4.1 OBJECTIVE

The preliminary studies were carried out before the Formulation and Evaluation of the Mouth Dissolving Tablets (MDTs) and the objective of this study involves

a. Characterization of the Drugs: To identify and characterize the drugs by UV Spectroscopy, Differential Scanning Calorimetry (DSC), FTIR etc.

b. Taste masking of drugs: To prepare taste masked mixture/complex of Levocetirizine by different methods to give pleasant, soluble complex free from grittiness.

c. Solubility Enhancement of the drug: To improve the solubility of poorly water soluble drug (Cefixime) by

   i) Formulation of inclusion complexes of Cefixime.
   
   ii) Formulation of solid dispersion of Cefixime with sugar derivative
   
   iii) Evaluate the potential of the complexes and solid dispersions for the enhanced solubility of Cefixime.

4.2 MATERIALS

β-Cyclodextrin (BCD) was used for inclusion complexation and was obtained as gift sample (Himalayan Laboratories, H.P.). For solid dispersion with sugar derivatives, Mannitol was selected as it is one of the most commonly used excipient (purchased from RFCL Limited, New Delhi, India). All other chemicals used were of analytical grade.

4.3 EQUIPMENTS

UV Spectrophotometer (UV 1800, Shimadzu, Japan), Differential Scanning Calorimeter (Perkin-Elmer DSC7, USA), X-ray Diffractometer (Philips PW 3710, Netherland), Scanning Electron Microscope (JEOL 457 V, Japan), Vortex shaker (Electro Lab, India), Water bath incubator shaker (Tanco Pvt. Ltd., India) were used.
4. Preliminary Studies

4.4 METHODOLOGY

4.4.1 Characterization of Drugs:

The selected drugs were identified and characterized by

4.4.1.1 UV Spectroscopy

UV absorption spectroscopy of Levocetirizine and Cefixime were carried out using UV–VIS scanning spectrophotometer (Shimadzu UV-1800, Japan). UV absorption spectra were recorded using pure Drugs (conc. of 20mcg/ml in 0.1N HCl) and absorption peaks were determined.

4.4.1.2 Differential Scanning Calorimetry (DSC)

Pure drugs (Levocetirizine and Cefixime) (5-10 mg) were heated in hermetically sealed aluminium pans with a heating rate of 10°C/min under nitrogen atmosphere (flow rate 20 ml/min) and thermograph were recorded using differential scanning calorimeter (Perkin-Elmer DSC7, USA).

4.4.1.3 Fourier-Transform Infrared (FTIR) Spectroscopy:

FTIR spectra of pure drugs (Levocetirizine and Cefixime) were recorded by suspending in liquid paraffin and placing in sodium chloride cell on FTIR spectrophotometer (IR Affinity, Shimadzu, Japan). The peaks were determined and observed peaks were compared with standard.

4.4.1.4 Scanning Electron Microscopy (SEM)

Pure drugs (Levocetirizine and Cefixime) were mounted on a double- faced adhesive tape and sputtered with thin gold- palladium layer using sputter coater unit and surface topography was analyzed with a scanning electron microscope (JEOL 457 V, Japan)
4. Preliminary Studies

4.4.2 Taste Masking of Levocetirizine

Taste masking of bitter drug is tedious work as the taste sensation varies person to person and involves taste masking efficiency as quality control parameter and done by masking the bitter taste of drugs by either decreasing its oral solubility on ingestion (using ion exchange resin) or decreasing the amount of drug particles exposed to taste buds (Inclusion Complex, solid dispersion) thereby reducing the perception of bitter taste.

a. Using Ion exchange Resins complex

Resin used: Tulsion 660 grade (drug : resin, 1:0.5, 1:1, 1:2, 1:3, 1:4, 1:5 w/w)

Method: Weighed amount of levocetirizine was dissolved in distilled water (1mg/ml) in 100ml volumetric flask. Resin in different ratios was added to the drug solution and placed on water bath shaker for one hour. The suspension was filtered under vacuum and dried in oven at 50°C for one hour. The dried mass was used for the taste evaluation study.

b. Inclusion complex method

Polymer used: β-Cyclodextrin (BCD)

Complex formation: Thick slurry of Levocetirizine with BCD in different ratios (drug : polymer, 1:0.5, 1:1, 1:2, 1:3, 1:4, 1:5 w/w) were prepared by using ethanol as solvent. The slurry was dried in hot air oven at 45°C until dry, pulverized and sieved (mesh size #100). The dried complex was used for the taste evaluation study.

c. Solid dispersion method using sugar derivative

Polymer used: Mannitol

Physical Mixture: Levocetirizine was mixed with Mannitol in different ratio (drug : carrier, 1:0.5, 1:1, 1:2, 1:3, 1:4, 1:5 w/w) in modified rotary flask shaker for two hours. The physical mixture was sieved (mesh size #100) and further evaluated.
4. Preliminary Studies

**Solid Dispersion:** Weighed amount of Levocetirizine was dissolved in ethanol and Mannitol in different ratios (1:0.5, 1:1, 1:2, 1:3, 1:4, 1:5w/w) was added to this drug solution (in ethanol) and mixed on Vortex shaker (Electro Lab, India) for one hour. The solvent was evaporated in hot air oven at 45°C until dry, pulverized and sieved (mesh size #100). This dried solid dispersion was used for further evaluation study.

