5.1 SUMMARY

Oral route is most preferred route of drug administration but solubility and first pass metabolism sensitivity of drug are important characteristic to be accepted by this route. Parental route is painful drug administration system. Topical drugs are limited for topical or local treatment only.

High molecular weight drugs, poor skin penetrating drugs, poor water insoluble drugs, and extensive first pass metabolism prone drugs need alternative routes. Mucoadhesive route is becoming popular alternative for all above drugs. Following are various mucoadhesive drug delivery systems:

<table>
<thead>
<tr>
<th>Mucus membrane</th>
<th>Surface area</th>
<th>Thickness</th>
<th>Layers</th>
<th>Mucus secretion/day</th>
<th>Turnover time of mucus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buccal</td>
<td>30 cm</td>
<td>500–800 µm</td>
<td>Epithelium, basement membrane, and connective tissues</td>
<td>800-1000 ml</td>
<td>5–6 days</td>
</tr>
<tr>
<td>Nasal</td>
<td>60 mm</td>
<td>150–200 cm</td>
<td>Columnar cells, goblet cells, and basal cells</td>
<td>20 mL</td>
<td>10–15 min</td>
</tr>
<tr>
<td>Ocular</td>
<td>3–10 µm</td>
<td></td>
<td>Epithelium, Bowman’s layer, stroma, Descemet’s membrane, and endothelium</td>
<td>2–3 µL</td>
<td>15–20 h</td>
</tr>
<tr>
<td>Vaginal</td>
<td>6 to 10 cm</td>
<td>3–10 µm</td>
<td>Lamina propria and stratified squamous epithelium</td>
<td>1–4 ml</td>
<td>7 days</td>
</tr>
<tr>
<td>Rectal</td>
<td>300 cm</td>
<td>10–20 cm</td>
<td>Epithelium consists of a single layer of cylindrical cells and goblet cells</td>
<td>3 ml</td>
<td>7 days</td>
</tr>
</tbody>
</table>
Antihypertensive Candesartan drug exhibits poor water solubility. Candesartan cilexetil is prodrug of candesartan, an antihypertensive angiotensin II receptor antagonist that on action of esterase enzyme present in the intestinal wall hydrolysces to active Candesartan cilexetil moiety in gastrointestinal tract.

Prodrug form of Candesartan cilexetil has not overcome poor oral bioavailability, approximately raised 40% from 15% in humans. The reasons for candesartan’s low bioavailability and low absorption are low water solubility and efflux by drug resistance pumps in the gastrointestinal tract.

Wide research is being carried out in design and development of such systems which could increase absorption, bioavailability of poorly water soluble and extensive first pass metabolism prone drugs.

Mucoadhesive drug delivery system through buccal, sublingual, rectal and nasal mucosa can be faster and systemic mode of noninvasive drug administration to bypass first pass metabolism. Faster delivery and enhanced bioavailability of drugs is observed through mucoadhesive administration.

Present thesis comprises five well elaborated chapters related to Candesartan cilexetil buccal film development.

Chapter 1 has started with introduction to cardiovascular system, cardiovascular diseases, hypertension, neurogenic regulation of blood pressure, diagnosis, treatment, pathophysiology, complications, treatment and risk management. Further routes of drug administration introduced. Mucoadhesive drug delivery system explained with reference to details of mucus, mechanism of mucoadhesion, mucoadhesion theories. Various mucoadhesive dosage forms like solid dosage forms (tablets, nanoparticles, wafers, lozenges) and semi-solid dosage forms (Medicated chewing gums, adhesive gels) and buccal patches/films introduced in detail.
Buccal film components like mucoadhesive polymers, plasticizers, penetration or permeation enhancers, enzyme inhibitors, sweetening agents, flavoring agents and coloring agents explained with examples. Mucoadhesive film preparation methods like solvent casting method, semisolid casting, hot melt extrusion, solid dispersion extrusion, rolling method described in brief. Various physicochemical evaluation parameters useful in characterization of buccal films explored.

Problem on hand, research objectives, scope of research work, hypothesis and plan of work (organization and methodology) discussed to have outline of framework of present research work.

Chapter 2 is related to exhaustive literature review for antihypertensive drugs, angiotensin-II receptor antagonists, antihypertensive mucoadhesive films developed, mucoadhesive buccal drug delivery system. Chitosan and gelatin literature in mucoadhesive product development reviewed in detail. Market analysis of selected antihypertensive drug candesartan also performed for dose strength and dosage forms available in market.

