Formulation and In-Vitro Evaluation of Mucoadhesive Diltiazem Hydrochloride Buccal Tablets

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Abstract
Mucoadhesive tablets for buccal administration of diltiazem hydrochloride were prepared as an alternative to available diltiazem HCl dosage forms. Two types of tablets were developed each containing two mucoadhesive components (hydroxypropylmethyl cellulose HPMC and sodium alginate) and (HPMC and carbopol) for each types, batches were produced by changing quantity of polymer. The formulations were tested for mucoadhesive performance and release pattern. In vitro bioadhesive strength studies showed that the HPMC/carbopol formulations were more bioadhesive and less drug release rate compared with HPMC/alginate formulations. Increasing the content of HPMC in HPMC/alginate tablets resulted in increase in detachment forces and swelling index but lower release rates were observed. The release behavior of all formulations was non-Fickian mechanism controlled by a combination of diffusion and chain relaxation mechanisms and best fitted zero-order kinetics. The buccoadhesive diltiazem HCl tablets containing 18.75% sodium alginate.
and 37.5% HPMC showed suitable release kinetics (n = 0.86, K₀ zero order release = 10.29 mg/h, MDT = 4.8 h), good adhesive properties and did not show any interaction between polymers and drug based on FT-IR study.

Introduction:

Among the various routes of drug delivery, oral route is perhaps the most preferred to the patient. However, peroral administration of drugs has disadvantages such as hepatic first pass metabolism and enzymatic degradation within the GI tract, that prohibit oral administration of certain classes of drugs especially peptides and proteins. Drug buccal administration, on the other hand, has many advantages such as rich vascularity, moderate permeability, suitability for both local and systemic drug delivery, less enzymatic activity and avoidance of first pass metabolism \[1\]. The accessibility of buccal cavity makes the application of drugs easy and acceptable to patient, while permitting easy removal in the event of adverse reaction \[2\]. Also reduced costs of the drug because of application of much lower doses than necessary for oral products. The major limitation associated with buccal route of administration is the lack of dosage form retention at the site of absorption. Consequently, during the past decade, bioadhesive polymers have received considerable attention for platforms of buccal controlled delivery because of their ability to localize the dosage form in specific regions to enhance drug bioavailability \[3\].

Therefore, bioadhesive polymers have extensively been employed and adhesive mucosal dosage forms are suggested for buccal delivery, including adhesive tablets \[4\], adhesive gels \[5\], adhesive film and patches \[6, 7\].

Diltiazem HCl is a calcium channel blocker widely used for its peripheral and vasodilator properties. It is also used for lowering blood pressure and has some effect on cardiac induction. It is given as oral dosage form in the treatment of angina pectoris and the management of hypertension. It has short biological half life (3.5 h) and subjected to extensive first pass effect. The oral bioavailability of diltiazem HCl is 40% in humans \[8\] make it a suitable candidate for buccal controlled release preparations.

The aim of this study is development and characterization of a buccoadhesive controlled-release tablet of diltiazem HCl using some hydrophilic polymers like carbopol 940 (CP), hydroxypropylmethyl cellulose (HPMC), and sodium alginate (SA). bioadhesion and in vitro release characteristics of diltiazem HCl from different buccoadhesive matrix tablets was evaluated to assess the suitability of such formulations.
Materials and Methods:

Diltiazem HCl (United Pharmaceutical, Jorden), carbopol 940 (J.Baker, USA), hydroxypropylmethyl cellulose 2280 (metolose 90sh 4000 SR, Seppic, Japan), sodium alginate (Himedia Lab, Mumbia, India), polyvinylpyrrolidone K-30 (Samar Drug Industry). All other reagents and chemicals used were of analytical reagent grade.

Formulation of mucoadhesive tablets:

Mucoadhesive tablets were prepared by direct compression method using the formula shown in Table 1. The drug and other excipients was mixed homogenously in glass mortar and then lubricated with 1% magnesium stearate. Finally, compressed into tablets using single punch tablet machine (Manesty Type F3, England).

