PREPARATION AND EVALUATION OF BUCCOADHESIVE COMPACTS OF LERCANIDIPINE HYDROCHLORIDE

GS Shantha Kumar¹*, R Narayanacharyulu², Divakar Goli¹

¹Acharya & B.M. Reddy College of Pharmacy, Soldevanahalli, Achitnagar(Post), Bangalore-560107, Karnataka, India.
²NGSM institute of Pharmaceutical sciences, Paneer, Mangalore-575018, Karnataka, India.

ABSTRACT

In the present study, an attempt was made to formulation and evaluation of Buccoadhesive compacts of LER(LER) in order to overcome bioavailability problems, to reduce dose dependent side effects and frequency of administration. Nine formulations were developed with varying concentrations of polymers like Carbopol 934P and HPMC by direct compression method. The compacts were tested for Physical parameters, surface pH, drug content uniformity, swelling index, bioadhesive strength and in-vitro drug dissolution study. FTIR studies showed no evidence on interactions between drug, polymers, and excipients. The surface pH, bioadhesive strength and swelling index of formulation F2 was found to be 6.27 - 7.00, 3.466 - 5.624N and 39.21% - 98.54%. The compacts (F2) which contain the Carbopol 934p and HPMC 4KM in the ratio of 1:1 exhibited drug release of 90.17 % in 8h. Ex vivo residence time of all formulations was found in the range of 460 to 680 min. The results of stability studies in human saliva showed that compacts stable in human saliva. In vivo mucoadhesion studies indicated that compacts were retained for more than 8h. It was revealed that there are no changes in color, irritancy, redness and dryness of mouth was found in rabbits after mucoadhesion studies. Short-term stability studies (40 ± 2°C/75±5% for 3 months) on the optimized formulation indicated that there are no significant changes in drug content and in vitro dissolution characteristics. The prepared compacts of LER were able to stay in the buccal cavity for a longer period of time, which indicates a potential use of buccoadhesive compacts of LER for treating blood pressure.
Keywords: Lercanidine HCl, HPMC 35KM, Bioadhesive strength, Surface pH, in vivo mucoadhesion.

INTRODUCTION
The mucosa is considered as a potential site for drug administration. Transmucosal routes of drug delivery such as ocular, oral cavity, nasal, rectal and vagina offer discrete advantage over peroral administration for systemic drug delivery. Transmucosal drug delivery have several advantages includes bypass of the first pass metabolism, avoidance of presystematic elimination of gastro intestinal track.\(^1\)

Buccal delivery of drugs provides an attractive alternative route to the oral route of administration, particularly in overcoming the deficiencies associated with the later mode of administration problems such as high first pass metabolism, drug degradation in gastro intestinal environment can be circumvented by administering a drug via buccal route.\(^{2,3}\) In case of toxicity of the drug, the buccal drug absorption can be terminated promptly by removing the dosage from the buccal cavity. The patients facing difficulty in swallowing can be administered in the buccal drug delivery. Therefore mucoadhesive dosage forms were suggested for oral drug delivery, which includes adhesive tablets, gels and patches.\(^4\)

The hypertensive patients are more prone to morning surge in blood pressure and hypertensive attacks during morning hours between 5 to 9 a.m. The development sustained release compacts of enalapril are expected to avoid acute overdose, and to prevent morning hypertension.\(^5\)

Lercanidine hydrochloride (LER) is chemically 2-[(3,3-diphenylpropyl) methylamine]-1,1-dimethylethylmethyl 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5 pyridine carboxylic ester hydrochloride. LER is used in treatment of hypertension, because of its selectivity and specificity on the smooth vascular cells.\(^6,7\) The drug is administered orally in a dose of 10–20 mg daily as its hydrochloride salt, reducing significantly the diastolic blood pressure.\(^7\) After oral administration, LER is completely and erratically absorbed from the gastrointestinal tract.\(^8\) However, absolute bioavailability is reduced to approximately 10% because of extensive first pass metabolism to inactive metabolites.\(^7\) Literature suggests mean half-lives of 2.8 and 4.4 h in humans after single dose of 10 and 20 mg of LER, respectively.\(^7\)
Carbopol polymers are high molecular weight, cross linked, acrylic acid-based polymers. All of the carbopol polymers have the same acrylic acid backbone. The main differences are related to the presence of a comonomer and the crosslink density. With very minor adjustments in the crosslink density and comonomer level, a large number of polymers have been engineered to provide specific application properties without substantially changing the gross molecular structure. \[9\]

