INTRODUCTION

Buccal delivery of drugs provides an attractive alternative to the oral route of drug administration, particularly in overcoming deficiencies associated with the latter mode of dosing. Problems such as first pass metabolism and drug degradation in the GIT environment can be circumvented by administering the drug via buccal route. Buccal delivery offers a safer mode of drug utilization, since drug absorption can be promptly terminated in cases of toxicity by removal of dosage form from the buccal cavity. A suitable buccal drug delivery system should possess good bioadhesive properties, so that it can be retained in the oral cavity for the desired duration [1, 2, 3].

In case of poorly soluble drugs, solubility can be improved by various approaches. Cyclodextrin complexation process has been emerged as effective tool to increase solubility of poorly soluble drugs. Cyclodextrin are cyclic oligosaccharides composed of α-D-glucopyranose units. Although represented on 2-dimensional paper and assayed for Ramipril using UV spectrophotometer (Varian Cary 100, Australia) at 210 nm against blank prepared using same concentration of β-CD and HP-β-CD in double distilled water.

Preparation of the physical mixture:
Physical mixtures, Ramipril: β-CD (1:1) and Ramipril: HP-β-CD (1:1), were prepared by simple blending in a glass mortar.

Preparation of solid inclusion complexes:
Kneading method (Kn):
Stoichiometric quantities of Ramipril and cyclodextrin triturated in a mortar with a small volume of water-methanol solution. The thick slurry was kneaded for 45 min and then dried at 40°C. Dried mass was pulverized and sieved through (#100).

Co evaporation method (COE):
The aq. solutions of cyclodextrin were added to an alcoholic solution of drug. The resulting mixture was stirred for 1 hr and evaporated at 40°C to get the required solid inclusion complex.
a temp of 45°C until dry. The dried mass was pulverized and sieved through (#100).

Co-grinding (COG)

Drug was triturated with minimum quantity of methanol in a glass mortar until it dissolved. Then cyclodextrin were added and suspension was triturated rapidly at room temperature until solvent evaporated.

Freeze –Drying Method (FD)

Physical mixtures of drug and cyclodextrin in a molar ratio of 1:1 were added to 500 ml double distilled water and stirred for 5 days. The suspension was freeze dried (Jishin® freeze Dryer), and obtained freeze-dried complex was pulverized and sieved through (<39μm).

Melting method (MELT)

The drug- cyclodextrin ratio (1:1 Molar) were accurately weighed, mixed in crucible, and the mixture was kept for melting on water bath with constant stirring. The mixture was cooled slowly at room temperature. The product was placed in desiccators. The solidified product was transferred to a clean mortar, triturated and passed through sieve no.16 and 20.

Spray Drying Method (SD)

A mixture of drug and cyclodextrin were dissolved in 250 ml of water. The resultant solution was spray dried using a spray dryer. The spray drying was done at the following sets of conditions: air flow rate at 400 Nl/h, spray nozzle with a diameter 0.7 mm. The inlet temperature was kept at 120°C and out let temperature 90°C ± 2°C. The vacuum in the system was 60 mmWc and aspiration rate was 40 m Bar. The product thus obtained was collected, packed, doubly wrapped in an aluminium foil and stored in a desiccators till further use.

Evaluation of Solid Complexes

Determination of drug content

Drug- cyclodextrin complex equivalent to 10 mg of drug was stirred with 100 ml of methanol for 60 minutes, and then the solution was filtered and treated as stock solution containing 100 μg/ml drugs. From this stock solution the concentration of 10 μg/ml was prepared and the drug content was determined using the calibration curve of pure drug in methanol spectrophotometrically at 210 nm using methanol as blank.

Saturation Solubility Studies

The saturation solubility study was carried out to determine increase in the solubility of pure Ramipril as compared with the physical mixture and inclusion complexes. Excess amount of drug, physical mixture and inclusion complexes were added to the 250 ml conical flasks containing 25 ml of double distilled water. The sealed flasks were shaken for 24 hr at room temperature followed by equilibrium for three days. Then, the aliquots were withdrawn through whatman filter paper. The concentration of Ramipril was determined by UV spectrophotometer at 210 nm.

