Development and optimization of hydralazine HCl sustained release mucoadhesive buccal tablets using $2^3$ factorial design

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Abstract
The purpose of the present study was to develop and optimize of mucoadhesive buccal tablet containing hydrophilic matrices of hydralazine hydrochloride, using the bioadhesive polymers such as xanthan gum, carbopol and hydroxypropyl methyl cellulose and in combination along with ethylcellulose and magnesiumsterate as an impermeable backing layer. The $2^3$ full factorial design was employed by selecting the independent three polymer variables at two levels (low and high level). Drug and excipients compatibility in physical mixture was investigated by Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC). The prepared buccal tablets were evaluated by different parameters such as weight variation, content uniformity, surface pH, swelling index, ex vivo mucoadhesive strength, in vitro drug release and ex-vivo permeation studies and release kinetics. The results were revealed to be within acceptable limit. The present study successfully undertook the development of an optimized mucoadhesive buccal formulation of hydralazine hydrochloride with excellent mucoadhesive and sustained release characteristics. Stability studies were performed in accelerated conditions and showed no considerable difference in physical appearance, drug content, and mucoadhesive strength.

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Key Words
Mucoadhesive bilayer buccal tablet, $2^3$optimization technique, hypotensive agent, hydralazine hydrochloride.
INTRODUCTION

Mucoadhesive drug delivery systems offer a promising approach for controlled and site-specific delivery to the GI tract by attaching the devices to the mucus and mucosa of the tract via the process of bioadhesion. These mucoadhesive systems are also known to provide intimate contact between the dosage form and the absorptive mucosa, resulting in high drug flux through the absorbing tissue with improved bioavailability. Drug delivery via buccal mucosa using bioadhesive dosage form offers such as novel route of drug administration. The route has successfully been tried for the systemic delivery with a number of drug candidates. The buccal mucosa provides excellent opportunities for the delivery of both locally and systemically active drugs. It has potential advantages over other mucosal routes available; it avoids the degradation by the gastrointestinal enzymes and acids, and first-pass metabolism. Because of its excellent accessibility, self-placement of a dosage form is possible.

The present study was an effort to develop a mucoadhesive buccal delivery system for hydralazine hydrochloride, a hypotensive agent. The drug is well absorbed through the gastrointestinal tract but is subjected to extensive first pass metabolism. So, the dose required to produce effective therapeutic serum concentration is relatively high. Oral bio-availability of the drug has been reported to range between 10 and 35%, depending upon the extent of acetylation. It also has a short biological half-life (2–4 h), high physicochemical stability. The small dose requirement and absence of objectionable taste and odour make it a suitable candidate for buccal administration.

MATERIALS AND METHOD

Hydralazine hydrochloride was obtained as a gift samples from Hetero drugs –Hyderabad. Xanthan gum, Carbopol 974-P (CP), Hydroxyl propylmethyl cellulose (HPMC K4M) was obtained as a gift samples from Micro labs-Bangalore. Ethyl cellulose (EC) (Loba Chemie Pvt. Ltd.), magnesium stearate (Himedia laboratories Pvt ltd. Mumbai) and all other reagents and chemicals used were of analytical grade.

Experimental design

A $2^3$ level full factorial design was constructed, where the amounts of xanthan gum, carbopol-974P and HPMC-K4M selected as the factors. In this design generally 3 factors (A, B, C) were evaluated, each 2 levels (High & Low), and experimental trials were performed at all 8 possible combinations. The levels of the three factors were selected on the basis of preliminary studies carried out before implementing the
experimental design. The levels of independent variables are shown in tab 1.

Tab1. Levels and Polymers variable

<table>
<thead>
<tr>
<th>Level</th>
<th>Factor A</th>
<th>Factor B</th>
<th>Factor C</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>60</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Low</td>
<td>35</td>
<td>25</td>
<td>20</td>
</tr>
</tbody>
</table>

Factor A - Xanthan gum (mg), Factor B - HPMCK4M (mg), Factor C - Carbopol-974P (mg)

Preparation of mucoadhesive bilayered tablets

The Mucoadhesive bilayered tablets were prepared by a direct compression technique procedure involving two consecutive steps. First step, the buccal adhesive layer was prepared by homogeneously mixing the drug of hydralazine hydrochloride, polymers such as xanthan gum, carbopol-974 P, HPMC-K4M, thoroughly mixed in a glass mortar for 15 min. The mixture was then compressed using a 10-mm-diameter die in the rotary multi-station tablet machine. Second step, the upper punch was raised and the backing layer of ethyl cellulose and magnesium stearate was placed on the above compact and the second layers were then compressed into a mucoadhesive bilayer tablets. The compositions of all eight formulations were represented in tab 2.