Detail drug and excipient profiles elaborated in this chapter. Chemical structure, IUPAC name, molecular weight, solubility, indications, pharmacokinetic parameters of selected drug candesartan are summarised. Profiles of excipients like chitosan, gelatin, polyethylene glycol and EDTA are discussed.

Chapter 3 is related to experimental methods/procedures followed with respect to pre-formulation studies, optimisation of buccal film composition by statistical analysis and lastly pharmaceutical, biological and stability evaluation of developed formulation. The pre-formulation studies like confirmation of pure drug by melting point, UVmax, thin layer chromatography and solubility.
Chapter 4 is of results and discussion which comprises tables, figures, images, charts, comparisons and clarifications of observations for various aspects of buccal film development and evaluation.

Appearance, thickness and diameter, weight variation studies, percent moisture absorption, percent moisture loss, surface pH, swelling Index, mechanical properties of films (folding endurance, tensile strength, elongation time and elongation break, Young’s modulus, tear resistance), drug Content uniformity, differential Scanning Calorimetry (DSC) studies, morphological analysis by Scanning Electron Microscopy (SEM), determination of the in-vitro bioadhesion strength, determination of ex-vivo mucoadhesion time and in-vitro drug release studies are various pharmaceutical evaluation parameters performed and discussed in detail.

Biological evaluation parameters like ex-vivo permeation studies, pharmacokinetics study, ex-vivo muco irritation by histological examination and in-vitro ACE Inhibitory activity are performed and elaborated. Stability Studies as per ICH guidelines performed to determine shelf life of buccal films.

Last chapter 5 has summarised research work in the form of summary, conclusion, scope, recommendations and limitations.

The pre-formulation studies like melting point, analytical methods like FTIR study, UV spectroscopic analysis was complied with pharmacopoeias standard. Assay of Candesartan cilexetil by UB-visible spectroscopy shoed linear relationship (R2 = 0.998) between absorbance and drug concentration passing through the origin, which obeys Beer-Lambert’s law.

Pre-formulation Studies of Polymer was done. Drug interaction studies were done using FTIR. No interaction found between drug, excipients and polymer. Initially polymers of various grade selected. Viscosity of polymeric solution was measured. HPMC K4M shows highest viscosity compared to HPMC E15.
Similarly, chitosan, gelatin as polymer and PEG, PG and glycerin as plasticizers were evaluated to choose better polymer and plasticizer. An increase in polymer concentration causes an increase in the viscosity of the gel as well as formation of a gel layer with a longer diffusional path length.

Formulation optimization process was carried out using a Box-Behnken design, as it requires few runs with three or four variables. Here three variables at three levels were studied using total 17 runs.

A set of points lying at the midpoints of each edge of the multidimensional design cube as well as replicated center points were utilized to construct mathematical models and response surfaces using Design Expert® software (Version 9.0.6, Stat-Ease Inc., Minneapolis, MN, USA).

The result of ANOVA demonstrates that the model was significant for all dependent variables. Regression analysis was carried out to determine the regression coefficients. All the independent variables were found to be significant for all response variables. The quadratic model was found to be significant for both responses Y1 (Percentage Cumulative drug release) and Y2 (Mucoadhesive strength).

ANOVA results for response Y1 (Percentage Cumulative drug release) of the quadratic regression model indicate in a highly significant model, as evidenced by the F value (19.48) and p value (0.0004<0.0001) in statistical analysis. The high value of R-Squared (0.7759) indicates a good fit of the quadratic regression model to the observed responses. The value of AdjR2 is also very high (0.9122), further demonstrating a high significance of the model.

ANOVA results of response Y2 (Mucoadhesive strength) of the quadratic regression model indicate in the form of Equation 1 and 2 as a highly significant model, as evidenced by the F value 8.47 and p value (0.0025<0.0001) in statistical analysis the high value of R2 (0.817) indicates a good fit of the quadratic regression model to the observed responses. The
value of AdjR2 is also very high (0.807), further demonstrating a high significance of the model.

The validation report generated by the design expert software, predicts a maximum CDR of 90.19 and mucoadhesive strength of 30.38 for optimized batch.

