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RESEARCH PAPER

Release of Diltiazem Hydrochloride from Hydrophilic Matrices of Polyethylene Oxide and Carbopol

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ABSTRACT

The mucoadhesion, swelling, and drug release behavior of polyethylene oxide (PEO) and carbopol (CP) matrices were studied using a water soluble model drug diltiazem hydrochloride. The mucoadhesive strength of the matrices increased with increase in polymer content. The results showed that PEO was more mucoadhesive than CP. Mucoadhesion of the tablets was dependent upon the swelling. Swelling was ascertained by measuring the axial and radial expansion of matrix tablets following exposure to media of physiological ionic strength. There was a marked increase in the swelling index of matrices containing high polymer content of PEO as compared to CP. Drug release kinetics were found to be closely related to dissolution and swelling properties of the matrices. The release was found to be non-Fickian with n (release exponent) values ranging from 0.45–0.58. At a constant polymer content (15.84% w/w), the main contributing factor for the mucoadhesion, swelling, and release was the amount of PEO.

Key Words: Polyethylene oxide; Carbopol; Diltiazem hydrochloride; Hydrophilic matrices; Non-Fickian; Swelling; Mucoadhesion.

INTRODUCTION

Polyethylene oxide (PEO) is a high molecular weight, nonionic homopolymer of ethylene oxide with good water solubility. Polyethylene oxide is characterized with flocculent, thickening, lubrication, dispersing, water retention, and sustained release properties. It can be applied to industries like medicine, fertilizers, pulps, ceramics, detergent, cosmetics, heat treatment, water treatment, fire fighting, and oil exploration, etc. In recent years, great interest has been shown in PEO for controlled drug delivery devices.[1] Polyethylene oxide finds official status in United States Pharmacopoeia (USP) 23 NF18.

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Polyethyene oxide has been successfully used in other drug delivery systems such as the geomatrix system,[2] pulsatile drug delivery,[3] osmotically controlled drug delivery,[4,5] solid dispersion,[6] micelles,[7] liposomes,[8] nanoparticles,[9] microparticles,[10] ophthalmics,[11] and injectables.[12] Polyethylene oxide possesses all the characteristics of an excellent mucoadhesive polymer, mucoadhesion capacity being greatly dependent on the average molecular weight.

All PEO grades are highly versatile water-soluble polymers. Upon exposure to water or gastric juices, they hydrate and swell rapidly to form hydrogels with properties ideally suited for controlled drug delivery vehicle. Polyethylene oxide is available in a wide range of molecular weights, which enable the formulator to readily custom design to individual specifications.

Dimitrov and Lambov[13] investigated the release of verapamil hydrochloride from the matrix system of high molecular weight PEO. The drug release proceeded as a controlled diffusion with the value of n ranging from 0.44 to 0.47. Similarly, Pillay and Fassihi[14] worked to probe the mechanism associated with induced matrix stiffening via textural analysis as a consequence of insitu electrolyte interactions within hydroxypropylmethylcellulose (HPMC) and PEO matrices in relation to their role in controlling the release of highly soluble drugs such as diltiazem hydrochloride. Measurements in textural transitions and electrolyte conductivity showed that PEO had a higher affinity for water molecules than HPMC.

Carbopols are used as emulsifying agent, suspending agent, tablet binder, and viscosity increasing agent.[15] Though hygroscopic, carbomers are stable and physiologically inert. Carbomer formulations demonstrate sustained release, under both simulated gastric and intestinal fluids. It is frequently used as the bioadhesive component, which has resulted in its application to various sites of drug delivery, such as buccal, peroral, nasal, vaginal, conjuctival, rectal, and cervical. Carbomers designated with the letter 'P' e.g., Carbomer 971P, Carbomer 974P, and carbomer 934P are the only pharmaceutical grade polymers for oral or mucosal contact products. Carbopol 934P, a bioadhesive polymer, has been used for buccal, nasal, gastrointestinal, and vaginal routes of administration.[16]

Diltiazem, a calcium channel blocking agent, is extensively used in the treatment of coronary ischaemia, hypertension, and certain kinds of arrhythmias.[17] Diltiazem is a good candidate for prolonged release preparations because of its lower incidence of side effects and specificity in treatment and prevention of angina pectoris. Diltiazem hydrochloride has been selected as the model drug due to its short biological half-life (3–5 hours), low dose (60–120 mg bid), and good water solubility.[18,19]

The aim of the present study was to develop a sustained-release mucoadhesive matrix system using the water-soluble model drug diltiazem hydrochloride. For the present study, CP 934P and PEO WSR-303 were selected on the basis of their mucoadhesive strength, release rate controlling ability, nontoxicity, and nonirritancy.[16,20] Since diltiazem is highly water soluble, high molecular weight PEO was selected so that the release can be retarded. The influence of PEO and CP content on the mucoadhesive, swelling and release behavior of diltiazem was studied.