Compatibility studies

In order to confirm the compatibility between drug and polymers were used; compatibility studies were carried out by using Fourier Transform Infrared Spectrophotometer (FTIR) and Differential scanning calorimetry (DSC). FTIR absorption spectra of pure drug, polymers used and the physical mixture of drug and polymers were taken individually, mixed thoroughly with potassium bromide (KBr) which was then compressed in a hydraulic press to form a pellet, and then scanned from 4000–400 cm⁻¹.

Tab 2. Composition of buccal tablets of hydralazine hydrochloride

<table>
<thead>
<tr>
<th>Formula code</th>
<th>Drug (mg)</th>
<th>Xanthan gum (mg)</th>
<th>HPMC K4M (mg)</th>
<th>CP-974P (mg)</th>
<th>EC (mg)</th>
<th>Mg. stearate (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FHX1</td>
<td>25</td>
<td>35</td>
<td>25</td>
<td>20</td>
<td>20</td>
<td>10</td>
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<td>FHX2</td>
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<td>20</td>
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<td>10</td>
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<td>FHX3</td>
<td>25</td>
<td>35</td>
<td>40</td>
<td>20</td>
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<td>FHX4</td>
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<td>60</td>
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<td>20</td>
<td>10</td>
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<tr>
<td>FHX5</td>
<td>25</td>
<td>35</td>
<td>25</td>
<td>40</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>FHX6</td>
<td>25</td>
<td>60</td>
<td>25</td>
<td>40</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>FHX7</td>
<td>25</td>
<td>35</td>
<td>40</td>
<td>40</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>FHX8</td>
<td>25</td>
<td>60</td>
<td>40</td>
<td>40</td>
<td>20</td>
<td>10</td>
</tr>
</tbody>
</table>


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Thermal analysis was performed on pure drug, physical mixture of drug and polymers. The samples were heated at the rate of 10°C/min over a temperature range of 50 to 450°C under a constant flow of nitrogen gas.

**Physicochemical evaluation of mucoadhesive buccal tablets**

Drug release from the mucoadhesive bilayer tablets of hydralazine hydrochloride influenced by the physicochemical parameters such as thickness, weight variation, hardness, friability, drug content, swelling index and surface pH. Hence evaluation of these parameters is very important to bring out the successful formulation.

**Surface pH**

The Surface pH of the buccal tablets was determined inorder to investigate the possibility of any side effects invivo due to pH difference between formulation and mucosal tissue. As an acidic or alkaline pH may cause irritation to the buccal mucosa, were necessary to keep the surface pH as close to neutral as possible. The tablet was allowed to swell by keeping it in contact with 5 ml of pH 6.8 phosphate buffer for 1 h. The pH was measured by bringing the electrode in contact with the surface of the tablets and allowing it to equilibrate for 1 min.

**Swelling studies**

The swelling rate of the bioadhesive tablet was evaluated by using 1% agar gel plate with the core facing the gel surface and incubated at 37 ± 0.1°C. The initial weight of the tablet was calculated (W1). 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) or percent hydration. The swelling index was calculated by the formula.

\[
\text{Swelling Index (S.I) = } \frac{[(W2-W1)/W1] \times 100}{(\text{Equation 1})}
\]

Where, W1- initial weight of tablet, W2- weight of tablet at time

**Measurement of mucoadhesive strength**

A modified physical balance method was used for determining the buccoadhesive strength. The method used fresh sheep buccal membrane as the model mucosal membrane. The fresh sheep buccal mucosa was cut into pieces and washed with phosphate buffer pH 6.8. The both pans were balanced by adding an appropriate weight on the left-hand pan. A piece of mucosa was tied to the surface of the beaker and placed below the left pan which was moistened with phosphate buffer pH 6.8. The tablet was stuck to the lower side of left pan with cyanoacrylate adhesive insulating tape. Previously weighed beaker was placed on the right hand pan and water (equivalent to weight) was added slowly to it until the tablet detach from the mucosal surface. The both pans were balanced by adding an appropriate weight on the left-hand pan. The weight required to detach the tablet from the mucosal surface gave the bioadhesive strength. The experiment was performed in triplicate and average value was calculated.

\[
\text{Force of adhesion (N) = (Bioadhesive strength (g) } \times 9.8)/1000 \quad (\text{Equation 2})
\]

\[
\text{Bond strength (N m}^{-2}) = \frac{\text{Force of adhesion}}{\text{surface area}} \quad (\text{Equation 3})
\]
**In-vitro drug release studies**

The USP type II rotating paddle method was used to study the *in-vitro* drug release of mucoadhesive bilayer tablets by little modification of tablet attaching to glass disk. The dissolution medium consisted of 900 ml of phosphate buffer pH 6.8. The release study was performed at 37 ± 0.5°C, with a rotation speed of 50 rpm. The backing layer of buccal tablet was attached to the glass disk with instant adhesive (cyanoacrylate adhesive). The disk was allocated to the bottom of the dissolution vessel. Aliquots (5 ml each) were withdrawn at regular time intervals and replaced with fresh medium. The samples were filtered, through 0.2-μm what-man filter paper after appropriate dilutions and were analyzed spectrophotometrically at 260 nm.

**Ex-vivo drug permeation study**

From the local slaughter house porcine buccal mucosa was collected and was immediately transported to the laboratory in cold normal saline solution. The buccal mucosa, with a part of sub mucosa was carefully separated from fat and muscles using scalpel. The buccal epithelium was used within two hours after removal. The *in vitro* buccal drug permeation study was performed using a Franz diffusion cell at 37°C ± 0.2°C. Buccal mucosa was mounted between the donor and receptor compartments. The receptor compartment (50 ml capacity) was filled with phosphate buffer pH 6.8. The buccal mucosa was allowed to stabilize for a period of one hour. The buccal compact was placed with the core facing the mucosa, and the compartments were clamped together. The hydrodynamics in the compartment was maintained by stirring with a magnetic bead at uniform slow speed. Samples were withdrawn at predetermined time intervals and analyzed for drug content by UV spectrophotometer at 260 nm.

**Drug release kinetics**

In order to know pattern drug release from the developed system, obtained data from in vitro drug release studies were fitted into various kinetic models: zero order (cumulative amount of drug released vs time), first order (log cumulative percentage of drug remaining vs time) and Higuchi’s model (cumulative percentage of drug released vs square root of time).

Drug release obeying Zero order can be described as represented in equation 4:
\[ C = K_0 t \]  
(Equation 4)

Where \( K_0 \) is the zero-order rate constant expressed in units of concentration/time and \( t \) is the time in hours. A graph of concentration vs time would yield a straight line with a slope equal to \( K_0 \) and intercept the origin of the axes.

Drug release obeying First order can be described as represented in equation 5:

\[ \log C = \log C_0 - k_1 t / 2.303 \]  
(Equation 5)

Where \( C_0 \) is the initial concentration of drug, \( k_1 \) is the first order constant, and \( t \) is the time.

Drug release obeying Higuchi model can be described as represented in equation 6:

\[ Q = K t^{1/2} \]  
(Equation 6)

Where \( K \) is the constant reflecting the design variables of the system and \( t \) is the time in hours. Hence, drug release rate is proportional to the reciprocal of the square root of time.

The kinetic data obtained from the in vitro dissolution studies were analyzed to obtain correlation coefficients for the different kinetic equations.

Tab 3. Interpretation of diffusional release mechanisms from polymeric.

<table>
<thead>
<tr>
<th>Release exponent (n)</th>
<th>Drug transport mechanism</th>
<th>Rate as a function of time</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>Fickian diffusion</td>
<td>( t^{-0.5} )</td>
</tr>
<tr>
<td>0.45 &lt; n = 0.89</td>
<td>Non-Fickian transport</td>
<td>( t^{n-1} )</td>
</tr>
<tr>
<td>0.89</td>
<td>Case II transport</td>
<td>zero-order release</td>
</tr>
<tr>
<td>Higher than 0.89</td>
<td>Super case II transport</td>
<td>( t^{n+1} )</td>
</tr>
</tbody>
</table>

**Stability study**

Prepared buccal tablet were properly packed in aluminium foil and kept for stability studies at the following temperature and relative humidity (RH) for three months as per ICH guidelines:

- 25º C and 65% RH
- 40º C and 75% RH

The humidity was maintained using saturated solution of sodium chloride.

**RESULTS AND DISCUSSION**

In the present work efforts have been develop to mucoadhesive bilayer buccal tablets of hydralazine hydrochloride using direct compression techniques involving mucoadhesive polymers like xanthan gum, carbopol and hydroxypropyl methyl cellulose. The ethylcellulose and magnesiumsterate as an impermeable backing layer to prevent the drug dissolve in saliva.

**Compatibility studies**

FTIR spectral result shows that there was no interaction between the drug and various mucoadhesive polymers. IR spectra of the drug showed major peaks at wave numbers 3217.37, 3029.31, 2808.45, 2031.11, 1674.27, 1589.40 and 1178.55 which compared with the physical mixture of various mucoadhesive polymers. It was observed from the spectra of drug and physical mixture of polymers that there was no remarkable shift in the wave number of the peaks which proved that there was no interaction between the drug and mucoadhesive polymers. It
was also confirmed from the DSC results, thermogram of hydralazine hydrochloride, physical mixture of polymers was carried out to study change in thermal properties of drug (Fig.3). Pure hydralazine hydrochloride thermogram was a single, sharp melting endothermic at 279.8°C. This corresponds to the peaks of individual drug and polymer without exhibiting any modification, which indicates that the drug did not interact with excipients used in the tablet.

**Physicochemical Evaluation**

The thickness, weight variation, friability, hardness and content uniformity were found to be within acceptable limits (Tab 3). Thus all the physicochemical evaluation of these buccal tablets were satisfactory as specified in the pharmacopoeia.

![Fig 2. FTIR Spectrum of (a) Hydralazine HCL ; (B) Hydralazine HCL and xanthan gum; (C) Hydralazine HCL and HPMCK4M; (D) Hydralazine HCL and carbopol](image)

**Surface pH**

Surface pH of all formulations was within range of 6.1 to 7.1 which is well close to neutral pH range. These results reveal that all the formulation provide an acceptable pH in the range of salivary pH (5.5 to 7.0). They did not produce any local irritation to the mucosal route.

**Swelling Studies**

The Bioadhesion and drug release profile are dependent upon swelling behaviour of the tablets. Swelling index increased as weight gain by the tablets increased proportionally with the rate of hydration. Swelling index was calculated with respect to time. The maximum swelling index was found in the batch FHX6 and lowest in the batch FHX1

![Fig 3. DSC Spectrum of (a) Hydralazine HCL ; (B) Hydralazine HCL and xanthan gum; (C) Hydralazine HCL and HPMCK4M; (D) Hydralazine HCL and carbopol](image)

**Mucoadhesive strength**

The ex-vivo mucoadhesive strength was found to be in the range of 18.2 ±1.051 to 32.3 ±1.21 g. The optimization phase was designed statistically using $2^3$ factorial design in which three variables namely concentrations of polymers such as xanthan gum, carbopol and HPMC were kept at two levels.
Fig 4. Swelling study of mucoadhesive buccal tablet of hydralazine hydrochloride

The results show that bioadhesive strength increased with increase in the concentration of xanthan gum and carbopol with the highest value exhibited by formulation FHX6 (30.3 ±1.21) which is due to increased molecular weight of the polymers, and swelling rate of the polymers and biological membrane.

**In vitro drug release studies**

Fig 6. Shows the drug release profiles of mucoadhesive buccal tablets formulated with different concentration levels of xanthan gum, HPMC-K4M and Carbopol 974-P.

The effects of different polymeric concentration variables on the release of hydralazine HCl from tablet is represented in fig 7A&B. To know effect of polymers concentration in the drug release, comparison was made with two levels of each polymer with two levels constant of other polymers used in the formulation, (i.e. lower and higher level as a constant). FHX1, FHX7 and FHX2, FHX8 are the formulations prepared with low and high level of xanthan gum respectively and compared the release effect with FHX1& FHX2 and FHX7 & FHX8 formulations of other polymers used in lower and higher level respectively.

FHX1 and FHX2 showed 38 and 62 % of drug release correspondingly at the end of 10h, increment in the xanthan gum increases drug release. In case of FHX7 & FHX8 formulation prepared with higher level of other polymers also confirmed, 63 % and 57.83 % at time of 10 h, increased drug release was pointed out with increment of xanthan concentration, possibly due to less swelling observed in low concentration and higher swells was noticed in high level concentration resulted in increased permeability (Fig 4).

Effect of HPMC concentrations with low and high levels of other polymers is shown in fig 7C&D. increased in drug release was observed with increased concentration, however, increment of HMPC concentration able to prolong the drug release when compared to tablet prepared with higher level of other polymers, this discrepancy results probably due to that a mixture of HPMC with CP results in the reduction of polymer viscosity owing to
reduced hydration of the matrix and impeded drug diffusion\textsuperscript{13}.

Effect of Carbopol 974-P in formulation shown in fig 7E&F, in the both level comparisons, it was observed that prolonged the release of drug from the developed system in increased concentration in the both cases. It seems that the rate of advancement of the swelling front (Fig 5) into the glassy polymer and attrition of the rubbery state polymer might be increased diffusional path length for the drug release\textsuperscript{14}.

As evident from the diverse nature of dissolution profiles, the influence of polymer levels seems to be vital in regulating the drug release. From the summary of the drug release data, FHX6 shows \( t_{95} \) release of drug up to 10 h which could be a great deal for buccal tablet and also depicts higher swelling index, which resulted in more mucoadhesive strength was observed and was compared with all other formulations and the tablet FHX6 was chosen for in vivo permeation studies in buccal membrane.

**Drug permeation study**

The oral mucosa represents a barrier to drug permeation and it is intermediate between skin epidermis and gut in its permeability characteristics.

The formulation FHX6 showed 73.18±0.95% respectively drug permeation in 6 hours through the buccal mucosa.

**Mechanism of release**

Drug releases from all formulations were kinetically evaluated and presented in tab 5, and all formulations were revealed that, follows first order mechanism (0.966), the values of correlation coefficient (r) for different mechanisms were found to be close to zero order and diffusion (the value of r for zero order is 0.976, and for diffusion mechanism is 0.952), this could be attributed to the rapid swelling of the matrix in the beginning of the release, which became constant by time\textsuperscript{15}, as well as the slow erosion rate of the polymer\textsuperscript{16}.

However, ‘n’ the release exponent of Korsemeyer-Peppas model was also taken into consideration as the parameter which depends on the release mechanism. Therefore, to characterize the release mechanism of hydrazine HCl from mucoadhesive tablets, the dissolution data’s were subjected to the Korsemeyer and
Tab 4. Physicochemical Evaluation of hydralazine hydrochloride tablet

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Thickness (mm)</th>
<th>Weight variation (%)</th>
<th>Friability (%)</th>
<th>Hardness (Kg/cm²)</th>
<th>Surface pH</th>
<th>Drug content (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FHX1</td>
<td>2.65±0.02</td>
<td>1.31±0.05</td>
<td>0.58±0.02</td>
<td>4.6±0.26</td>
<td>6.52±0.151</td>
<td>23.25±0.10</td>
</tr>
<tr>
<td>FHX2</td>
<td>2.49±0.02</td>
<td>1.43±0.11</td>
<td>0.49±0.03</td>
<td>4.1±0.38</td>
<td>6.83±0.01</td>
<td>22.87±0.01</td>
</tr>
<tr>
<td>FHX3</td>
<td>2.55±0.02</td>
<td>1.28±0.09</td>
<td>0.62±0.03</td>
<td>4.2±0.26</td>
<td>6.29±0.06</td>
<td>23.17±0.02</td>
</tr>
<tr>
<td>FHX4</td>
<td>2.18±0.06</td>
<td>1.23±0.03</td>
<td>0.54±0.02</td>
<td>3.9±0.35</td>
<td>6.51±0.01</td>
<td>24.18±0.02</td>
</tr>
<tr>
<td>FHX5</td>
<td>2.61±0.06</td>
<td>1.31±0.05</td>
<td>0.68±0.04</td>
<td>4.5±0.529</td>
<td>6.63±0.06</td>
<td>23.74±0.02</td>
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<tr>
<td>FHX6</td>
<td>2.45±0.04</td>
<td>1.21±0.03</td>
<td>0.55±0.02</td>
<td>4.2±0.26</td>
<td>6.12±0.09</td>
<td>24.51±0.03</td>
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<tr>
<td>FHX7</td>
<td>2.16±0.04</td>
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<td>0.63±0.03</td>
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<td>7.12±0.05</td>
<td>22.98±0.01</td>
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<tr>
<td>FHX8</td>
<td>2.19±0.06</td>
<td>1.17±0.02</td>
<td>0.43±0.05</td>
<td>3.9±0.35</td>
<td>6.95±0.03</td>
<td>23.37±0.02</td>
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</table>

Mean±SD (n=3)

Tab 5. Release kinetic model for hydralazine hydrochloride release pattern

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>First order</th>
<th>Exponential (Korsmeyer – Peppas model)</th>
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<tbody>
<tr>
<td></td>
<td>Zero order</td>
<td>Higuchi</td>
</tr>
<tr>
<td></td>
<td>r²</td>
<td>n</td>
</tr>
<tr>
<td>FHX1</td>
<td>0.923</td>
<td>3.74</td>
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<tr>
<td>FHX2</td>
<td>0.916</td>
<td>5.95</td>
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<td>FHX3</td>
<td>0.898</td>
<td>5.23</td>
</tr>
<tr>
<td>FHX4</td>
<td>0.971</td>
<td>10.04</td>
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<tr>
<td>FHX5</td>
<td>0.879</td>
<td>5.74</td>
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<td>FHX6</td>
<td>0.976</td>
<td>9.95</td>
</tr>
<tr>
<td>FHX7</td>
<td>0.985</td>
<td>5.96</td>
</tr>
<tr>
<td>FHX8</td>
<td>0.967</td>
<td>5.21</td>
</tr>
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Peppas diffusion model. The ‘n’ values for all formulations ranged from 0.49 to 0.92, according to many investigators, if 0.50 < n < 1.0 this indicate an anomalous (non-Fickian or coupled diffusion/relaxation) drug release. These results inferred that the release was dependent on both drug diffusion and polymer relaxation.

The tablet FHX6 was chosen for in vivo release studies in porcine buccal mucosa, because of the complete release of the loaded drug *invitro* (about 97% after 10 h), its superior bioadhesive properties. Fig. 8 shows the relationship between percent of hydralazine HCl released *in vitro* and permeation rate by taking the corresponding percentages released in vivo and in vitro at the time intervals upto 6 and 10 h respectively. The correlation between in vitro release rate and permeation across porcine membrane was found to be positive with correlation coefficient of 0.9752.
Stability study

The stability study was carried out on optimum buccal tablets formulation FHX6 and its results reflect that there is no significant change such as color and shape, and their drug content, mucoadhesive strength, suggesting the satisfactory stability of the buccal tablets.

CONCLUSION

The current studies are aimed at successful development and optimization of hydralazine HCl with high regulation of the release rate and bioadhesive strength. A $2^3$ full factorial design was performed to study the effect of polymers variables (concentration) on the release properties by applying optimization technique. Suitable balancing between the levels of two polymers (Xanthan gum, and Carbopol) is imperative to acquire reasonably extension in drug release and maximum bioadhesion. Mucoadhesive bilayer tablets of hydralazine hydrochloride could be promising one as they increases bioavailability, minimizes the dose, reduces the side effects and improves patient compliance. Hence, hydralazine hydrochloride might be a right and suitable candidate for sustained drug delivery via buccal mucoadhesive tablets for the therapeutic use.

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