From the technological point of view, Successful buccal drug delivery using buccal adhesive systems requires at least three of the following

1. A bioadhesive to retain the system in the oral cavity and maximize the intimacy of contact with mucosa.
2. A vehicle the release the drug at an appropriate rate under the conditions prevailing in the mouth and
3. Strategies for overcoming the low permeability of the oral mucosa.\[10\]

From the technological point of view, an ideal buccal dosage form must have three properties; It must maintains its position in the mouth for a few hours, release the drug in controlled fashion and provide drug release in a unidirectional way towards mucosa. \[10\]

The main objective of this study was to formulate buccoadhesive compacts of LER using some selective polymers such as HPMC 4KM, HPMC 15KM, HPMC 35KM, HPMC 100KM and Carbopol 934P for releasing the rug unidirectionally in the buccal cavity in order to bypass the first pass metabolism for improving the oral bioavailability thus can reduce the dose, dosing frequency and maintain the prolonged therapeutic levels of the drug.

**MATERIAL AND METHOD**

**Preparation of Buccoadhesive Compacts of LER**

Buccoadhesive compacts of LER were prepared as reported in Table 1. The tablet contains two layers i.e. core layer and backing layer. Core layer was prepared by transferring specified quantity of lactose, microcrystalline cellulose pH 102, mannitol, carbopol 934P and HPMC to the mortar and pestle and mixed well. LER was added to the above mixture and mixed well. Then specified quantity of magnesium stearate was added to the above mixture and mixed well. From the above directly compressible mixture specified of powder was transferred to 8mm die cavity of compression machine [Karnavati Minipress] and compressed at low pressure. Then add specified quantity of the backing layer powder containing ethyl cellulose, magnesium stearate and color above the core layer compact and compressed.
Table 1: Formulation chart of BC’s of lercanidipine HCL

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Ingredients</th>
<th>Formulation Code</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>Core layer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Lercanidipine HCL</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>HPMC K4M</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>HPMC K15M</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>HPMC K35M</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>HPMC K100M</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Carbopol 934P</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>Microcrystalline cellulose</td>
<td>44</td>
</tr>
<tr>
<td>8</td>
<td>Lactose</td>
<td>44.5</td>
</tr>
<tr>
<td></td>
<td>Magnesium stearate</td>
<td>1.5</td>
</tr>
<tr>
<td>Backing layer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Ethyl cellulose</td>
<td>48.5</td>
</tr>
<tr>
<td>2</td>
<td>Colouring agent</td>
<td>1*</td>
</tr>
<tr>
<td>3</td>
<td>Magnesium stearate</td>
<td>0.5</td>
</tr>
</tbody>
</table>

*FD & C yellow,  +FD & C yellow and Erythrosine,  #Erythrosine, @ Allake of blue

EVALUATION

A. Precompressional parameters

Moisture content was determined using Sartorious IR moisture analyzer MA35wM. [7] Percentage of moisture was noted by using digital indicator.

a. Carr’s index (or) % compressibility (I)

Carr’s index (or) % compressibility (I) indicates granules flow properties. Carr’s index was determined using bulk density apparatus. It was expressed in percentage and calculated by using following formula. [11]

Carr’s Index = (Tapped density – Bulk density) x 100
Tapped density

b. Hausner’s ratio

Hausner’s ratio indicates granules flow properties. It was calculated by the following equation.

\[
\text{Hausner’s ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}
\]

Where, TD and BD are tapped density and bulk density respectively. \[11\]

c. Angle of Repose (θ)

Specified quantity of granules blend was allowed to pass through the funnel freely. The diameter and height of the granules cone was measured. The angle of repose was calculated using the following equation. \[12\]

\[
\tan \theta = \frac{h}{r}
\]

Where, h and r are the height and radius of the powder cone.