MATERIALS

Diltiazem was obtained ex gratis from Cipla, Bombay, India. Polyethylene oxide and Carbopol were obtained as gift samples from Union Carbide USA and B.F. Goodrich, Cleveland, OH, respectively. Dicalcium phosphate and methanol were obtained from E. Merck, Bombay, India. Potassium dihydrogen phosphate, disodium hydrogen phosphate, and mercury were purchased from S. D. Fine Chemicals Ltd., Boisar, India. Talc was obtained from Ajanta Chemicals Ltd., Bombay India.

METHODS

Preparation of Matrices

The amounts of ingredients as per Table 1 were mixed and blended. Tablet batches consisting of 50 tablets were prepared by direct compression method (Cadmach single stroke tablet compression machine, bench model, Modern mechanical works, New Delhi, India). All the product and process variables (other than concentration of two polymers) like mixing time, compaction force, etc., were kept practically constant. All the materials were accurately weighed and mixed by trituration for 20 minutes and subsequently compressed into tablets using flat-faced, round punches of 9.6 mm diameter.

Evaluation of the Matrices

Twenty tablets from each batch were weighed individually and their average weight and standard

Table 1. Concentration of drug and polymer in different formulations.

Formulation code	Weight of polymer mg (%)		Wt. of dical. phosphate mg (%)	Drug mg (%)	Talc mg (%)
	PEO	CP			
A_1	36 (14.25)	44 (17.42)	80 (31.68)	90 (35.64)	2.5 (0.99)
A_2	40 (15.84)	40 (15.84)	80 (31.68)	90 (35.64)	2.5 (0.99)
A_3	48 (19.00)	32 (12.67)	80 (31.68)	90 (35.64)	2.5 (0.99)
A_4	30 (11.88)	30 (11.88)	100 (39.60)	90 (35.64)	2.5 (0.99)
A_5	40 (15.84)	–	120 (47.52)	90 (35.64)	2.5 (0.99)
A_6	30 (11.88)	10 (3.96)	120 (47.52)	90 (35.64)	2.5 (0.99)
A_7	25 (9.90)	15 (5.94)	120 (47.52)	90 (35.64)	2.5 (0.99)
A_8	20 (7.92)	20 (7.92)	120 (47.52)	90 (35.64)	2.5 (0.99)
A_9	15 (5.94)	25 (9.90)	120 (47.52)	90 (35.64)	2.5 (0.99)
A_{10}	10 (3.96)	30 (11.88)	120 (47.52)	90 (35.64)	2.5 (0.99)
A_{11}	–	40 (15.84)	120 (47.52)	90 (35.64)	2.5 (0.99)

deviation were calculated. The hardness and friability were measured by taking three and six tablets, respectively, from each batch. The diameter and thickness of 10 tablets from each batch were also determined.

Content Determination

Five tablets were accurately weighed and powdered. A quantity equivalent to 10 mg of diltiazem hydrochloride was shaken with 5 mL of methanol in a test tube on vortex mixer for 2 min and centrifuged for 15 min at 1200 rpm. Subsequently, the clear supernatant was decanted in another test tube and the whole procedure was repeated twice to complete the triple extraction. A 50-μL of the above solution was diluted to 10 mL with methanol, and the absorbance of the resulting solution was measured at 239 nm.[18]

Mucoadhesion Studies

Fabrication of the Mucoadhesion Assembly

Mucoadhesion studies were carried out by modification of the method reported in the literature.[21] The technique utilized the concept of a double-beam physical balance (M3P, Modern Balance Works, India) with a few modifications. The left-hand side pan of the balance was replaced with a lighter pan (Fig. 1). The right-hand side pan of the balance was replaced with a shorter glass pan with a teflon cylinder attached to its base, for the attachment of the disc under investigation. The height of this glass pan was adjusted for enough space for placing a tissue-holding beaker beneath this pan. The tissue-holding beaker was placed beneath the glass pan in a water-jacketed assembly. The gap between the teflon cylinder and the tissue-mounting beaker was kept constant (approximately 1.0 mm). The two sides of the pan (after attachment of the disc under investigation) were balanced such that there was an additional 5.0-g weight on the left-hand side pan.