So above result indicates that both the factors play an important role in the formulation of film containing candesartan. The data of pure error and lack of fit can provide a mean response and an estimate of pure experimental uncertainty.

The residuals are the difference between observed and predicted values. The ANOVA for the dependent variables demonstrates that the model was significant for all response variables. The effects are like, the amount of chitosan, HPMC and gelatin were found to be significant, along with its quadratic and interaction terms for all the dependent variables.

Five different batches from Box-Behnken design suggested from overlay graph were selected for preparation and further details evaluation.

Finally five batches with changes in concentration and composition of HPMC, EDTA, glycerin, gelatin and chitosan were developed. (Table 5.1) Formulation of mucoadhesive film was done by solvent casting method and specialized film forming instrument manufactured by VJ instrument, Karanja Lad, Washim, MS, India.

<table>
<thead>
<tr>
<th>Table 5.1: Formulae for various film formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ingredients</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
</tr>
<tr>
<td>HPMC K4M</td>
</tr>
<tr>
<td>Chitosan</td>
</tr>
<tr>
<td>Component</td>
</tr>
<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td>Gelatin</td>
</tr>
<tr>
<td>Glycerin</td>
</tr>
<tr>
<td>EDTA</td>
</tr>
<tr>
<td>1% Glacial acetic acid</td>
</tr>
<tr>
<td>Purified water</td>
</tr>
</tbody>
</table>

The prepared film are evaluated their physical appearance. Candesartan-chitosan films of F-1, F-3 and F-4 were homogenous, clear and flexible. F2 and F-5 was found less transparent and flexible. The additions of enhancers like EDTA to the prepared films increased their flexibility and enhanced their moisture uptake.

All the films were found uniform in weight variation study. Standard deviation of all the films ranged between 0.684 and 1.103. The optimized F-3 film was found to have weight of 22.1±1.103 mg.

All the drug-loaded films have uniform thickness throughout. The average thickness of all the films ranged between 0.110 ± 0.059 to 0.183 ± 0.066 cm, The optimized F-3 film was found to have thickness of 1.127± 0.078 cm.

The surface pH of the patches was determined in order to investigate the possible side effects; since an acidic or alkaline pH may cause irritation to the buccal mucosa. The surface pH was measured by placing a pH paper on the surface of the swollen film. The surface pH of all formulations was within ± 0.5 units of the neutral pH and hence no mucosal irritation were expected and ultimately achieve patient compliance.

In swelling index study, all the films hydrated very quickly and reached 80% hydration after just few minutes. Maximum hydration (115-120%) was obtained with formulations containing Chitosan i.e. F3. Films containing only HPMC showed a slightly lower hydration by 4-8%.
Fragmentation was already evident at 60 minute in all formulae. The highest losses were observed for films containing Chitosan as mucoadhesive polymer; for some of these films fragmentation was so high that it was not possible to recover and handle the film from the PBS 6.6, even immediately after the beginning of the experiment (F-3).

Percent elongations, folding endurance, Young's modulus, tensile strength and tear resistance like mechanical properties of films evaluated by developing Stress-strain curves. Texture analyser instrument used in measurement of these properties.

Folding endurance of 3 films was determined by repeatedly folding one film at the same place up to 200 times till it broke or folded, which is considered satisfactory to reveal good film properties. Hence it was taken as the end point. Folding endurance did not vary when the comparison was made between plain films and drug loaded films.

The mechanical properties of the film gives idea about to what extent the film can withstand the force or stress during processing, packaging, transport and handling. The desirable characteristics of film are moderate tensile strength, low elastic modulus, high % strain and high load at yield. The polymer should give soft but tough film.

Tensile strength (TS) is the maximum stress applied to a point at which the patch specimen breaks and can be computed from the applied load at rupture as a mean of three measurements and cross sectional area. Tensile strength of formulae F-1 to F-5 found in range 3.96 to 9.06 MPa. 8.21, 8.10, 9.06, 4.53 and 3.96 Mpa were tensile strengths of F1 to F5 formulae respectively.

Changing plasticizer concentration showed different mechanical properties than the gelatin and glycerin. F-3 film exhibited good mechanical properties.
The results of content uniformity indicated that the drug was uniformly dispersed. Recovery was possible to the tune of 88 to 97%. Maximum drug content was F3 Batch was 97± 0.74 found.