Evaluation of physical properties of mucoadhesive tablets:

The thickness, hardness and friability were determined in a similar manner as stated for conventional oral tablets. Friability was determined by subjecting 20 tablets to falling shocks in friabilator (Roche friabilator, England) for 4 min at 25 rpm. Hardness of the tablets was determined using Monsanto hardness tester [9].

Drug content uniformity:

Five tablets from each formulation were crushed and each tablet was weighed. then extracted with 20 ml of phosphate buffer pH 6.4 and was centrifuged at 4000 rpm for 10 min, the supernatant was then analyzed after dilution with buffer in such a way that theoretical concentration was same as that of standard concentration. Resultant solutions were analyzed by using a spectrophotometer (Carry UV, Varian, Australia) at 237 nm [10].

Surface pH study:

The designed tablets were first allowed to swell in contact with 5mL of distilled water (pH 6.5 ± 0.05) for 2 h. The surface pH was measured by bringing glass electrode of pH meter (Hanna Instrument pH 221 Microprocessor, Italy) in contact with the surface of tablets and allowing it to equilibrate for 1 min. The surface pH of the tablets was determined in order to investigate the possibility of any discomfort in oral cavity as acidic or alkaline pH may lead to irritation [3].

Swelling studies:

Buccal tablets were weighed individually (W₁) and placed separately in 2% agar gel surface in Petri dish and incubated at 37 ± 1°C. At regular 1-hour time intervals until 6 hours, the tablet was removed from the Petri dish and excess surface water was removed carefully using filter paper. The swollen tablet was then reweighed (W₂) and the swelling index (SI) were calculated using the following formula [11].

\[
SI = \frac{(W₂ - W₁)}{W₁} \times 100
\]
Ex vivo mucoadhesion time:

The ex vivo mucoadhesion time was examined after application of the buccal tablet on freshly cut sheep buccal mucosa. The fresh sheep buccal mucosa was tied on the glass slide, and a mucoadhesive tablet was wetted with 1 drop of phosphate buffer pH 6.8 and pasted to the sheep buccal mucosa by applying a light force with a fingertip for 30 seconds. The glass slide was then put in the beaker, which was filled with 200 ml of the phosphate buffer pH 6.8 and kept at 37°C ± 1°C. After 2 minutes, a slow stirring rate was applied to simulate the buccal cavity environment, and tablet adhesion was monitored for 12 hours. The time for detachment or complete erosion of tablets from the sheep buccal mucosa was recorded as the mucoadhesion time [3].

Ex vivo mucoadhesive strength:

Bioadhesive strength of the tablets was measured by using a modified balance method described by Emami [12]. Briefly, fresh sheep buccal mucosa (2x2cm) was tied to the open mouth of smaller beaker which was filled completely with phosphate buffer pH 6.8 then placed in the center of bigger beaker containing phosphate buffer pH 6.8 just touching the mucosal surface. The tablet was stuck to the lower side of balance pan and the platform was slowly raised until the tablet surface came in contact with mucosa. After a preload time of 5 minutes, water was added to the polypropylene bottle until the tablet was detached from the buccal mucosa. The water collected in the bottle was measured and expressed as weight (g) required for the detachment.

Dissolution studies:

The dissolution of the buccoadhesive tablets was performed in 500 ml of phosphate buffer (pH 6.8) using the USP dissolution apparatus II (Coply Scientific, England ) at 37 ± 0.5°C and 50 rpm. At appropriate time intervals, 5 ml of samples were withdrawn and an equal volume of medium was added to maintain the volume constant. Samples were filtered through a 0.45 μm millipore filter and suitably diluted, the amount of diltiazem HCl which was released determined spectrophotometrically at 237nm and the release data were evaluated kinetically.

FTIR Study:

The buccoadhesive tablet (A32) were compressed and powdered. The palletized powder, along with KBr, was used for FTIR studies. The IR spectra were recorded using an IR-spectrophotometer (Shimadzu, Japan).