B. Characterization buccoadhesive compacts of LER.

1. Physicochemical characterization

Twenty compacts were randomly selected from each formulation and weighed using balance to determine the average weight and were compared with the individual weight of the compacts. The standard deviation was calculated. Five compacts were taken from each formulation randomly and measured for hardness by using Pfizer hardness tester. From this average and standard deviation were calculated. The thickness and diameter of the compacts was determined by selecting 5 compacts randomly from each formulation and measured by using digital vernier callipers. From this average and standard deviation were calculated. \[13\]

Friability test was carried out by randomly selecting 10 dedusted compacts and were accurately weighed. Then compacts were subjected to rotating drum of Electrolab friability apparatus. After completion of 100 revolutions, the compacts were removed, dedusted and reweighed. Percentage friability was calculated by the following equation. \[13, 14, 15, 16\]

\[
\text{Percentage friability} = \frac{(W_1 - W_2) \times 100}{W_1}
\]

Where, \(W_1\) = Initial Weight, \(W_2\) = Final weight

2. Swelling studies

The swelling index of compacts was determined using 1% W/W agar gel plate. Three compacts from each formulation were weighed and noted as \((W_1)\). The compacts were placed
with core layer facing the gel surface in 3 separate Petri dishes containing 5 ml of 1% W/W agar gel and placed in an incubator at 37 ± 1°C. Compacts were removed at regular intervals of 0.5, 1, 2, 4 and 6 hour, excess water on the surface was carefully removed using filter paper and swollen compacts were weighed and noted as (W2). Swelling index was calculated by using following equation. \[ \frac{\text{% Swelling index}}{\text{W1}} = \frac{(W2 - W1) \times 100}{W1} \]

3. Surface pH
Surface pH of compacts was measured using systronics pH meter. The compacts were allowed to swell by keeping it in contact with 1 ml of distilled water (pH 6.5 ± 0.5) for 2 hours at room temperature in separate 3 Petri dishes for each formulation. The pH was measured by bringing the electrode in contact with the surface of the tablet and allowing it to equilibrate for 1 minute.

4. Content uniformity
Ten compacts of LER were taken from each formulation and crushed in mortar and pestle. Weigh 10 mg equivalent weight of powder and dissolve in mixture of pH 6.8 phosphate buffer & 2.5% tween 80 solution. Measure the absorbance of samples at 260.5nm using Shimadzu UV-Visible spectrophotometer.

5. In vitro bioadhesion studies
The modified two arm balance apparatus used for in vitro bioadhesion studies is shown in Fig 1. In vitro bioadhesion studies were carried out using rabbit buccal mucosa. The beaker on one side of the balance was counter balanced by using suitable weights on the other side. The compact was fixed to the surface of tissue holder with cyanoacrylate adhesive. A circular piece of rabbit buccal mucosa was fixed to the tissue holder with cyanoacrylate adhesive and kept in contact with tyrode solution to maintain buccal mucosal viability during the experiment. The temperature was maintained at 37±1°C. Then the BC was placed on the buccal mucosa by using a preload of 50gms and kept it aside for 5 min to facilitate adhesion bonding between compact and buccal mucosa. After preloading time, the preload was removed and the water was allowed to flow into the beaker kept on the other side of the balance at specified flow rate until the compact detaches from the buccal mucosa. The weight required to detach the BC from the buccal mucosa was noted as bioadhesion strength. The force of adhesion is calculated by using the following equation.
Force of adhesion (N) = \frac{(Bioadhesive strength X 9.81)}{100}