In-vitro drug release from the film was studied using USP rotating paddle dissolution test apparatus. The release studies were performed at 37 ± 0.5 °C, at a rotation speed of 50 rpm. Buccal film of dimensions (1x 1 cm), found to be equivalent to 1 mg candesartan /film. The amount of drug released at each time interval was calculated and the cumulative amount of drug released was calculated as a function of time to construct the drug release profile. Marketed Tablet form of Candesartan cilexetil showed considerably poor releases pattern compared to films.

In vitro drug release of prepared film showed that Candesartan cilexetil was rapidly released during the first 1.5 h (30%), and the release was completed after 5 hours. Percent drug release after 3 hours was found out to be 82% for film F-3 and for films of batches F1, F-2, F-4 and F-5 found to be above 65 to 74%.

Data of drug released of batches also evaluated and it showed that prepared buccal films follows Higuchi pattern of drug release. The percentage of the released drug was found in range of 74 - 96%. F-3 batch shown highest drug release of 96.21% as compared to other batches.

Mucoadhesive strength was determined by using modified physical balance method. Film mucoadhesion times varied from 90 to 120 min in various batches. However, F-3 showed the highest adhesion time of 121 min whereas the films from F-4 showed the lowest mucoadhesion time of 91 min. This difference depends upon several factors (Polymer selection and film thickness are most important) that affect the effectiveness of such a formulation.

First of all, the use of Chitosan favors hydration and the outward diffusion of the drug from the film matrix. In fact, when using Chitosan, mucoadhesion time always resulted high, because the polymer although manifesting
decisively higher swelling is less water affined and hence tends to retain its structure better than gelatin that, in turn, is better dissolved.

The ex-vivo residence time of Candesartan cilexetil films was evaluated by assessing the time required for these films to detach from goat buccal mucosal membrane fixed in a well stirred beaker. The Buccal permeation test planned for optimized batch only. The percentage of the released drug was 72.37% Found. Buccal film is intended to be delivered by buccal route for either local or systemic action. In either case, it has to be adhered to the buccal mucosa for a prolonged period of time.

Therefore, it must display good mucoadhesive characteristics. It was interesting to note that there was no noteworthy effect of either penetration enhancer or plasticizer in the mucoadhesive strength of films. Bioadhesion strength was found in range of 34.41 to 49.02 gm for F-1 to F-5 formulae. The maximum buccoadhesive strength has observed in the formulation F-3 of 49.25.

Thermal analysis of film was carried out using DSC. The DSC pattern of film, showed complete disappearance of the polymer characteristic melting point peak indicating that no interaction between polymer and drug.

Film morphology the optimized selected formulation was characterized by scanning electron microscopy (SEM). It shows a uniform distribution of the drug within the film matrix. Fresh and stored film showed no variation which indicated good stability of selected optimized composition.

Stability studies stable as per ICH guidelines shown that product is fairly stable. The films does not show any change in appearance and flexibility. The drug content and surface pH was found almost constant for up to two months. The in-vitro dissolution time of the films after the stability study was also found to be not changed. In vitro stability evaluation of optimized formulation F-iii with different environmental conditions, confirms the potential of films for longer storage.
Absolute bioavailability of antihypertensive angiotensin II receptor blocker Candesartan cilexetil is relatively poor at 15% (Candesartan cilexetil tablets) to 40% (Candesartan cilexetil solution). Its IC50 is 15 µg/kg. Oral administration shows low bioavailability, approximately 15% in humans, due to its low water (pKa 6.0).

Hence, solubility and efflux by drug resistance pumps in the gastrointestinal tract overcome by developing mucoadhesive buccal film of Candesartan cilexetil with satisfactory physicochemical parameters, permeability, drug release and stability too.

Thus present research work has successfully overcome this poor bioavailability problem through mucoadhesive buccal film formulation using HPMC, chitosan, gelatin as polymer blend, glycerin as plasticizer and EDTA as permeation/penetration enhancer.