Results and discussion:

Carbopol (CP), sodium alginate (SA) and hydroxypropylmethyl cellulose (HPMC) polymers were selected owing to their excellent bioadhesive strength [3, 13], release rate controlling ability, non-toxicity, non-irritancy, stability at different pH ranges and compatibility with the drug. Successful use of the polymer combination of anionic polymer (like CP, SA) and a nonionic polymer
(like HPMC) is known to provide the formulation with controlled drug release along with desired mucoadhesive properties\textsuperscript{[14]}. 

**Physical properties of mucoadhesive Tablets:**

All the formulations showed acceptable hardness, friability and uniformity of content\textsuperscript{[9]} as shown in the table 2. Hardness of tablets was optimized on the basis of trial preparation of tablets. Hardness of tablets was maintained in the range of 3.5-5 kg/cm\textsuperscript{2} with SA/HPMC and 4-6 kg/cm\textsuperscript{2} with CP/HPMC formulas. Percentage weight loss in the friability test was found to be less than 1 % in all the formulations. The drug contents were also within limit for all formulations ranging from 96.97 % - 101 %\textsuperscript{[10]}. The surface pH of all formulation was found to be near the neutral pH as shown in table 2 and hence these formulations did not cause any irritation to the mucus membrane when applied\textsuperscript{[15]}.

**Swelling studies:**

Adequate swelling behaviour of a buccal adhesive system is an essential property for uniform and prolonged release of drug and effective mucoadhesion\textsuperscript{[16]}. the swelling as well as the release of diltiazem HCl from buccoadhesive tablets varied according to the type and ratio of the matrix forming polymers. Swelling index of buccoadhesive tablets as a function of time was shown in Figure 1 and 2. The rate and extent of swelling increased with an increasing concentration of polymers in the formulations due to more gel forming abilities of polymers. The formulas A1 and A2 showed decrease in swelling index after a time which indicates the erosion of the polymer\textsuperscript{[15]}. Also, it has been shown that higher swelling was observed in formulas containing SA/HPMC. This result agreed with that obtained by Choi and Kimal\textsuperscript{[13]}.

**Bioadhesive properties:**

The term "bioadhesion" is defined as an adhesion to biological surface and when adhesion occurs between the polymer and mucus layer only then it is referred as mucoadhesion. In general, mucoadhesion is considered to occur in three stages: wetting, interpenetration and mechanical interlocking\textsuperscript{[2]}. The degree of swelling of bioadhesive polymers is an important factor affecting adhesion. Adhesion occurs shortly after the beginning of swelling. Uptake of water results in relaxation of the originally stretched entangled or twisted polymer chains, resulting in exposure of all polymer bioadhesive sites for bonding to occur. The faster swelling of the polymer, the faster initiation of diffusion and formation of adhesive bonds\textsuperscript{[18]}.

All formulations showed good mucoadhesive performance with mucoadhesion resistance time range from 5 hours for A1 to more than 12 hours for A31, A32, A33 and all B formulations. The bioadhesive strength for the prepared buccoadhesive tablets were showed in figure 3. It was revealed that increasing the polymer amount increased bioadhesive strength due to providing more adhesive sites and polymer chains for interpenetration with mucin\textsuperscript{[19]}.

Also, the buccal tablets formulated with CP/HPMC (B1 to B4) showed stronger
mucoadhesion than SA/HPMC formulations (A1 to A4). This may be due to the ability of CP to form secondary bioadhesion bonds with mucin and interpenetration of the polymer chains in the interfacial region, while other polymers, SA and HPMC undergo only superficial bioadhesion.\textsuperscript{[17,20]}

It also showed that increasing in the HPMC/SA ratio from 1:1 (A31) to 2:1 (A32) and 3:1 (A33) increased the mucoadhesive strength which due to the hydrosolubility of HPMC, despite its moderate swelling properties, promoted liquid entry and entrapment in the polymer network.\textsuperscript{[20]}