Characterization of the physical mixture and inclusion complexes

UV spectroscopic study [9]

Complex formation between Ramipril and cyclodextrin were studied by UV spectroscopic method. 10 mg Ramipril were weighed accurately and dissolved in 100 ml methanol. Diluted suitably and spectra of drug recorded at 210 nm. Same method was used only Ramipril –cyclodextrin complex equivalent to 10 mg of Ramipril were weighed accurately and dissolved in 100 ml methanol. Diluted suitably and spectra of complexes were recorded at 210 nm. The change in the absorbance of drug in the complexes was recorded.

Fourier Transform Infrared spectrophotometry [FT-IR]

FT-IR has been employed as a useful tool to identify the drug excipient interaction. Samples were analyzed by potassium bromide pellet method in an IR spectrophotometer (Varian, Australia) in the region between 4000 to 400 cm⁻¹. Complex formation was evaluated by comparing the IR spectra of the solid complex and of the drug.

Powder X-ray Diffraclometry [PXRD]

The drug Ramipril, β-CD, HP-β-CD, drug-β-CD complexes, drug-HP-β-CD were subjected to powder XRD. To study X-Ray Diffraction pattern, the sample was placed into aluminium holder and the instrument was operated between initial and final 28 angle of 5-50° respectively.

Differential Scanning Calorimetry [DSC]

The drug Ramipril, β-CD, HP-β-CD, drug-β-CD complexes and drug-HP-β-CD complexes were subjected to DSC study. Differential scanning Calorimetry was performed on a METTLER DSC 30. Ramipril, β-CD, HP-β-CD, drug-β-CD complexes, drug-HP-β-CD complexes analyzed by heating at scanning rate of 20°C/minute over a temperature range 25 to 300°C.

In-vitro dissolution studies

Drug release studies were performed in triplicate at 37 ± 0.5 °C employing USP apparatus II at 75 rpm. Dissolution study was carried out in two dissolution media (Phosphate buffer of pH 6.8 and double distilled water). Dissolution studies were performed on pure drug (10 mg) and the complexes containing an equivalent amount of the drug. Aliquots of the periodically withdrawn samples (5 ml) were analyzed spectrophotometrically at 210 nm, and were replaced with an equal volume of plain dissolution medium [10].

Formulation of buccal patches

Kneading complex of β-CD and complex of HP-β-CD was selected for the formulation of buccal patch. The buccal patches were prepared by solvent casting method. HPMC K15 and Poloxamer WSR205NF polymers in ratio of 0.5 to 1 % were incorporated in different buccal patches. The concentration of plasticizer was finalized differently for the two polymers from the plasticity of the film. It is varied from 10% to 13% for the patch. The composition of different formulation is shown in Table 1.

Table 1: Composition of Mucoadhesive buccal patch

<table>
<thead>
<tr>
<th>Component</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramipril</td>
<td>0.5%</td>
</tr>
<tr>
<td>β-CD</td>
<td>1%</td>
</tr>
<tr>
<td>HP-β-CD</td>
<td>1.5%</td>
</tr>
<tr>
<td>Plasticizer</td>
<td>10%</td>
</tr>
</tbody>
</table>

Evaluation of buccal patch

Folding Endurance:

Folding endurance was determined by repeatedly folding at the same place until it broke. The number of times the film folded at the same place without breaking was the folding endurance value.

Patch thickness

Patch thickness measured at five different randomly selected spots using screw gauge.

Content uniformity

The buccal Patch dissolved in phosphate buffer pH 6.8. The n solution is diluted and filtered through whatman filter paper, and analyzed at 210 nm using a UV Double beam spectrophotometer.