Selection and Isolation of the Biological Membrane

Pig stomachs were obtained from the local abattoir, and differentiated by region according to the key provided by Sisson and Grossman.[22] The stomach was gently washed with distilled water and the mucosa separated from the underlying tissue, taking care to maintain the integrity of the mucosal layer, which was subsequently stored at −20°C prior to use. Care was also taken to complete the isolation procedure within

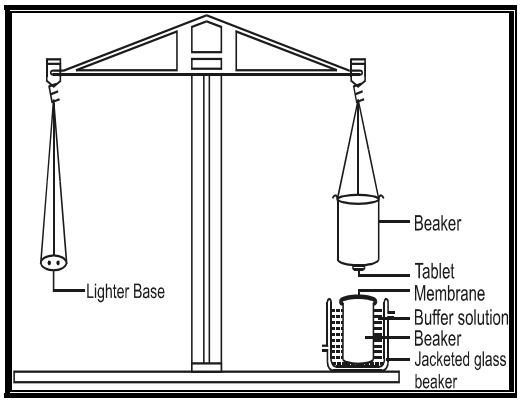

Figure 1. Bioadhesion assembly.

2 hours of the sacrifice of the animals. It has been reported previously that this procedure did not significantly affect the mucus quality and enabled a uniform content and reproducibility of the experimental observations.[23]

Determination of the Force of Detachment

The tissue was removed from the deep freezer and kept overnight at 4°C. Mucus membrane was subsequently allowed to attain an equilibrium with the room temperature over a period of 2 h and tied onto the tissue-mounting beaker, which was then placed inside the jacketed beaker and layered with the media in which the mucoadhesion studies were to be performed. Since the formulation was meant for sustained release, phosphate buffer pH 7.4 was used as the medium. The media was maintained at 37°±0.5°C for 0.5 h for equilibration, following which the additional 5.0-g weight was removed from the left pan of the balance. This permitted the lowering of the right pan (along with the disc) onto the mucosa with a constant weight (i.e., 5.0 g). The assembly was kept undisturbed for 3 min, after which the weights were gradually added on the left-hand pan until such time as the disc got detached from the mucosal surface. This weight minus the additional weight (i.e., 5.0 g) gave the weight required for detachment Eqs. 2–4.

$$\text{Actual weight for detachment (g)} = \text{weight for detachment (g)} - 5.0 \quad (1)$$

$$\text{Force of detachment (dynes)} = \text{Actual weight for detachment (g)}\ \xi\ g \quad (2)$$

where g=the acceleration due to the gravity (980 cm/sec^2), and

$$\text{Force of detachment per unit area(dynes/cm}^2) = \frac{\text{Force of detachment (dynes)}}{\pi x(9.6/2)^2} \quad (3)$$

Swelling Studies

A modification of the method reported by Talukdar and Kinget[24] was adopted for the determination of swelling index. Radial swelling of the matrices was monitored by immersing the tablet in a beaker containing phosphate buffer (PB) pH 7.4 (250 mL, 37°±0.5°C). At predefined time intervals, an increase in the tablet diameter was determined over a period of 10 h, the same measured in at least two different axes perpendicular to each other, and their mean value was taken. Swelling index (SI), expressed as percent, was calculated as per Eq. (1).

$$SI = \frac{\text{Tablet diameter at time (t)} - \text{Initial diameter of tablet}}{\text{Initial diameter of tablet}} \times 100 \quad (4)$$

The tablets were observed for the physical stability throughout the study period. A set of three tablets was taken for each combination for the determination of SI in the medium. Phosphate buffer pH 7.4 was used as the medium, as the swelling of carbopol has been reported to be dependent upon pH.