**Dissolution studies:**

The in vitro drug release data obtained over a period of 8 hours, as expected, the drug release was significantly (p < 0.05) decreased with increasing in polymer content when 18.75%, 37.5%, 56.25% and 75% of SA/HPMC incorporated into formulations. The released amount of diltiazem HCl decreased from 97.5% to 75.3%, 66.65% and 35.24%, respectively at the end of 5 hours as shown in the figure 4. CP/HPMC formulations showed similar results for the same concentrations. The amount released was decreased in 6 hours from 46.87% to 42.23%, 30.9% and 28%, respectively, as shown in the figure 5. These results of study were consistent with the finding in previous report by Yamsant et al.\textsuperscript{(21)} which showed that an increase in the polymer concentration not only causes increase in the viscosity of the gel but also leads to formation of gel layer with a longer diffusional path. This leads to a decrease in the diffusion of the drug and therefore a reduction in the drug release rate.

The formulations containing CP/HPMC (B1, B2, B3 and B4) showed incomplete drug release (which was less than 60%) within 8 hours compared with SA/HPMC formulations. It was reported for Carbopol that there are acid weakening inductive effects of ionized carboxylate residues that affect the ionization potential of neighbouring groups. This may lead to high coiling and proximity of carboxylic groups compared with linear polymer (SA) which leads to intramolecular hydrogen bonding. The cross linking of Carbopol affects also elasticity of the chains as water penetrates inside the polymer network and this leads to entrapment of the drug inside the cross linked network of the polymer.\textsuperscript{[22,23]}

Also, it was revealed that increase the ratio of HPMC in HPMC/CA formulations from 1:1 (A31) to 2:1 (A32) and 3:1 (A33) was significant (p < 0.05) decrease the release rate from 91.4% to 80.11% and 73.3%, respectively, at the end of 8 hours as shown in figure 4. This may be due to the increased viscosity produced by the gelling of the hydrophilic HPMC polymer.\textsuperscript{[4,24]}

In order to describe the kinetics of drug release from controlled release preparations, various mathematical equations have been proposed (i.e zero, first, Higuchi and Hexon-Crowel equations). Furthermore, in order to better characterize the drug release mechanisms for the polymeric systems studied, the Korsmeyer-Peppas semi-empirical model was applied:

\[
\frac{Q_t}{Q_\infty} = K \cdot t^n
\]
Where $Q_t/Q_\infty$ is the fraction of drug released at time $t$, $k$ constant compromising the structural and geometric characteristics of the device, and $n$ the release exponent, which is indicative of the mechanism of drug release [25]. For the case of cylindrical geometries such as tablets, $n=0.45$ corresponds to a Fickian diffusion release (Case I), $0.45<n<0.89$ to a non-Fickian (Anomalous) transport, $n = 0.89$ to a zero order (Case II) release kinetics and $n>0.89$ to a super Case II transport [25].

The release exponent (Table 3) in all formulation is significantly greater than 0.5, which indicates anomalous (non-Fickian) drug release. When liquid diffusion rate and polymer relaxation rate are of the same order of magnitude, anomalous or non-Fickian diffusion is considered [12, 26]. The value of $n$ was greater in tablets containing SA-HPMC than that containing CP-HPMC. This observation could be attributed to the high swelling nature of alginate polymer which is in accordance with the higher swelling indices observed for these formulations.

The linear nature of the curves obtained for zero-order, first order, Higuchi model and Hixon-Crowel model as demonstrated by very close and higher $r$ squared values Table 3 suggests that the release from the formulations may follow any one of these models. When the higher correlation coefficient values are considered, the release data seem to fit better with the zero order kinetics Table 3. Therefore, the release rate $dQ/dt = k_0$ is independent on its concentration or amount of drug incorporated in the formulation which could be considered as an advantage for fabricated systems.