Buccal film composition optimised by Box-Behnken design and manufactured by solvent casting method. Based on pharmaceutical characterization, in-vitro and ex-vivo biological evaluation and stability studies, batch F-III found to be more promising buccal film composition in treatment of hypertension.
Table 5.2 Summary of Results of Pharmaceutical Evaluation of Various Candesartan-Chitosan buccal film batches

<table>
<thead>
<tr>
<th></th>
<th>F -1</th>
<th>F -2</th>
<th>F -3</th>
<th>F -4</th>
<th>F -5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mass Uniformity (mg)</td>
<td>35.2 ± 1.003</td>
<td>30.6 ± 0.684</td>
<td>32.1 ± 1.103</td>
<td>32.4 ± 0.007</td>
<td>43.2 ± 0.892</td>
</tr>
<tr>
<td>Thickness (cm)</td>
<td>0.110 ± 0.059</td>
<td>0.157 ± 0.033</td>
<td>0.107 ± 0.078</td>
<td>0.140 ± 0.010</td>
<td>0.183 ± 0.066</td>
</tr>
<tr>
<td>Percent moisture absorption</td>
<td>4.3± 0.06</td>
<td>3.2± 0.84</td>
<td>6.8± 1.13</td>
<td>4.6± 1.07</td>
<td>3.4± 1.82</td>
</tr>
<tr>
<td>Percent moisture loss</td>
<td>4.3 ± 0.032</td>
<td>3.4 ± 0.45</td>
<td>2.6 ± 0.04</td>
<td>3.2 ± 0.07</td>
<td>5.7 ± 0.2</td>
</tr>
<tr>
<td>Surface pH</td>
<td>6.5± 0.42</td>
<td>6.5± 0.51</td>
<td>6.5 ± 0.37</td>
<td>6.0± 0.12</td>
<td>6.0± 0.32</td>
</tr>
<tr>
<td>Folding Endurance (Times)</td>
<td>&gt;200</td>
<td>&gt;200</td>
<td>&gt;200</td>
<td>&gt;200</td>
<td>&gt;200</td>
</tr>
<tr>
<td>Tensile Strength (MPa)</td>
<td>8.219 ± 0.105</td>
<td>8.103 ± 0.028</td>
<td>7.068 ± 0.124</td>
<td>4.537 ± 0.173</td>
<td>3.965 ± 0.013</td>
</tr>
<tr>
<td>% elongation</td>
<td>39.5</td>
<td>42.5</td>
<td>44.5</td>
<td>33.5</td>
<td>43.8</td>
</tr>
<tr>
<td>Tear resistance (gm)</td>
<td>800</td>
<td>700</td>
<td>1100</td>
<td>800</td>
<td>900</td>
</tr>
<tr>
<td>Young's Modulus</td>
<td>130.5</td>
<td>150.7</td>
<td>124.6</td>
<td>145.6</td>
<td>136.5</td>
</tr>
<tr>
<td>Swelling Index (60 min)</td>
<td>97</td>
<td>109</td>
<td>112</td>
<td>106</td>
<td>99</td>
</tr>
<tr>
<td>DSC Studies</td>
<td>No polymer –drug interaction found</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEM Studies</td>
<td>Uniform, homogeneous and continuous appearance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Average % Drug Content ± SD</td>
<td>In-vitro drug release After 350 min</td>
<td>Bioadhesive Strength (gm)</td>
<td>Ex- vivo Muco-adhesion time (min)</td>
<td>In-vitro ACE Inhibitory Activity</td>
</tr>
<tr>
<td>--------------------------</td>
<td>----------------------------</td>
<td>-------------------------------------</td>
<td>---------------------------</td>
<td>----------------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td></td>
<td>91±0.31</td>
<td>74.37</td>
<td>46.77±0.720</td>
<td>92 ± 2.951</td>
<td>92 ± 0.082</td>
</tr>
<tr>
<td></td>
<td>92 ± 0.082</td>
<td>79.66</td>
<td>35.02 ± 0.034</td>
<td>102 ± 2.842</td>
<td>70.21±0.083</td>
</tr>
<tr>
<td></td>
<td><strong>97 ± 0.74</strong></td>
<td><strong>96.21</strong></td>
<td><strong>49.25 ± 0.082</strong></td>
<td><strong>121 ± 1.987</strong></td>
<td><strong>89.44±0.03</strong></td>
</tr>
<tr>
<td></td>
<td>88 ± 0.59</td>
<td>80.12</td>
<td>34.41 ± 0.833</td>
<td>91 ± 2.923</td>
<td>74.41±0.065</td>
</tr>
<tr>
<td></td>
<td>79 ± 0.49</td>
<td>81.25</td>
<td>39.07 ± 0.134</td>
<td>94 ± 2.956</td>
<td>79.71±0.105</td>
</tr>
</tbody>
</table>

Figure 5.2: Optimised F-3 batch of Candesartan cilexetil
Specialized designed film former machine of VJ instrument, Karanja Lad, Amravati used to prepare films from final optimized batch F-3.