Dissolution Studies

Dissolution studies of diltiazem hydrochloride tablets were performed in water.[25,26] The tablets were stuck onto the bottom of the dissolution vessel with a drop of dissolution medium. Prewarmed (37°±0.5°C) dissolution medium was gently poured into the vessel and dissolution conducted as per United States Pharmacopoeia (USP) method II with a paddle speed of 100 rpm. Water was used as the dissolution medium because diltiazem is highly soluble in water and thus water maintains good sink conditions for the drug. Waterhas also been used as a dissolution medium for diltiazem hydrochloride tablets in United States Pharmacopoeia 23 National Formulary 18. Samples (5.0 mL) were withdrawn at regular intervals and replaced with an equal volume of medium. Samples were filtered and subsequently analysed at 236 nm.[17]

Data Analysis

The raw data obtained from in vitro dissolution was analysed using the ZOREL Software.[27] The kinetic constant (K), diffusional release exponent (n) using logarithmic transformation of Eq. (5),[28] the contribution due to Fickian diffusion (k_1), and polymer relaxation (k_2) in a swellable matrix were also determined. Based on phenomenological analysis, the type of release, whether Fickian, non-Fickian (anomalous), or zero-order, was predicted.

$$\log (M_t/M_\alpha) = \log k + n \log t \quad (5)$$

The value of time taken for 50–90% release as described by t_{50}–t_{90} was also calculated.

RESULTS AND DISCUSSION

Evaluation of Matrices

The tablet weights varied between 249.9–251.3 mg, diameter 9.6 mm, and hardness between 4–5 kg/cm^2. The drug content of diltiazem hydrochloride varied between 97.6–99.2% and tablet friability ranged between 0.2–0.5%. Thus, all formulations were found to comply with compendial guidelines.

Mucoadhesion Studies

Mucoadhesives are generally polymers with numerous hydrophilic functional groups, capable of forming hydrogen bonds.[29] This is due to the fact that upon hydration, the expansion of the polymeric surface area takes place, thereby resulting in an increased area of contact between the polymer and the mucin, thus, permitting a greater degree of interpenetration and interdiffusion process. The data shown in Table 2 construes an increasing trend in the bioadhesive strength with the increase in the amount of polymer content (A_1, A_4, and A_5), in consonance with the literature.[30] The hydrogels are known to swell readily when they come in contact with hydrated mucous membrane. The water sorption reduces the glass transition temperature below ambient conditions, and hydrogels become progressively rubbery due to uncoiling, increased mobility of the polymer chains. This glass-rubbery transition provides adhesive surface for maximum contact with the mucin, and flexibility to the polymer chains for interpenetration with mucin. Increasing the polymer amount may provide more adhesive sites and polymer chains for interpenetration with mucin resulting consequently in the aggrandization of bioadhesive strength.

Table 2. Measurement of force of detachment using porcine stomach.

Formulation	Weight of detachment (g) from porcine stomach (n=10)
A_1	32.27±2.58
A_2	32.17±4.32
A_3	32.57±5.13
A_4	30.00±5.23
A_5	27.75±1.83
A_6	20.87±3.43
A_7	19.20±2.14
A_8	16.25±4.09
A_9	14.00±2.34
A_{10}	12.50±2.42
A_{11}	13.56±2.40

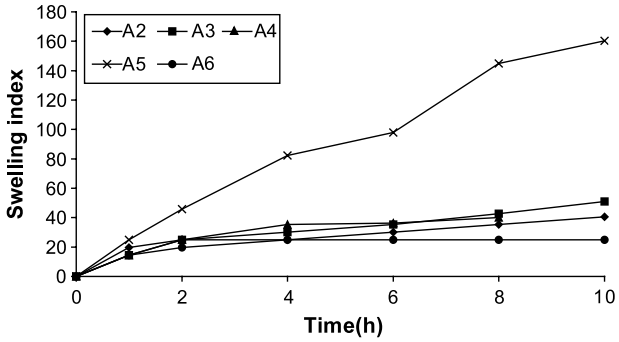

Figure 2. Plot of swelling index (SI) vs. time for formulations A_2–A_6.

The maximum detachment force per unit area was exhibited by A_5, i.e., when the polymer content was optimized to 40 mg per tablet. The force of detachment for tablets containing only PEO (A_5) was found to be more than for tablets containing only CP (A_{11}, Table 2). Also, with a decrease in PEO content, the force of detachment decreased (Table 2, A_5 to A_{11}). Park and Robinson[31] reported that the phenomenon of mucoadhesion proceeds via two mechanisms:

- A chemical interaction between the hydrophilic groups of polymer and mucus at their preswollen interface.
- Interpenetration of the polymer chains into the mucus, which is favored by a higher swelling of the polymer.