The same mechanism of drug release was seen when verapamil hydrochloride, a water soluble drug, was formulated in hydrophilic matrix tablet [12] and also when cinnarazine, a water soluble drug, was formulated in hydrophilic matrix tablet [27]. Figure 6 showed the FT-IR studies, the characteristic bands for important functional groups of pure drug, and tablet were observed without any change in their position indicating no chemical interaction between the drug and other polymer.

**Conclusion:**

From the results of present investigation, it may be concluded that sodium alginate / HPMC polymers are suitable for developing buccoadhesive tablet of diltiazem HCl. Formulation containing higher HPMC over SA exhibit higher mucoadhesion strength, swelling index and sustained release pattern. Thus, the study revealed that buccoadhesive formulation (A32) showed good mucoadhesion properties with sustain released of diltiazem HCl for more than 8 hours.
Acknowledgements:
The author is very thankful to Mrs. Ghaidaa S. Al-Bayeti (M.Sc. pharmaceutics), College of Pharmacy, University of Al- Mustansiriya for her great help in supplying diltiazem HCl.

<table>
<thead>
<tr>
<th>ingredients (mg/tab)</th>
<th>A1</th>
<th>A2</th>
<th>A31</th>
<th>A32</th>
<th>A33</th>
<th>A4</th>
<th>B1</th>
<th>B2</th>
<th>B3</th>
<th>B4</th>
</tr>
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<tr>
<td>Diltiazem HCl</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Sodium alginate</td>
<td>15</td>
<td>30</td>
<td>45</td>
<td>30</td>
<td>22.5</td>
<td>60</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Carbopol</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>15</td>
<td>30</td>
<td>45</td>
<td>60</td>
</tr>
<tr>
<td>HPMC</td>
<td>15</td>
<td>30</td>
<td>45</td>
<td>60</td>
<td>67.5</td>
<td>60</td>
<td>15</td>
<td>30</td>
<td>45</td>
<td>60</td>
</tr>
<tr>
<td>PVP</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
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<tr>
<td>Mannitol q.s to</td>
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<td>160</td>
<td>160</td>
<td>160</td>
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<td>160</td>
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</table>

Table-1: Formulation of Diltiazem hydrochloride Buccoadhesive Tablets Prepared.

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Thickness (mm)</th>
<th>Hardness (kg/cm²)</th>
<th>friability</th>
<th>% drug content</th>
<th>Surface pH</th>
</tr>
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<tbody>
<tr>
<td>A1</td>
<td>3.74 ± 0.023</td>
<td>3.6 ± 0.321</td>
<td>0.29</td>
<td>101 ±</td>
<td>6.66 ± 0.055</td>
</tr>
<tr>
<td>A2</td>
<td>3.34 ± 0.009</td>
<td>4.7 ± 0.642</td>
<td>0.15</td>
<td>0.56</td>
<td>6.61 ± 0.017</td>
</tr>
<tr>
<td>A3</td>
<td>3.31 ± 0.063</td>
<td>5 ± 0.5</td>
<td>0.154</td>
<td>98.87 ±</td>
<td>6.49 ± 0.015</td>
</tr>
<tr>
<td>A32</td>
<td>3.63 ± 0.023</td>
<td>4.6 ± 0.212</td>
<td>0.14</td>
<td>1.15</td>
<td>6.75 ± 0.051</td>
</tr>
<tr>
<td>A33</td>
<td>3.47 ± 0.005</td>
<td>4.8 ± 0.353</td>
<td>0.12</td>
<td>100.17 ±</td>
<td>6.93 ± 0.05</td>
</tr>
<tr>
<td>A4</td>
<td>3.49 ± 0.011</td>
<td>4.6 ± 0.577</td>
<td>0.29</td>
<td>1.36</td>
<td>6.66 ± 0.057</td>
</tr>
<tr>
<td>B1</td>
<td>3.62 ± 0.021</td>
<td>4.2 ± 0.404</td>
<td>0.36</td>
<td>99.26 ±</td>
<td>5.99 ± 0.018</td>
</tr>
<tr>
<td>B2</td>
<td>3.77 ± 0.005</td>
<td>5.4 ± 0.361</td>
<td>0.096</td>
<td>0.64</td>
<td>6.03 ± 0.03</td>
</tr>
<tr>
<td>B3</td>
<td>3.96 ± 0.0492</td>
<td>5.13 ±</td>
<td>0.12</td>
<td>96.97 ±</td>
<td>6.1 ± 0.017</td>
</tr>
<tr>
<td>B4</td>
<td>3.81 ± 0.005</td>
<td>0.321</td>
<td>0.062</td>
<td>0.72</td>
<td>5.8 ± 0.16</td>
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Table-2: Physical Properties, Surface pH of Diltiazem HCl Buccoadhesive Tablets.
Table-3: Correlation coefficient ($r^2$) of different models, drug release exponents (n), zero-order release rate constants ($k_0$), and MDT of different formulations of buccoadhesive diltiazem HCl tablets in phosphate buffer pH 6.8.