Figure 5.1: Film former Machine by VJ Instrument, Amravati used for final optimized buccal film formation
5.2 CONCLUSION

The ease of access and avoidance of the hepatic metabolism enable buccal drug delivery for being a potential alternative conventional oral drug delivery and parental administration which suffer from certain limitations. Almost 80% of the current commercially available formulations are limited to tablet.

Oral buccal dosage forms will continue to be an exciting research focus for improving drug absorption especially for the new generation of the so called ‘biologics’, however, the palatability, irritancy and formulation retention at the site of application need to be considered during design of such formulation.

Patient compliance always remains the major concern of research for all researchers working in the field of pharmacy and specially pharmaceutics. In the resent era research is carried out extensively to formulate and fabricate a drug delivery system with improved effectiveness, safety and patient compliance.

One of those delivery systems is buccal film dosage form. Mucosal membrane of oral cavity allows high permeation to certain drugs having high blood perfusion. Drugs with poor bioavailability as well as with shorter half-life can be administered easily.

Candesartan ciloxetil is a potent, highly specific angiotensin II type 1 receptor antagonist with anti-hypertensive activity and blood pressure response is dose related over the range of 2 to 32 mg. It is facing challenge of poor water solubility and bioavailability in traditional dosage forms.

*Candesartan- Chitosan* buccal films provide large surface area that leads to rapid disintegration and dissolution in the oral cavity due to which it promotes the systemic absorption of Active pharmaceutical ingredient. There is no need of chewing and swallowing or no risk of choking.

The film increases the systemic bioavailability of the drugs, as it by passes the hepatic first pass metabolism. Drug can be protected from degradation by GI
enzymes and the acidic environment. There is rapid onset of action and minimum side effects. Self-administration and taste masking is possible. Accurate dosing compared to liquid dosage forms is possible. It prolongs the residence time of the dosage form at the site of absorption, hence increases the bioavailability.

There is ease of administration to pediatric, geriatric patients, and also to the patients who are mentally retarded, disabled or non-cooperative. Films give good mouth feel and good stability as compared to tablets or lozenges.

Candesartan, an antihypertensive angiotensin II receptor blocker, is rapidly and completely bio-activated by ester hydrolysis at the ester link to form the active Candesartan cilexetil during absorption from the gastrointestinal (GI) tract.

Candesartan cilexetil is prodrug of candesartan, an antihypertensive angiotensin II receptor antagonist that on action of esterase enzyme present in the intestinal wall hydrolyses to active Candesartan cilexetil moiety in gastrointestinal tract.

Prodrug form of Candesartan cilexetil has not overcome poor oral bioavailability, approximately raised 40% from 15% in humans. The reasons for candesartan’s low bioavailability and low absorption are low water solubility and efflux by drug resistance pumps in the gastrointestinal tract.

In the present study, buccal films of Candesartan cilexetil were prepared by solvent casting method employing polymer such as HPMC\textsubscript{K4M}, Chitosan, and gelatin along with permeation enhancers EDTA in different combinations. Films evaluated for following parameters:

- Appearance
- Weight variation studies
- Thickness and Diameter
- Percent moisture absorption
- Percent moisture loss
- Surface pH
- Swelling Index
- Mechanical properties of films
  - Folding endurance
  - Tensile Strength
  - Elongation time and elongation break
  - Young’s modulus
  - Tear resistance
- Drug Content uniformity
- Differential Scanning Calorimetry (DSC) studies
- Morphological analysis by Scanning Electron Microscopy (SEM)
- Determination of the in-vitro bioadhesion strength
- Determination of ex-vivo mucoadhesion time
- In-vitro drug release studies

Technological issues such as rheology of the casting solution, mechanical properties of the film, upscaling and the stability of produced films taken into consideration with required efforts. Appearance, taste, drug load, mucosal irritation, safety and pharmacokinetic and pharmacodynamics properties are also evaluated with equal importance.