Similarly, Leung and Robinson[32] found a correlation between tensile strength and water uptake of the cross-linked copolymer, thus leading to the conclusion that the expanded nature of the polymer appeared to be very important for mucoadhesion. As the mobility of the polymer chains play a critical role in mucoadhesion, A_{10}, because of its highly cross-linked structure, exhibited the lowest forces of detachment.

Swelling Studies

All the matrices were observed to be stable throughout the period of swelling (10 h), with no disintegration being apparent. On comparing the swelling index for A_5 and A_{11} formulations, it was observed that PEO swelled more than CP (Figs. 2 and 3). As the PEO content decreased from 15.84% to 3.96 % (A_5 to A_{10}), there was a decrease in swelling index. It is

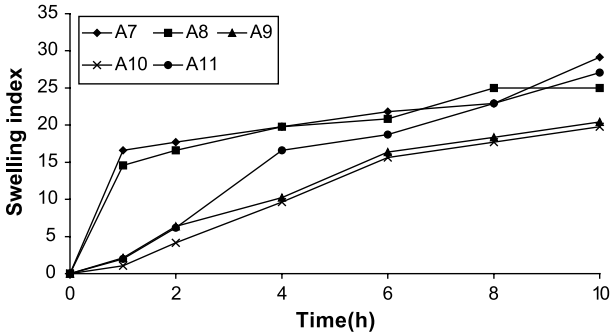

Figure 3. Plot of swelling index (SI) vs. time for formulations A_7–A_{11}.

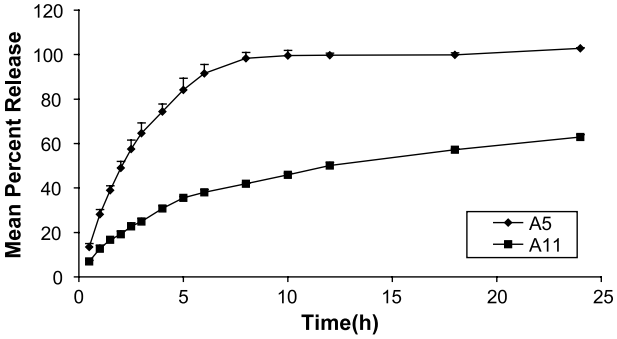

Figure 5. Release of diltiazem as a function of time from A_5 and A_{11} formulations.

postulated that polymers having a higher cross-linking have more cross-link sites to constrain the polymer and therefore, the polymer does not ''open up'' easily. Such results have been reported by Ch'ng et al.[31] Since cross-linking density of CP 934P is higher than PEO,[20] CP showed less swelling than PEO.

Dissolution Studies

The release of diltiazem as a function of time from different formulations is given in Figs. 4 and 5. Table 3 enlists dissolution parameters obtained for different formulations. In the present study, the value of release exponent (n) as per algorithm[28] was found to be 0.44–0.57 (Table 3). Hence, the release of the drug was declared to be non-Fickian. The release of the drug from the matrices was dependent upon the total polymer content. It was observed that at high polymer contents (A_1 to A_4), only up to 56% of the drug was released in 10 h (Table 3). Therefore, low polymer content (15.84%) was tried (A_5 to A_{11}) where the drug release was in the range of 45–99% depending upon the content of PEO and CP. At 15.84% polymer content, when PEO content was decreased (A_5 to A_{11}) and CP content was increased, the amount of drug released in 10 h decreased. The release of diltiazem from PEO matrix system (A_5) was fast as compared to CP formulation (A_{11}). The values of polymer relaxation coefficients (k_2) and amount of drug released by relaxation for formulations A_5 and A_{11} indicate that mode of release of drug from the two polymeric formulations was different. This difference in the release of drug from the two polymeric matrices can be attributed to the following discussion.