Surface pH study

The Patch was allowed to swell by keeping it in contact with 2% agar gel plate for 2 hrs at room temperature. The pH was measured by bringing the electrode in contact with the surface of the patch and allowing it to equilibrate for 1 min.

Swelling study

Buccal patches were weighed individually (W1) and placed separately in 2% agar gel plates with the core facing the gel surface
and incubated at 37 ± 1°C. At regular intervals (1, 2, 3, 4, 5 & 6 hours) the patches were removed from Petri dishes and excess water removed carefully using filter paper. The swollen patch was then reweighed (W2) and the swelling index (SI) were calculated using the formula given in equation 1.

\[
SI = \frac{[W2-W1] + W1 \times 100}{W1} \quad \text{---------------- (1)}
\]

Where, W1 = initial weight of the patch
W2 = final weight of the patch [11].

In Vitro Drug Release:
The in vitro drug permeation study was carried out using Keshery chien diffusion glass cell. The upper and lower compartment was filled with saline phosphate buffer solution. Cellophane membrane was kept in between two compartment and whole assembly kept at 37 ± 0.2°C. The amount of drug permeated was determined by removing an aliquot of 1ml sample at appropriate time interval and stirred at 50 rpm on magnetic stirrer.

In vitro mucoadhesive strength [12]
The strength of bond formed between the patch and mucosa membrane excised from goat mucosa was determined using two-arm balance method. Fresh goat mucosa section was fixed on the plane surface of glass slide (3×5 cm) attached (with adhesive tape) to bottom of smaller beaker, kept inverted in 500 ml beaker attached to the bigger beaker. Isotonic phosphate buffer (pH 6.8) was added to the beaker up to the upper surface inverted beaker with goat mucosa. The patch was stuck to the lower side of the upper clamp with cyanoacrylate adhesive. The exposed patch surface was moistened with phosphate buffer (pH 6.8) and left for 30s for initial hydration and swelling. Then the platform was slowly raised until the patch surface came in contact with mucosa. Two sides of the balance were made equal before study. After a pread (50 gm) time of 2 minutes, water was added to the polypropylene bottle present in another arm, until the patch was detached from the mucosa. The water collected in the bottle was measured and expressed as weight (gm) required for the detachment. The force measurement was repeated 3 times for each formulation. The following parameters were calculated from the bio adhesive strength using equation 2 & 3.

\[
\text{Force of adhesion (N)} = \frac{( \text{Bio adhesive strength (gm)} \times 9.81 )}{1000} \quad \text{---------------- (2)}
\]

\[
\text{Bond strength (Nm)} = \frac{\text{Force of adhesion}}{\text{Disk surface area}} \quad \text{----- (3)}
\]

Ex-Vivo drug permeation studies
Permeation studies were carried out using the Keshery chien diffusion glass cell. Goat oral mucosa was used as the model membrane. The buccal pouch of the freshly sacrificed goats was procured from the local slaughter house. The buccal mucosa was excised and trimmed evenly from the sides and then washed in phosphate buffer of pH 6.8 and used immediately. The membrane was stabilized before mounting in order to remove the soluble components. The mucosa was mounted between the donor and receptor compartments. The receptor compartment was filled with phosphate buffer of pH 6.8 which was maintained at 37 ± 0.2°C and the hydrodynamics were maintained by stirring with magnetic bead at 50 rpm.

FT-IR study of buccal Patch
The sample of Ramipril with HPMC K15 was prepared by simple blending with KBr. The scanning range used was 4000 to 400 cm⁻¹. Then the spectra were comparatively analyzed for drug-carrier interaction.

RESULTS AND DISCUSSION
Dissolution study shows that the dissolution rate of Ramipril has been enhanced to a great extent. The drug release with β-cyclodextrin was 78.87 ± 1.96 in distilled water and 83.7 ± 1.72 in phosphate buffer pH 6.8 with kneading method. The drug release with HP β-cyclodextrin was 81.4 ± 1.34 in distilled water and 85.34 ± 1.32 in phosphate buffer pH 6.8 with Kneading method. Drug-excipient compatibility study using UV spectroscopy and FTIR showed absence of any well-defined chemical interactions. DSC and XRD analysis data concludes that Ramipril cyclodextrin complex showed enhancement of Ramipril dissolution due to the conversion of Ramipril in to a less crystalline and/or amorphous form. All formulations gave the satisfactory results in terms of thickness, drug content, swelling index, folding endurance and surface pH as shown in table 2. Appropriate swelling behaviour of a buccal adhesive system is essential for uniform and prolonged release of the drug and effective mucoadhesion. The Patch of 0.5% HPMC K15 exhibited in vitro release of 81.16% through cellophane membrane and 75.72% release through egg membrane and the Patch of 0.5% Poloxomer WSR205 NF exhibit in vitro release of 77.24% through cellophane membrane and 71.08% release through egg membrane in 8 hrs showing good mucoadhesive strength and mucoadhesive time. The Optimized patch was subjected to ex vivo studies through goat buccal mucosa showed 63.49% release in 8 hrs. Kinetic treatment of drug release data revealed that the Matrix model most appropriately fits the in vitro diffusion data.

Phase Solubility Analysis
Phase solubility diagrams for Ramipril with β-CD and HP-β-CD in distilled water are shown in fig.1 and fig.2. The solubility of Ramipril increased in linear fashion as a function of the concentration of β-CD and HP-β-CD, showing A1 type phase solubility diagram with slopes of less than unity. According to Ito and Connors, these A1 type solubility curves indicate the first order dependency of the interaction on the concentration of CD and the formation of soluble Ramipril-β-CD and Ramipril-HP-β-CD complexes with Stoichiometric ratio of 1:1. The value of the stability constants for β-CD was 84.26, while K13 value of HP-β-CD was 333.97.

Fig. 1: Phase solubility analysis plot for inclusion complexes (Drug:β-CD)
Fig. 2: Phase solubility analysis plot for inclusion complexes (Drug:HP-β-CD)

Evaluation of Complexes
Drug Content in drug:β-CD (1:1) and Drug:HP-β-CD(1:1) complex
Percentage drug content of the complexes are shown in Table 3 was found within the range of 87 to 98%. The maximum percent drug content was found to be 98.02 % and 94.4% in the drug:βCD(1:1) and drug:HPβCD(1:1) spray-dried complex.

Saturation solubility study
The saturation solubility data for drug and complexes are presented in Table 3. The solubility showed a steep increase from 3.24 μg/ml to 11.03 μg/ml for β-CD complexes while 12.67 μg/ml for HP-β-CD complexes. The spray- dried complex of β-CD and freeze-dried complex of HP-β-CD shows maximum saturation solubility (11.03 μg/ml,12.67 μg/ml).

Table 3: Percentage drug content and saturation solubility of drug:βCD(1:1) and drug:HPβCD(1:1) complex FT-IR
FTIR spectroscopy has been used to assess the interaction between drug and cyclodextrin molecules in the solid state. Fig.5 & 4 illustrates the FT-IR spectra of the samples under study. The chemical interaction between the drug and the cyclodextrin often leads to identifiable changes in the infrared profile of dispersion. Drug spectrum shows prominent peaks at IR spectra of Ramipril showing the peaks at 3400 cm⁻¹ for –NH and –OH, 2900 cm⁻¹ for –CH aromatic stretching,1730 cm⁻¹ for –CO, 1320 cm⁻¹ for –CH aliphatic bending. Physical mixture of drug with β-CD (1:1) and drug: HP-β-CD complexes shows the prominent peaks of drug, but there was reduction in peak intensity of drug peak which was obscured by cyclodextrin peak indicating formation of complexes.

Fig. 3: IR spectral analysis of a)Ramipril b) β-CD c)physical mixture d) kneading method e) co evaporation method f)co-grinding, g) spray drying h) melting method i)freeze drying
Powder X-ray diffraction spectroscopy has been used to assess the degree of crystallinity of the given sample. When complexation of drug and β-CD / HP-β-CD are formed, the overall number of crystalline structure is reduced and the number of amorphous structures is increased. The final product sample shows less number as well as less intensity of peaks. This shows that overall crystallinity of complexes is decreased and due to more amorphous nature, the solubility is increased. The PXRD spectra of Ramipril, cyclodextrin and its complex are shown in Fig.6. Ramipril showed its highly crystalline nature, as indicated by the numerous distinctive peaks at 2θ values of 8.26, 10.13, 12.4, 13.2, 17.8, 19.1, 19.9, 21.1, and 21.6. The powder X-ray diffractogram of pure Ramipril showed numerous distinctive peaks that indicated a high crystallinity. The diffractogram of complexes were found to be more diffuse compared to drug, there is no characteristic peak i.e formation of amorphous solid state (inclusion complex formation).

In vitro release profile of complexes

Dissolution profiles of pure Ramipril and complexes are presented in Fig.9, Fig.10, Fig.11 and Fig.12. It was found that the complex prepared as 1:1 by kneading method of drug-β-CD and drug-HP-β-CD has shown improve in dissolution behaviour as compare to drug and other complexes. This might be due to the inclusion complex formation, which indicates the improved solubility phenomenon.

Fig. 9: % drug release of drug and its complexes in Distilled Water (Drug:β-CD complex)

Fig. 10: % drug release of drug and its complexes in Distilled Water (Drug:HP-β-CD complex)

Fig. 11: % drug release of drug and its complexes in Phosphate buffer pH 6.8.(Drug:HP-β-CD complex)

Evaluation of Buccal patches

To formulate a buccal patch of Ramipril, the kneaded complex of β-CD and Kedane complex of HP- β-CD was selected based on its saturation solubility and in-vitro dissolution performance. The patches were prepared by solvent casting method and evaluated for thickness, weight uniformity, drug content, swelling index, folding endurance, surface pH, in vitro diffusion study and ex vivo studies on goat buccal mucosa.

CONCLUSION

β-CD and HP-β-CD formed 1:1 complexes with Ramipril as indicated by A type plot in phase solubility study. X- Ray diffraction, differential scanning calorimetric data and IR and UV spectral analysis results indicated that there was no probable interaction between drug and β-CD and HP-β-CD. DSC and XRD confirmed the inclusion complex formation. The inclusion complexes with cyclodextrin prepared by Kneading method showed highest solubility and fast dissolution profile.

ACKNOWLEDGEMENT

Authors are thankful to Cipla Ltd., Mumbai for providing the drug sample of Ramipril. Authors are very much thankful to Principal and management of MAER's Maharashtra Institute of Pharmacy, Pune for their help and support.

Table 1: Composition of Mucoadhesive buccal patch

<table>
<thead>
<tr>
<th>Formulation batch</th>
<th>Cyclodextrin complex equivalent to Ramipril (mg)</th>
<th>HPMC K15 (%)</th>
<th>Poloxomer WSR 205NF (%)</th>
<th>Polyethylene Glycol (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1</td>
<td>10</td>
<td>0.5</td>
<td>---</td>
<td>10</td>
</tr>
<tr>
<td>B2</td>
<td>10</td>
<td>1</td>
<td>---</td>
<td>10</td>
</tr>
<tr>
<td>B3</td>
<td>10</td>
<td>---</td>
<td>0.5</td>
<td>13</td>
</tr>
<tr>
<td>B4</td>
<td>10</td>
<td>---</td>
<td>1</td>
<td>13</td>
</tr>
</tbody>
</table>

Table 2: Gibbs free energy of transfer (ΔG°r), for solubilisation process of Ramipril in aqueous solutions of β-CD and HP-β-CD at 37°C