The optimized batch found transparent, uniform, flexible, and without bubbles. It showed maximum in-vitro drug release and fairly good amount of drug permeation through the membrane in 6 hr with satisfactory physical stability. The present study indicated enormous potential of mucoadhesive buccal films containing *Candesartan cilexetil* for systemic delivery with an added advantage of circumventing hepatic first pass metabolism.

Following are most important remarks of present research work:
- Mucoadhesive films containing candesartan can be formulated by solvent casting techniques, using different mucoadhesive polymers (Chitosan, HPMC, gelatin) alone and in combination with EDTA. Five films showed satisfactory mucoadhesive characteristics.
➢ Incorporation of EDTA in the films enhanced the permeability of candesartan
➢ The mechanism of drug release from all films was found to be diffusion controlled release and permeation of drug followed Higuchi kinetics.
➢ It can be concluded that after 3 months storage under the specified conditions, negligible changes were observed in the drug content.
➢ It can be concluded that mucoadhesive films of candesartan containing chitosan, HPMC, gelatin with glycerol amongst optimized batches exhibit best formulation can be a promising drug delivery system in maintaining buccal cavity hygiene and used as a better alternative drug delivery system for the controlled release with improved bioavailability in the treatment of hypertension.

Successful mucoadhesive films of Candesartan cilexetil are prepared and evaluated with more than 97 % of Candesartan cilexetil release which will surely give relief for hypertensive patients as non-invasive delivery system of candesartan.

Novel buccoadhesive film for systemic release of Candesartan cilexetil is developed by using chitosan, gelatin and HPMC in appropriate ratio.

Chitosan is not only film forming but also possess good bioadhesion properties. The drug release rate increases on inclusion of gelatin into the chitosan base matrix system and modified kinetic study with drug Candesartan.

It is already proven and observed in study that chitosan-EDTA conjugates exhibits the lowest amount of remaining free amino groups, seem to be a useful tool in overcoming the enzymatic barrier for perorally administered therapeutic drug.

So lastly, we conclude that, chitosan with HPMC and gelatin can meet the ideal requirement for buccal mucoadhesive Candesartan cilexetil film, which can be good way to bypass the extensive hepatic first pass metabolism of candesartan, substantial dose reduction and increase bioavailability.
5.3 SCOPE, RECOMMENDATION

The present research will have significant impact in the community, as this will provide a novel efficacious formulation for drug Candesartan cilexetil which will protect drug from first pass hepatic metabolism and degrading effects of pH and different enzymes.

There is need to administer drugs through new drug delivery systems to improve bioavailability, absorption and to avoid first pass metabolism. Mucoadhesive system is a good option to attain above drug delivery targets.

In mucoadhesive, buccal adhesive systems are more advantageous in terms of application, accessibility, withdrawal, long contact time, less enzyme attack and high patient compliance.

Bio-adhesions to mucosal surface lead to better local delivery with increased drug concentration gradient at the application site and thus enhances bioavailability of drugs. Local administration of buccal film is very useful in treatment of oral ulcers, inflammation, cancer, allergy and many more local disorders.

Bio-adhesions to mucosal surface lead to systemic delivery of drug also and bypasses hepatic first pass metabolism. Use of penetration and permeation enhancers, pH modifiers, enzyme inhibitors and nanoparticulate drug incorporation improves bioavailability through mucoadhesive dosage forms.

Solubility and efflux by drug resistance pumps in the gastrointestinal tract overcome by developing mucoadhesive buccal film of Candesartan cilexetil with satisfactory physicochemical parameters, permeability, drug release and stability too.

Developed mucoadhesive films can be preferred over adhesive tablets in terms of flexibility and comfort. In addition, they can circumvent the relatively short residence time of oral gels on the mucosa, which are easily washed
away and removed by saliva. Moreover, due to local delivery, the films also bypass the first pass metabolism, releases drug rapidly and treat the disease more effectively than tablet. An ideal film is developed which is flexible, elastic, and soft, yet adequately strong to withstand breakage due to stress from mouth movements. It also possesses good mucoadhesive strength in order to be retained in the mouth for the desired duration of action.

Further buccal films can be made which comprise of an impermeable backing layer, a drug-containing reservoir layer which releases the drug in a controlled manner, and a mucoadhesive surface for mucosal attachment. Such films may be used to deliver drugs directly to a mucosal membrane only from one side.