### 4.4.3 Solubility Enhancement of Cefixime

**a. Inclusion complex method**

**Polymer used:** β-Cyclodextrin (BCD)

**Complex formation:** Thick slurry of Cefixime with BCD in different ratios (1:0.5, 1:1, 1:2, 1:3, 1:4, 1:5w/w) were prepared by using Methanol as co-solvent. The slurry was dried in hot air oven at 45°C until dry, pulverized and sieved (mesh size #100). The dried complex was further evaluated.

**b. Solid dispersion method using sugar derivative**

**Polymer used:** Mannitol

**Physical Mixture:** Cefixime was mixed with Mannitol in different ratio (1:0.5, 1:1, 1:2, 1:3, 1:4, 1:5w/w) in modified rotary flask shaker at 30 rpm (inclined an angle of 50°) for 2 hours. The physical mixture was sieved (mesh size #100) and further evaluated.

**Solid Dispersion:** Weighed amount of Cefixime was dissolved in Methanol and Mannitol in different ratios (1:0.5, 1:1, 1:2, 1:3, 1:4, 1:5w/w) was added to this drug solution (in methanol) and shakes on Vortex shaker (Electro Lab, India) for one hour. The solvent was evaporated in hot air oven at 45°C until dry, pulverized and sieved (mesh size #100). This dried solid dispersion was used for further evaluation study.
4. Preliminary Studies

4.5 EVALUATION

4.5.1 Characterization of Complexes:

All the prepared complexes and solid dispersions of the drug with the polymers were characterized to assess any possible interaction by following methods.

4.5.1.1 UV Spectroscopy

UV absorption spectroscopy of samples was carried out using UV–VIS scanning spectrophotometer (Shimadzu UV-1800, Japan). UV overlay spectra were recorded (in 0.1N HCl and in simulated saliva) and any changes in absorption peaks were analyzed.

4.5.1.2 Differential Scanning Calorimetry (DSC)

Samples (5-10 mg) were heated in hermetically sealed aluminium pans with a heating rate of 10°C/min under nitrogen atmosphere (flow rate 20 ml/min) and thermogram were recorded on a differential scanning calorimeter (Perkin-Elmer DSC7, USA).

4.5.1.3 Powder X-ray Diffraction Studies

Powder X-ray Diffraction study were carried out using X-ray Diffractometer (Philips PW 3710, Netherland) with CuKα radiation, collimated by a 0.08° divergence slit and a 0.2° receiving slit and scanned at a rate of 2.4°/min over the 2θ range of 2-300°C.

4.5.1.4 Scanning Electron Microscopy (SEM)

Samples were mounted on a double-faced adhesive tape and sputtered with thin gold-palladium layer using sputter coater unit and surface topography was analyzed with a scanning electron microscope (JEOL 457 V, Japan). The SEM of samples was compared with the pure drug and any change in crystallinity was determined.
4. Preliminary Studies

4.5.2 Evaluation of Taste Masking

Object: - Evaluation of taste masking effectiveness of prepared complexes and solid dispersions of Levocetirizine.

Protocol Approval Detail: - Protocol no. IEC/21 approved by the Institutional Ethical Committee, M.M. University, Mullana.

Selection of volunteers: - A panel of 10 healthy volunteers selected randomly from age group of 20 to 30 and the consent form was filled and signed by the volunteers.

Standard Stimuli: - Pure active ingredient (Levocetirizine DiHCl).

Test Stimuli: - Levocetirizine DiHCl complexes and solid dispersion

Sample Delivery method- Each volunteer received all 6 formulations of one batch in 4 hr after morning breakfast in 1 day.