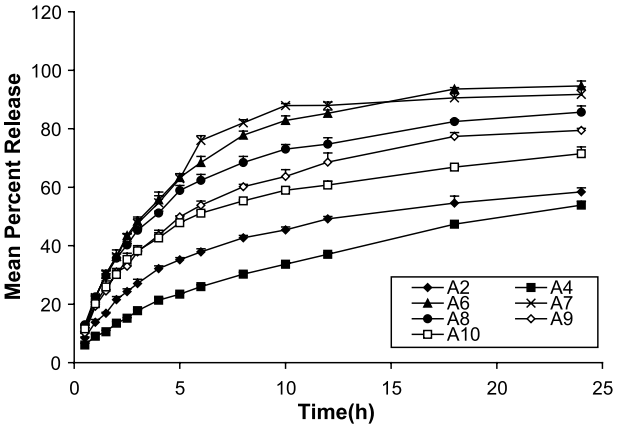

Figure 4. Plot of mean percent drug released and time for formulations.

It has been reported that during the release of drugs from hydrophilic matrices of PEO, two mechanistic phenomena take place: the swelling and the erosion of the polymer. The release kinetics of the drug from the tablet are dependent upon the relative magnitude of the rate of polymer swelling at the moving rubbery/glassy front and the rate of polymer erosion at the swollen polymer/dissolution medium front.[26] The data from the swelling studies (Figs. 2 and 3) indicate that the mean swelling index for A_5 was high as compared to A_{11}. Since the swelling index for the formulation A_5 was highest, therefore the water-soluble drug diltiazem diffused fast as compared to A_{11}.

In the case the of CP (A_{11}) formulation, the carboxyl group of CP highly dissociate repulsion between the negatively charged carboxyl groups, causing uncoiling and expansion of molecules and resulting in gel formation. The gel thus formed consists of closely packed swollen particles, particularly in the case of 934P. The presence of water-insoluble excipient DCP in the above-mentioned gel layer might have decreased the swelling of the particles, leading to

Table 3. Dissolution parameters for all the tablet formulations prepared by direct compression.

Formulation	Release exponent (n)	Kinetic constant K	Fickian diffusion constant k_1	Polymer relaxation constant k_2	Relaxational release (%)	Amount of drug release up to 10 h	t_{50}	t_{60}	t_{70}	t_{80}	t_{90}
A_1	0.47	0.12	0.13	0.0040	0.21	40.28	15.78				
A_2	0.49	0.14	1.15	0.0046	0.39	45.42	12.54	–	–	–	–
A_3	0.54	0.16	1.16	0.0160	1.35	56.52	7.13	10.91	14.67	–	–
A_4	0.57	0.09	1.08	0.0149	1.35	33.66	21.03	–	–	–	–
A_5	0.49	0.30	1.41	−0.0026	−0.18	99.56	2.06	2.66	3.55	–	–
A_6	0.53	0.23	1.27	0.0128	0.99	87.93	3.33	4.67	5.53	7.73	21.17
A_7	0.52	0.23	1.28	0.0110	0.85	82.83	3.22	4.56	6.31	8.73	17.08
A_8	0.47	0.23	1.28	−0.0005	−0.03	73.00	3.81	5.30	8.60	18.12	–
A_9	0.51	0.19	1.22	−0.0081	−0.66	63.68	5.04	7.92	12.73	–	–
A_{10}	0.44	0.20	1.24	−0.0057	−0.45	58.98	5.62	11.17	22.73	–	–
A_{11}	0.55	0.12	1.13	0.0128	1.11	45.98	11.98	20.25	–	–	–

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slow diffusion of the drug and thus decreasing the release of the drug.

As the content of PEO decreased from 15.84% to 3.96% (A_5 to A_{10}), the amount of drug released in 10 h and the rate of release decreased. The same effect was observed at high polymer content (A_1 to A_3).

CONCLUSION

The aim of the present study was to develop a sustained-release mucoadhesive matrix system for a water-soluble drug utilizing PEO and CP as the polymeric base. The technique employed in the preparation of the matrix system i.e., direct compression, is highly practical and economical from the industrial point of view. The swelling and mucoadhesion of matrices increased with increase in PEO content. The release behavior was non-Fickian, as shown by the value of n ranging from 0.45–0.58. The release of diltiazem from the matrices decreased with decrease in PEO content and simultaneous increase in CP content, keeping the total polymer content same. At low PEO content (3.96% and 5.94%) and high CP content (11.8% and 9.9%) respectively, the swelling, mucoadhesion and release of the drug from the matrices were low. While at high PEO content (15.84%, 11,88%, 9.9%, and 7.2%), the swelling, mucoadhesion, and release of the drug were high. In this study we conclude that PEO can be used as a promising polymer for controlled release of diltiazem hydrochloride.

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