These are similar to those used in transdermal drug delivery. They present a greater patient compliance compared with tablets owing to their physical flexibility that causes only minor discomfort to the patient. They also offer advantages over creams and ointments in that they provide a measured dose of drug to the site.

Prepared candesratan cilexetil buccal film is ready to transfer technology made available by researcher.

*Candesartan* cilexetil - *Chitosan* buccal films provide large surface area that leads to rapid disintegration and dissolution of drug in the oral cavity due to which it promotes the systemic absorption without need of chewing and swallowing or no risk of choking.

In-vitro and ex-vivo studies films confirms that this developed buccal film increases the systemic bioavailability of the drugs, as it by passes the hepatic first pass metabolism. Drug can be protected from degradation by GI enzymes and the acidic environment. There is rapid onset of action and minimum side effects. Self-administration and taste masking is possible.
Figure 5.3: Graphical representation of Candesartan cilexetil buccal film

Characteristics of film:

- From simple perti dish to sophisticated film former machine can provide desire size and shape film
- 2 cm² is the most suitable size for administration and handling by patients
- 2-4 mg of drug can be loaded from a 2-cm² film in 1 day
- Square or circular shape appears to be most acceptable for buccal film use
- Thickness of film is important for drug loading as well as retention time and drug release over a period of desired time
- Maximal duration of buccal drug retention and absorption is approximately 1-2 h because due to food and/or liquid intake may require removal of delivery device.
5.4 LIMITATIONS

In present research work, *Candesartan* cilexetil buccal films are prepared using chitosan, HPMC-K4M, gelatin, glycerin and EDTA and evaluated for various pharmaceutical as well as ex-vivo biological evaluation parameters including *in-vitro* ACE Inhibitory activity. *Candesartan* cilexetil approved dose is 4-32 mg per day. 2cm² surface area of approximately 1 mm thickness film is loaded with 1-2 mg drugs. Hence different dose range from 4-32 mg per day can be easily managed by cutting appropriate size. Developed films in treatment of hypertensive patients possesses following characteristics:

- Mechanically strong still flexible film
- Soft film for ease of buccal administration
- Dose management by cutting films in appropriate size
- Rapid, maximum drug release
- Improved solubility, bioavailability and permeation reduces dosing frequency
- Better patient compliance compared to tablets/injections

Still there can be few limitations of developed *Candesartan- Chitosan* buccal films like:

- This buccal film can lead to fast elimination of drugs with saliva or ingestion of film along with food intake, which will require frequent dosing.
- Buccal films are generally hygroscopic in nature and hence longer preservation through costly packaging systems needs precaution
- High degree of accuracy in dosing management through unit dose of the film lead to critical studies for therapeutic failure, non-reproducible effects and sometimes toxicity incidence.
- Sophisticated instrument which can give control over uniform heating, humidity, dust and thickness of film is key requirement for production of films at large scale.

Following are few more specific limitations of study:

- *In-vivo* determination of buccal mucosa diffusion must be carried out to establish *in-vitro* and *in-vivo* correlation comparison with prepared formulation and marketed formulation.
Anti-hypertensive studies with animal model will again provide clearer picture about exact efficacy of Candesartan cilexetil buccal film.

There is also lack of detail toxicological evaluation of the prepared Candesartan cilexetil buccal film, which is must to bring dosage forms in market.

Key factor for producing suitable buccal films is the mucoadhesive time and drug release, which depends on polymer selection, properties of active pharmaceutical ingredient and excipients combination. Acceptable taste, palatability like properties of buccal films also depends on viscosity. Safe and inert excipients are required for optimal patient compliance.

Thickness, mucoadhesive time and swelling index are important factors for drug release and thus pre-clinical and clinical studies will be most reproducible than in-vitro or ex-vivo studies. Actual patient use of buccal films can be get affected by saliva secretion, spitting, eating or drinking of liquid food. Effect of swallowing buccal films on drug concentration and overall therapeutic efficacy is also key factor.

Appropriate, safe and inert packaging requirement increases cost of film production. Bio-relevant data, appropriate definitions, methods, requirement and evaluation parameters are not provided by any Pharmacopoeias. Hence, present research can be further evaluated to perform in-vivo drug release studies in suitable animal model.

Further work is also recommended to support its efficacy claims by long-term pharmacokinetic and pharmacodynamic studies in human beings. Thus clinical investigation will only decide its suitability of dosage form in the actual clinical practice and market success.