Fig 1: Modified two arm balance apparatus

6. **In vitro drug release studies**

*In vitro* drug release study of all the formulations were carried out using USP XXIV dissolution apparatus with rotating basket method at 37 ± 0.5°C and 50 rpm. Study was conducted in triplicate. Dissolution medium used for the dissolution studies was 900ml of mixture of pH 6.8 phosphate buffer and 2.5% tween 80 solution. Aliquot samples (5ml) were withdrawn at predetermined time intervals and replaced with fresh dissolution medium. The samples were filtered through Whatman filter paper number 42. After suitable dilutions samples were analyzed using Shimadzu UV-Visible spectrophotometer at 260.5nm.\(^{[12]}\)

7. **In vitro permeation studies**

*In vitro* diffusion studies were carried out using Vertical diffusion cell. Mixture of pH 6.8 phosphate buffer solution & 2.5% tween 80 solution was used as dissolution medium for *in vitro* permeation studies. The vertical diffusion cell with rabbit buccal mucosa containing magnetic bead was kept on the magnetic stirrer and stirred at 50rpm. The temperature maintained during the studies was 37 ± 0.5°C. Aliquot samples (1ml) were withdrawn at specified time intervals and replaced with fresh dissolution medium. The samples were filtered through Whatman filter paper #42 and suitably diluted. After suitable dilutions samples were analyzed using Shimadzu UV-Visible spectrophotometer at 260.5nm.\(^{[19]}\)

8. **Stability studies in human saliva**

Stability studies were performed in normal human saliva using the optimized formulation selected based on the results of swelling, release, and bioadhesion strength studies. The human saliva was collected from humans (aged 18-55) and filtered. The compacts will be placed in separate Petri dishes containing 5 ml of human saliva and placed in a temperature-
controlled oven for 6 hours at 37°C ± 0.2°C. At specified time intervals (0, 1, 2, 3 and 6 hours), the compacts were examined for change in color, shape, thickness, swelling of the compact and pH content. [18] The experiments should be repeated in triplicate (n = 3) in a similar manner.

9. **Ex vivo residence time**

*Ex vivo* residence time for the compacts were determined by using a locally modified disintegration apparatus. 800ml of pH 6.8 phosphate buffer solution was used as disintegration medium. Rabbit buccal mucosa was glued to the glass slab by using feviquick, and a mucoadhesive core side of each compact was wetted with 1 drop of pH 6.8 phosphate buffer and stuck to the rabbit buccal mucosa by applying a light force with a fingertip for 30 sec. The glass slab was vertically fixed so that the compact was completely immersed in the buffer solution at the lowest point and was out at highest point and was maintained at 37±1°C. After 2 minutes, disintegration apparatus was started and tablet adhesion was monitored until it dethatches from buccal mucosa. The time necessary for the compact to detach from the buccal mucosa was recorded. [20]

10. **In vivo mucoadhesion test**

Six New Zealand rabbits were selected for the study. The rabbits were anesthetized with I.M. injections of ketamine (35 mg/Kg) and xylazine (3 mg/Kg). The experiment was carried out with blank as well as drug containing patches. The dummy compact was placed on the buccal mucosa between the cheek and gingiva in the region of the upper canine and gently pressed onto the mucosa for about 30 sec. The compact and associated buccal area was observed for a period necessary for the compact to detach was recorded. The observations were made by lifting the upper lip. Either complete erosion or dislodgement of the compact would indicate the adhesion period. In addition the animals were also observed for irritancy, redness, dryness of mouth, salivation and colour of the mucosa. [21]

11. **Stability studies**

The optimized formulation was subjected to stability testing at 40±2°C (75 ± 5% RH) for three months. Tablets were evaluated periodically for physical parameters, bioadhesion strength and *in vitro* drug release. [22]
RESULTS AND DISCUSSION.

A. Precompressional parameters granules

The results of angle of repose, carr’s index, hausner’s ratio and moisture content were shown in Table 2. From the results it observed that the angle of repose and carr’s index (%) were found in the range of 27.74 -29.80° and 10.47-14.81%. Hausner’s ratio was found in the range of 27.74 -29.80° and 10.47-14.81%. Hence the powder mixture shows good flow properties. All the formulations were found to be free flowing (angle of repose value lies between 25-30° and Carr’s index <15). The moisture content of all formulations was found in the range of 3.26 to 4.1 %.