<table>
<thead>
<tr>
<th>formulation</th>
<th>n</th>
<th>$r^2$ Peppas</th>
<th>MDT (hr)</th>
<th>$k_0$ (mg/h)</th>
<th>$r^2$ zero-order</th>
<th>$r^2$ First-order</th>
<th>$r^2$ Higuchi</th>
<th>$r^2$ Hixon-Crowel</th>
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<tr>
<td>A1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>14.9</td>
<td>0.9136</td>
<td>0.9951</td>
<td>0.959</td>
<td>0.9767</td>
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<tr>
<td>A2</td>
<td>0.776</td>
<td>0.9595</td>
<td>3.57</td>
<td>12.531</td>
<td>0.9855</td>
<td>0.911</td>
<td>0.9703</td>
<td>0.9616</td>
</tr>
<tr>
<td>A31</td>
<td>0.8672</td>
<td>0.9652</td>
<td>4.3</td>
<td>11.702</td>
<td>0.9777</td>
<td>0.9397</td>
<td>0.9558</td>
<td>0.9652</td>
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<tr>
<td>A32</td>
<td>0.8681</td>
<td>0.975</td>
<td>4.8</td>
<td>10.296</td>
<td>0.9868</td>
<td>0.9694</td>
<td>0.9656</td>
<td>0.9754</td>
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<tr>
<td>A33</td>
<td>0.935</td>
<td>0.9883</td>
<td>5.33</td>
<td>8.809</td>
<td>0.9891</td>
<td>0.984</td>
<td>0.9522</td>
<td>0.9734</td>
</tr>
<tr>
<td>A4</td>
<td>0.847</td>
<td>0.9811</td>
<td>7.4</td>
<td>8.613</td>
<td>0.9809</td>
<td>0.9323</td>
<td>0.9356</td>
<td>0.9517</td>
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<tr>
<td>B1</td>
<td>0.5986</td>
<td>0.9858</td>
<td>8.1</td>
<td>5.83</td>
<td>0.9959</td>
<td>0.9936</td>
<td>0.984</td>
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<tr>
<td>B2</td>
<td>0.6485</td>
<td>0.9827</td>
<td>9.3</td>
<td>5.57</td>
<td>0.994</td>
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<td>B3</td>
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<td>0.9781</td>
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Figure-1: Swelling profile of sodium alginate / HPMC formulations.
Figure-2: Swelling profile of carbopol / HPMC formulations.

Figure-3: In vitro bioadhesion strength of diltiazem HCl buccoadhesive tablets
Figure-4: Release profile of diltiazem HCl from buccoadhesive tablet containing SA/HPMC at phosphate buffer pH 6.8.

Figure-5: Release profile of diltiazem HCl from buccoadhesive tablet containing CP/HPMC at phosphate buffer pH 6.8.
Figure-6: FTIR spectra of (A) diltiazem HCl (B) diltiazem HCl buccal tablet (A32).

References:


