higher concentrations showed slight increase of viscosity (Figure 3). Findings indicated that marked differences were noted in viscosity of carbopol gels of various pH. The increase of pH in various concentrations of carbopol gels showed

increased viscosity, showing the highest viscosity when neutralized to pH 6 (Figures 2 and 3). This finding is related to the increase in ionization as a result of increase in electrostatic repulsion between adjacent carboxylic groups and the subsequent expander polymer network [9, 10]. Non-neutralized carbopol gels showed significantly weaker gel structure, as expected, due to the constricted gel network [9]. The structures of these non-neutralized systems are predominantly built up by hydrogen bonds, which are easily breakable under shear stress (Figure 3).

#### 3.3. Mucoadhesion force

The mucoadhesive force is an important physicochemical parameter for local anesthetic used for surface anesthesia [1]. The effect of different concentrations of benzocaine gel formulation on mucoadhesive force is shown in Table 2. The bioadhesive force has significantly increased as the concentration of mucoadhesive polymers increased over the range of 0.5-3% ( $p < 0.05$ ). The maximum mucoadhesive strength could be showed at 2-3% concentration of carbopol and similar results are reported [11]. Furthermore, Ahuja *et al.* [12] stated that high molecular weight is important to maximize adhesion through entanglements

**Table 4.** Recovery study results for benzocaine gels (n=3).

Theoretical value (g)	Parctical value (g)	Recovery (%)	Mean recovery ±SD
6.3	6.27	99.52	98.73±0.72
6.3	6.18	98.10	
6.3	6.21	98.57	

**Table 5.** The release characteristics of benzocaine from different formulations of gel.

Formulation code	Flux <sup>a</sup> ( $\mu\text{g}/\text{cm}^2\cdot\text{min}$ )	Intercept ( $\mu\text{g}/\text{cm}^2$ )	r <sup>2</sup>	Q <sub>180</sub> <sup>b</sup> ( $\mu\text{g}/\text{cm}^2$ )
F1	0.9455 $\pm$ 0.0075	6.9373 $\pm$ 2.2720	0.9867 $\pm$ 0.0058	167.04 $\pm$ 0.6940
F2	0.5151 $\pm$ 0.0485	25.8183 $\pm$ 1.877	0.9648 $\pm$ 0.0075	115.70 $\pm$ 6.9311
F3	1.0112 $\pm$ 0.0146	19.0400 $\pm$ 0.6170	0.9539 $\pm$ 0.0088	189.12 $\pm$ 4.2496
F4	0.8878 $\pm$ 0.0093	13.2920 $\pm$ 0.9595	0.9895 $\pm$ 0.0023	169.20 $\pm$ 0.7937
F5	0.8884 $\pm$ 0.0153	12.4363 $\pm$ 0.6613	0.9935 $\pm$ 0.0013	171.10 $\pm$ 0.9962
F6	0.7182 $\pm$ 0.0124	46.0490 $\pm$ 0.5659	0.9518 $\pm$ 0.0023	170.50 $\pm$ 2.2271
Vision-gel	0.6979 $\pm$ 0.0066	45.2933 $\pm$ 0.9907	0.9328 $\pm$ 0.0212	165.96 $\pm$ 4.4418

<sup>a</sup> Flux was obtained from regression analysis between the amount of drug release per unit surface area and time.

<sup>b</sup> Q<sub>180</sub> is the cumulative amount of drug release per unit surface area during 80 min.

and Van der Waals forces. The reinforcement of the mucoadhesive forces of gel by the used polymer could be explained by the fact that secondary bond forming groups (e.g. hydroxyl, ether oxygen and amine) are the principle source of mucoadhesion [13, 14].

### 3.4. Results of assay procedures

#### 3.4.1. Results of assay of benzocaine

Calibration curve is shown in Table 3. Analytical parameters for the determination of benzocaine by UV spectrophotometric method are given in Table 3.

#### 3.4.2. Results of recovery studies

Recovery study results of benzocaine gels are given in Table 4. Each dose contains 6.3 g of benzocaine.

As it can be seen from Table 4, high percentage recovery results show that the method is free from the interferences of the excipients used in the formulation.

### 3.5. In vitro release studies

The release profile of benzocaine from the gel formulations and Visio-gel<sup>®</sup> are shown in Figure 4. Different kinetic models (first-order release, Higuchi equation and zero order release) were employed to fit the data relating to the kinetics of the release of benzocaine from the gels. The release kinetics was compared on the basis of the highest r<sup>2</sup> valued and lower %D (ss). The results of F<sub>2</sub>, F<sub>3</sub> and F<sub>6</sub> formulations and Vision-gel<sup>®</sup> (disperse the carbopol in polyethylene glycol instead of

water) showed that the release kinetics best-fitted to Higuchi kinetic model (r<sup>2</sup>=0.999) while the other formulations were best fitted to the first order model (r<sup>2</sup>= 0.997). So, in all graphs, regression analyze performed and showed a linear relationship between Q (the cumulative amount of drug penetrated through the unit surface area of the membrane) and time was obtained after 15 min (see r<sup>2</sup> values in Table 5). Slopes of the linear portion of release profiles were calculated. These slopes represented the rate of release or Flux of benzocaine from different formulations (Table 4). The table shows the rate of release of benzocaine or flux (mg/cm<sup>2</sup> min.) as a function of drug release and it depends on the effects of composition of gel formulations. Analysis of Tukey showed that these correlations are statistically significant (p<0.05). Flux and Q<sub>180</sub> (Table 5) for F<sub>3</sub> formulation observed was higher than for other formulations. The results indicated that the Fluxes and Q<sub>180</sub> (Table 5) for F<sub>3</sub> formulation and Vision-gel were 1.0112, 0.6979  $\mu\text{g}/\text{cm}^2\cdot\text{min}$  and 189.12, 165.96  $\mu\text{g}/\text{cm}^2$ , respectively (p<0.05). The results represented that F<sub>3</sub> formulation had Flux and Q<sub>180</sub> higher than Vision-gel<sup>®</sup>. The results showed that increasing the carbopol concentration at F<sub>2</sub> reduced the Flux and Q<sub>180</sub> (0.5151  $\mu\text{g}/\text{cm}^2\cdot\text{min}$  and 115.7  $\mu\text{g}/\text{cm}^2$ , respectively). The results indicated that increases of alcohol could reduce the release rate (comparing formulations F<sub>1</sub>, F<sub>3</sub> and F<sub>4</sub> in

Table 5,  $p < 0.05$ ). When the concentration of camphor was decreased, the Flux was decreased (comparing  $F_4$  and  $F_5$ ,  $p < 0.05$ ). Table 5 also shows that when the amount of glycerin was increased the release rate decreased (comparing  $F_5$  and  $F_6$ ,  $p < 0.05$ ). Ethanol is a solvent for benzocaine, and when the alcohol volume increases the drug is released slower from the solvent and it penetrates less into the mucus surface. Glycerin is a co-solvent for benzocaine and hygroscopic material. Glycerin influenced the gel viscosity and prevents loss of water from the gel. It showed similar results for alcohol [15].

Therefore, the results indicated that increasing amount of alcohol, carbopol 934P and glycerin could reduce the release rate. All of gel formulations had higher Flux and Q180 than Vision-gel® (except  $F_2$  with high concentration of carbopol). The findings showed that release rate from carbopol-water system are higher than carbopol-polyethylene glycol. Previously, Chu *et al.* [3] reported that carbopol 934P polymeric systems were studied in different mixtures of propylene glycol and glycerin, with the addition of a certain amounts of water in order to make carbopol neutralization possible, and to show that the addition of water to non-aqueous carbopol samples increased strongly their elasticity and enhancement of release rate. Similar to other studies [3], increasing the addition of water amount in the formulations (except  $F_2$ ) increased their release rate (see in Table 1 and 5). In carbopol-PEG gel, the drug release rate is slower than carbopol-water (Figure 4). The release rate in water rather than in PEG can be explained with carbopol desolvation and precipitation occurring in PEG after saltification of the carboxylic groups, with a consequent reduction of the gel consistency [16].

#### 4. Conclusion

Carbopol is one of the most common thickening agents for water phases. It is used after neutralization and its mucoadhesive properties in the aqueous medium are well known. Carbopol 934P system with different concentrations showed different release characteristics. Carbopol-water and carbopol-PEG gels (Vision-gel®) are different. In fact, generally, carbopol-water system has higher release rate than carbopol-PEG system. Both of them ( $F_3$  and Visio-gel) had similar release kinetic. Benzocaine penetrates through the mucosal surface of buccal, and in this environment exerts its anesthesia, antibacterial and etc. Gel formulation of benzocaine with mucoadhesive properties is promising for prolonging buccal residence time and thereby higher oral absorption. In addition, they provide intimate contact between a dosage form and the absorbing tissue which may result in high drug concentration in local area and hence high drug flux through the absorbing tissue.

#### Acknowledgment

The financial support from the research council of Tabriz University of Medical Sciences is greatly acknowledged.

#### References

- [1] "Martindale the extra Pharmacopeia", London: Pharmaceutical Press, 2005; Vol.2; p. 1370.
- [2] Wade A, Weller PJ. *Handbook of pharmaceutical excipients*. London: American Pharmaceutical Association and Pharmaceutical Society of Great Britain press, 2003, pp. 7, 204, 71, 336.
- [3] Chu JS, Yu DM, Amidon GL, Weiner ND, Goldberg AH. Viscoelastic properties of polyacrylic acid gels in mixed solvents. *Pharm Res* 1992; 9: 1659-63.
- [4] Waite J. Marine adhesive proteins: Natural composite thermosets. *Int Biol Macromol* 1990; 12: 139-44.
- [5] Ponchel G, Touchard F, Duchene D, Peppas NA. Bioadhesive analysis of controlled release systems. I. Fracture and interpenetration analysis and poly (acrylic acid)-containing systems. *J*



- Control Release* 1987; 5: 129-41.
- [6] Ch'ng HS, Park H, Kelly P, Robinson JR. Bioadhesive polymers as platforms for oral controlled drug delivery II. Synthesis and evaluation of some swelling water-insoluble bioadhesive polymers. *J Pharm Sci* 1985; 74: 339-405.
- [7] Wong CF, Yuen KH, Peh KK. An *in vitro* method for buccal adhesion studies: Importance of microparticles with mucosa. *J Control Release* 1990; 12: 31-7.
- [8] Daniel WW. *Biostatic: A foundation for analysis in the health sciences*, 6<sup>th</sup> ed. John Wiley & Sons Inc., 1995; pp. 295-6.
- [9] Tur KM, Ch'ng HS. Evaluation of possible mechanism of bioadhesion. *Int J Pharm* 1998; 160: 61-74.
- [10] Nakanishi T, Kaiho F, Hayashi M. Improvement of drug release rate from carbopol 934P formulation. *Chem Pharm Bull* 1998; 46: 171-3.
- [11] Hunt G, Kearney P, Kellaway IW. Mucoadhesive polymers in drug delivery systems. In: Johnson P, Lloyd Jones JG, and Ellis H. (editors). *Drug delivery systems: Fundamentals and techniques*. Chichester: Ellis Horwood, 1987; pp. 180-99.
- [12] Ahuja A, Khar RK, Ali J. Mucoadhesive drug delivery systems. *Drug Dev Ind Pharm* 1997; 23: 489-515.
- [13] Choi HK, Jung JH, Ryu JM, Yoon SJ, Oh YK, Kim IS. Trails of *in situ* gelling and mucoadhesive acetaminophen liquid suppository. *Int J Pharm* 1998; 165: 33-44.
- [14] Mikos AG, Peppas NA. Bioadhesive analysis of controlled-release systems. IV. An example method for testing the adhesion of microparticles with mucosa. *J Control Release* 1990; 12: 31-7.
- [15] Tas C, Ozkan Y, Savaser A, Baykara T. *In vitro* and *ex vivo* permeation studies of chlorpheniramine maleate gels prepared by carbomer derivatives. *Drug Dev Ind Pharm* 2004; 30: 637-47.
- [16] Bonacucina G, Martelli S, Palmieri GF. Rheological, mucoadhesive and release properties of carbopol gels in hydrophilic cosolvents. *Int J Pharm* 2004; 282: 115-30.