Table 2: Precompressional parameters

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Angle of repose* (°) Mean ± SD</th>
<th>Carr’s index* (%) Mean ± SD</th>
<th>Hausner’s ratio* (%) Mean ± SD</th>
<th>Moisture content* (%) Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>F₁</td>
<td>28.39 ± 0.00</td>
<td>11.54 ± 0.78</td>
<td>1.13 ± 0.00</td>
<td>4.04</td>
</tr>
<tr>
<td>F₂</td>
<td>28.39 ± 0.00</td>
<td>14.81 ± 0.00</td>
<td>1.17 ± 0.00</td>
<td>4.07</td>
</tr>
<tr>
<td>F₃</td>
<td>29.80 ± 0.26</td>
<td>13.49 ± 0.22</td>
<td>1.16 ± 0.00</td>
<td>3.99</td>
</tr>
<tr>
<td>F₄</td>
<td>27.74 ± 0.29</td>
<td>11.25 ± 0.21</td>
<td>1.13 ± 0.00</td>
<td>3.90</td>
</tr>
<tr>
<td>F₅</td>
<td>28.93 ± 0.00</td>
<td>10.85 ± 0.16</td>
<td>1.21 ± 0.00</td>
<td>4.1</td>
</tr>
<tr>
<td>F₆</td>
<td>29.58 ± 0.00</td>
<td>10.47 ± 0.18</td>
<td>1.12 ± 0.00</td>
<td>3.29</td>
</tr>
<tr>
<td>F₇</td>
<td>27.97 ± 0.25</td>
<td>13.96 ± 0.20</td>
<td>1.16 ± 0.00</td>
<td>3.82</td>
</tr>
<tr>
<td>F₈</td>
<td>28.73 ± 0.28</td>
<td>13.49 ± 0.22</td>
<td>1.16 ± 0.00</td>
<td>3.26</td>
</tr>
<tr>
<td>F₉</td>
<td>29.20± 0.00</td>
<td>13.05 ± 0.17</td>
<td>1.15 ± 0.00</td>
<td>4.03</td>
</tr>
</tbody>
</table>

*n=3

2. Characterization of compacts

Table 3: Physicochemical parameters data of compacts of LER

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Weight variation* (mg) Mean ± SD</th>
<th>Hardness# (Kg/cm²) Mean ± SD</th>
<th>Thickness# (mm) Mean ± SD</th>
<th>Diameter# (mm) Mean ± SD</th>
<th>Friability@ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F₁</td>
<td>199.3 ±1.02</td>
<td>6.00 ± 0.00</td>
<td>3.50±0.00</td>
<td>8.00 ±0.00</td>
<td>0.049</td>
</tr>
<tr>
<td>F₂</td>
<td>199.0 ±0.72</td>
<td>6.00 ±0.11</td>
<td>3.52±0.22</td>
<td>8.00 ±0.00</td>
<td>0.050</td>
</tr>
<tr>
<td>F₃</td>
<td>199.7 ±0.77</td>
<td>6.18 ±0.02</td>
<td>3.54±0.03</td>
<td>8.00 ±0.00</td>
<td>0.09</td>
</tr>
<tr>
<td>F₄</td>
<td>199.85 ± 0.62</td>
<td>6.14 ± 0.05</td>
<td>3.54 ±0.03</td>
<td>8.00 ±0.00</td>
<td>0.07</td>
</tr>
<tr>
<td>F₅</td>
<td>199.6 ± 0.67</td>
<td>6.00 ± 0.00</td>
<td>3.56 ±0.03</td>
<td>8.00 ± 0.00</td>
<td>0.05</td>
</tr>
<tr>
<td>F₆</td>
<td>199.65 ± 0.51</td>
<td>6.24 ± 0.03</td>
<td>3.50 ±0.00</td>
<td>8.00 ± 0.00</td>
<td>0.08</td>
</tr>
<tr>
<td>F₇</td>
<td>200.00± 0.43</td>
<td>6.10 ± 0.00</td>
<td>3.60 ±0.00</td>
<td>8.00 ± 0.00</td>
<td>0.08</td>
</tr>
<tr>
<td>F₈</td>
<td>199.80 ± 0.73</td>
<td>6.22 ± 0.05</td>
<td>3.54 ±0.03</td>
<td>8.00 ± 0.00</td>
<td>0.08</td>
</tr>
<tr>
<td>F₉</td>
<td>199.85 ± 0.49</td>
<td>6.18 ± 0.02</td>
<td>3.52 ±0.02</td>
<td>8.00 ± 0.00</td>
<td>0.15</td>
</tr>
</tbody>
</table>
From the above observations it was concluded weight variation, hardness, thickness, diameter and friability of tablets were lying within IP limit (Table 3.)