<table>
<thead>
<tr>
<th>Moles of β-CD/ HP-β-CD in water</th>
<th>ΔG°r (kJ/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β-CD</td>
</tr>
<tr>
<td>0</td>
<td>-5.93</td>
</tr>
<tr>
<td>0.003</td>
<td>-6.03</td>
</tr>
<tr>
<td>0.006</td>
<td>-6.23</td>
</tr>
<tr>
<td>0.009</td>
<td>-6.42</td>
</tr>
<tr>
<td>0.012</td>
<td>-6.56</td>
</tr>
<tr>
<td>0.015</td>
<td>-6.77</td>
</tr>
</tbody>
</table>
Table 3: Percentage drug content and saturation solubility of drug:βCD(1:1) and drug:HPβCD(1:1) complex.

<table>
<thead>
<tr>
<th>Complexes</th>
<th>% Drug Content</th>
<th>% increase in Solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β-CD</td>
<td>HPβCD</td>
</tr>
<tr>
<td>Physical mixture</td>
<td>91.99±0.11</td>
<td>88.99±0.45</td>
</tr>
<tr>
<td>Kneading</td>
<td>96.16±0.25</td>
<td>92.91±0.32</td>
</tr>
<tr>
<td>Co-grinding</td>
<td>95.46±0.32</td>
<td>89.42±0.21</td>
</tr>
<tr>
<td>Co-evaporation</td>
<td>89.87±0.43</td>
<td>90.96±0.13</td>
</tr>
<tr>
<td>Melting</td>
<td>87.23±0.34</td>
<td>89.2±0.54</td>
</tr>
<tr>
<td>Freeze Drying</td>
<td>95.11±0.13</td>
<td>93.11±0.32</td>
</tr>
<tr>
<td>Spray Drying</td>
<td>98.02±0.19</td>
<td>94.4±0.12</td>
</tr>
</tbody>
</table>

Table 4: Characteristics of mucoadhesive buccal patches containing β-cyclodextrin complex

<table>
<thead>
<tr>
<th>Batch code</th>
<th>C1</th>
<th>C2</th>
<th>C3</th>
<th>C4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patch Thickness</td>
<td>0.64</td>
<td>0.84</td>
<td>1.1</td>
<td>0.59</td>
</tr>
<tr>
<td>Surface pH</td>
<td>6.16</td>
<td>7.2</td>
<td>6.23</td>
<td>6.4</td>
</tr>
<tr>
<td>Folding Endurance</td>
<td>279</td>
<td>312</td>
<td>287</td>
<td>238</td>
</tr>
<tr>
<td>Swelling Index</td>
<td>34±0.12</td>
<td>27±0.45</td>
<td>31±0.32</td>
<td>25±0.21</td>
</tr>
<tr>
<td>%Drug content</td>
<td>97.3</td>
<td>94.7</td>
<td>96.5</td>
<td>93.2</td>
</tr>
<tr>
<td>Mucoadhesive strength (gm)</td>
<td>8.91±0.034</td>
<td>7.8±0.12</td>
<td>10.13±0.042</td>
<td>8.93±0.23</td>
</tr>
<tr>
<td>% Drug release after 8 hrs</td>
<td>74.88</td>
<td>69.14</td>
<td>71.9</td>
<td>60.44</td>
</tr>
</tbody>
</table>

Table 5: Characteristics of mucoadhesive buccal patch containing Hydroxy Propyl β-cyclodextrin complex