3. Swelling studies

Swelling index data was reported in Fig 2. F8 showed least swelling index (39.21%) whereas F3 showed highest swelling index (98.54%). The optimized formulation (F2) showed swelling index (85.41%). It is evident from the above data, that the compacts containing HPMC alone showed higher swelling index than compared to the compacts containing carbopol 934P. Also as viscosity of HPMC increases the swelling index is decreased because of more viscous nature. The swelling index of HPMC was found in the following order: HPMC 4KM > HPMC 15KM > HPMC 100KM.

![Swelling index of compacts of LER (F1-F9)](image)

4. Surface pH

The surface pH of compacts was found to be in between 6.27 to 7.00 (Fig 5), which was lying within 7 ± 1.5 units of the neutral pH. It was revealed that compacts should not cause any irritation in the buccal cavity; more over there is no significant difference in the pH among all formulations.
5. Content uniformity

The content uniformity of all formulations was shown in Fig 5. The content uniformity was found within IP limit.

6. In vitro biadhesion studies

Bioadhesion force data was reported in Fig 5. The highest bioadhesion force was observed with the formulation F9 (5.624N), whereas showed F1 (3.466N), showed least Bioadhesion force. The optimized formulation (F2) showed bioadhesion force of 4.054N. It is evident from the N of below data, that the compacts containing Carbopol 934P & HPMC showed higher bioadhesion force than compared to compacts containing Carbopol 934P & HPMC alone. The bioadhesive characters were found to be affected by the nature and proportions of the bioadhesive polymers used in the formulations. In all the formulations, as the polymer mixture concentration increased, the bioadhesion was increased. However there is increase in
the bioadhesion force was found, when the viscosity of HPMC is increased.

![Bioadhesion force profile of compacts of LER (F1-F9)](image)

**Fig 5: Bioadhesion force profile of compacts of LER (F1-F9)**

Bioadhesion force exhibited by the formulation F2 was considered satisfactory for maintaining them in the oral cavity for 9hrs. Very strong mucoadhesion could damage the epithelial lining of the buccal mucosa.

### 7. *In vitro* release studies

It has been revealed that the amount of polymer blend has the significant effect on the drug release profile. Maximum drug release was found in F1(98.42) and minimum drug release was found in F9(64.13). The results were shown in Fig 6. From the results, F2 was considered as optimized formulation. The drug release from the formulations decreased with increase in the amount of polymer blend added in each formulation. The release of drug from polymer blend matrix takes place after complete swelling of the polymer blend and as the amount of polymer blend in the formulation increase the time required to swell also increase thereby decrease in the drug release.

![In vitro drug release profile of compacts of LER (F1-F9)](image)

**Fig 6: In vitro drug release profile of compacts of LER (F1-F9)**
8. *In vitro* permeation studies

The release rate of optimized formulation (F₂) was found after 8 hours was 87.42% and observation were shown in Fig 7. It showed that there is no much significant change in the release rate compared to the *in vitro* drug release.

![Fig 7: In vitro drug permeation profile of F2 formulation](image)

9. *Ex vivo* residence time

The *Ex vivo* residence time was determined by using specially designed disintegration apparatus. The results were shown in Fig 8. The residence time of all formulations was found in the range of 460 to 680 min. As the concentration of HPMC increased, the residence time also increased. This examination reveals that the mucoadhesive capacity of polymers used in formulations. The results showed that the mixture of carbopol 934 and HPMC K4M containing group formulations showed more residence time than carbopol 934P and HPMC alone.

![Fig 9: Ex vivo residence time profile of compacts of LER](image)
10. Stability studies in human saliva
The information obtained from stability studies performed in normal human saliva would be more accurate to mimic the stability of drug and device in the oral cavity in vivo. Hence, the stability studies were performed only on the optimized formulation (F2), and obtained data are presented in Table 4. The compacts did not exhibit change in color or shape, suggesting the satisfactory stability of the drug. Physical properties of the compacts such as thickness and diameter increased slightly owing to swelling of the system in human saliva. But compacts did not collapse in the human saliva until the end of the study, confirming the sufficient strength of the compacts. It was revealed that there is no significant change in the pH.

Table 4: Stability studies in human saliva of compacts of LER

<table>
<thead>
<tr>
<th>Formulation No.</th>
<th>Color*</th>
<th>Shape*</th>
<th>Thickness(mm)*</th>
<th>Swelling Index (%)*</th>
<th>pH*</th>
</tr>
</thead>
<tbody>
<tr>
<td>F2</td>
<td>No change</td>
<td>No change</td>
<td>3.66 ± 0.011</td>
<td>344.3 ± 0.89</td>
<td>6.77 ± 0.04</td>
</tr>
</tbody>
</table>

12. *In-vivo* mucoadhesion study
The *in vivo* mucoadhesion time was determined by using rabbits for optimized formulation (F9) showed mucoadhesion time of 9 h 45 min. During the *in vivo* mucoadhesion studies, animals were also observed for irritancy, redness, dryness of mouth, salivation and colour of the mucosa. From the studies it was revealed that there was no change response of rabbits for various parameters for the optimized formulation.

Table 5: Response of rabbits for optimized formulation F2

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Color*</th>
<th>Irritancy*</th>
<th>Redness*</th>
<th>Dryness of mouth*</th>
<th>Salivation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>F2</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>None</td>
<td>No change</td>
</tr>
</tbody>
</table>

11. Stability studies
From the stability studies, it was revealed that there are no significance changes in physical parameters, bioadhesive strength and in vitro release studies.
CONCLUSION
The present research work was aimed to prepare the buccoadhesive drug delivery system for larcainidapine HCl with prolonged effect, improve bioavailability and reduce the dose and to avoid the first pass metabolism. From the study, formulation F2 was considered as best in terms of drug release, bioadhesive performance, in vivo mucoadhesion, and stability studies properties. Finally it was concluded that stable formulation could be developed by incorporating carbopol 934P and HPMC 4KM in the ratio of 1:1 for the controlled release of LER from buccoadhesive compacts with adequate bioadhesiveness and swelling properties without risk of mucosal damage. The developed formulation overcome and alleviates the drawbacks and limitations of other LERcontrolled release formulations.

ACKNOWLEDGEMENT
Authors very thankful to Apotex Research Pvt. Ltd., Bangalore and Colorcon Asia Pvt. Ltd., Verna, Goa for providing the gift samples of LER and Polymers. Authors thankful to Dr. R. Narayana Charyulu, NGSM institute of Pharmaceutical sciences, Paneer, Mangalore, Karnataka, India, for his continuous encouragement, valuable suggestions, dynamic guidance, ever readiness to solve my problems, moral support and blessings shown on me throughout the period of this work. Authors also thankful to parents and family members for his continuous encouragement, moral support and blessings shown on him throughout the period of this work. Authors also thankful to chairman, Principal, and staff, Acharya & B.M. Reddy College of Pharmacy, Bangalore for their support and providing the facilities for my project work.

REFERENCES