<table>
<thead>
<tr>
<th>Batch code</th>
<th>D1</th>
<th>D2</th>
<th>D3</th>
<th>D4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patch Thickness</td>
<td>0.91</td>
<td>1.06</td>
<td>0.79</td>
<td>0.83</td>
</tr>
<tr>
<td>Surface pH</td>
<td>6.8</td>
<td>6.23</td>
<td>7.3</td>
<td>6.45</td>
</tr>
<tr>
<td>Folding Endurance</td>
<td>312</td>
<td>278</td>
<td>305</td>
<td>255</td>
</tr>
<tr>
<td>Swelling Index</td>
<td>38±0.23</td>
<td>33±0.1</td>
<td>41±0.4</td>
<td>39±0.5</td>
</tr>
<tr>
<td>%Drug content</td>
<td>97.3</td>
<td>91.4</td>
<td>95.7</td>
<td>93.5</td>
</tr>
<tr>
<td>Mucoadhesive strength (gm)</td>
<td>7.12±0.021</td>
<td>6.34±0.098</td>
<td>9.01±0.03</td>
<td>7.35±0.1</td>
</tr>
<tr>
<td>% Drug release after 8 hrs</td>
<td>81.16</td>
<td>74.68</td>
<td>77.24</td>
<td>65.58</td>
</tr>
</tbody>
</table>

Table 6: Best fit model for diffusion study of optimized batches of buccal patch of Ramipril

<table>
<thead>
<tr>
<th>Sr. no.</th>
<th>Formulation code</th>
<th>Best Fit model</th>
<th>n</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>D1cel</td>
<td>Matrix</td>
<td>0.3899</td>
<td>0.9915</td>
</tr>
<tr>
<td>2</td>
<td>D3cel</td>
<td>Matrix</td>
<td>0.3857</td>
<td>0.9914</td>
</tr>
<tr>
<td>3</td>
<td>D1egg</td>
<td>Matrix</td>
<td>0.3762</td>
<td>0.9877</td>
</tr>
<tr>
<td>4</td>
<td>D2egg</td>
<td>Matrix</td>
<td>0.3802</td>
<td>0.9908</td>
</tr>
<tr>
<td>5</td>
<td>D1go.at</td>
<td>Matrix</td>
<td>0.3754</td>
<td>0.9894</td>
</tr>
</tbody>
</table>

Fig. 1: Phase solubility analysis plot for inclusion Complexes (Drug:β-CD).

Fig. 2: Phase solubility analysis plot for inclusion complexes (Drug:HP-β-CD).
Fig. 3: IR spectral analysis of a) Ramipril, b) β-CD, c) physical mixture, d) kneading method, e) co-evaporation method, f) co-grinding method, g) melting method, h) spray drying, i) freeze drying.

Fig. 4: IR spectral analysis of a) Ramipril, b) HP β-CD, c) physical mixture, d) kneading method, e) co-evaporation method, f) co-grinding method, g) melting method, h) spray drying, i) freeze drying.

Fig. 5: X-Ray Diffraction of a) Ramipril, b) β-CD, c) kneading method, d) co-grinding.

Fig. 6: X-Ray Diffraction of a) Ramipril, b) HP β-CD, c) kneading method, d) co-grinding.

Fig. 7: DSC study of a) Ramipril, b) β-CD, c) kneading complex, d) co-grinding complex.

Fig. 8: DSC study of a) Ramipril, b) HP β-CD, c) kneading complex, d) co-grinding complex.

Fig. 9: % drug release of drug and its complexes in Distilled Water (Drug: β-CD complex).

Fig. 10: % release of drug and its complexes in Phosphate buffer pH 6.8 (Drug: β-CD complex).
Fig. 11: % drug release of drug and its complexes in Distilled Water (Drug:HP-β-CD complex).

Fig. 12: % release of drug and its complexes in Phosphate buffer pH 6.8 (Drug:HP-β-CD complex).

Fig. 13: Release profile of Ramipril from buccal patches containing β-cyclodextrin complex on cellophane membrane.

Fig. 14: Release profile of Ramipril from buccal patches containing Hydroxy propyl β-cyclodextrin complex on cellophane membrane.

Fig. 15: Release profile of Ramipril optimised buccal patch on cellophane, egg membrane and goat mucosal membrane.

Fig. 16: IR spectral analysis of a) Ramipril b) HP β-CD c) HPMC K15 d) optimised formulation.

REFERENCES