Scale of measurement- Taste evaluation was started immediately after administration and continued for upto 15 secs. The scale used a ranking system from +++ tasteless to -- Extremely bitter for taste and * or # for gritty particle or soluble complex

4.5.3 Phase Solubility Studies

Known excess amount of drug (Cefixime) complex/solid dispersion in different ratios (physical mixture and solid dispersion separately) was added in 30ml of simulated gastric fluid (0.1N HCL) in a series of 100ml volumetric flask. The flasks were placed overnight in water bath incubator shaker (30rpm, 37°±0.5°C). After 24 hours, the flasks were kept aside for equilibrium to achieve followed by filtration of the solution though micro-syringe filters (mesh size #0.22micron). The filtered Samples were diluted and studied by UV-VIS spectroscopic method (Shimadzu UV-1800) at 288nm. The whole phase solubility study was also carried out at pH 6.2 (simulated saliva)
4. Preliminary Studies

4.6 RESULT AND DISCUSSION

4.6.1 Characterization of Levocetirizine diHCl:

4.6.1.1 UV Spectroscopy

Fig. 4.1 UV Absorption Spectra of Levocetirizine diHCl in 0.1N HCl (A) and in Simulated saliva Solution (B)

Levocetirizine shows UV Absorption peak at 231nm in acidic solution (0.1N HCl solution). In simulated saliva (pH 6.2), identical peak at 231nm was observed (Fig. 4.1B). From UV Spectroscopic study, no change in the absorption peaks with pH was observed.

4.6.1.2 Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimeter (DSC) allows the fast evaluation of possible impurities as any shift of melting endothermic and exothermic peaks indicates impurities in drug. Pure Levocetirizine diHCl have M.P. of 215-225°C.
The results of DSC study are given in Figure 4.2. DSC thermogram showed endothermic peak of levocetirizine at 221.7°C, which corresponded to its melting point. There was no change in the melting point of drug indicating its purity with the reference standard. The sharp endothermic peak shows crystalline nature of Levocetirizine diHCl.

4.6.1.3 Scanning Electron Microscopy (SEM)

Levocetirizine SEM images were taking on different magnification to define its surface morphology and nature of the drug. The Figure 4.3 was taken on 1000x magnification in which the small crystals of Levocetirizine were clearly visible. The crystals are small size; elongated, cylindrical shape and have negligible porosity.
4. Preliminary Studies

Fig. 4.3 SEM Photograph of Levocetirizine diHCl pure drug (1000x)

4.6.1.4 Fourier-Transform Infrared (FTIR) Spectroscopy:

Fig. 4.4 FTIR spectra of Levocetirizine diHCl pure drug
4. Preliminary Studies

The prominent peaks of levocetirizine (Fig. 4.4) was observed at a peak of 3392.72 cm⁻¹ due to the N-H stretching, a peak at 2906.15 cm⁻¹ due to C-H stretching, a peak at 1697 cm⁻¹ observed due to the carbonyl group and a peak at 1479.40 due to ether group. At the lower frequencies 1334.09 (C-N stretching), 1085.08 cm⁻¹ (CO stretching) observed.

4.6.2 Characterization of Cefixime Trihydrate:

4.6.2.1 UV Spectroscopy

**Fig. 4.5 UV Absorption Spectra of Cefixime in 0.1N HCl (A) and in Simulated saliva Solution (B)**

Form the UV absorption spectra (fig 4.5 A), Cefixime shows the absorption peaks at 286nm in 0.1N HCl solution and almost same peak (288nm) was observed in simulated saliva solution at pH 6.2 (Fig. 4.5 B).
4. Preliminary Studies

4.6.2.2 Differential Scanning Calorimetry (DSC)

Pure Cefixime Trihydrate has M.P. of 218-225°C. DSC thermogram (Fig. 4.6) of Cefixime Trihydrate shows endothermic peak at 223°C, which is its melting point. Before melting point, DSC shows two endothermic peaks (122°C, 149°C) shows the removal of hydrates from Cefixime trihydrate.

Fig. 4.6 DSC Thermogram of Cefixime Trihydrate pure drug
4. Preliminary Studies

4.6.2.3 Fourier-Transform Infrared (FTIR) Spectroscopy:

![FTIR Spectra of Cefixime Trihydrate pure drug](image)

The FTIR spectra of Cefixime (Fig 4.7) has -NH2, -COOH, -CONH and C=O lactam groups which are the potential sites for coordination with metal ions. IR spectrum of the Cefixime indicates that the lactam (C=O) band appears at 1732 cm⁻¹. The phenyl ring substitution is occurring at 1894.10 cm⁻¹. The amide carbonyl band, (C=O)–NH in the free Cefixime appears at 1572 cm⁻¹ with a weak shoulder at 1296 cm⁻¹. The asymmetrical and symmetrical stretching bands of carboxylate groups appear from 1543 cm⁻¹ to 1398 cm⁻¹.
4. Preliminary Studies

4.6.3 Characterization of Complexes

4.6.3.1 UV Spectroscopy

a. Levocetirizine Taste Masked complexes

Fig. 4.8 UV Overlay Spectra of Levocetirizine, Levocetirizine BCD Complex and Levocetirizine Mannitol Solid Dispersion in 0.1N HCl and in Simulated saliva

In UV overlay spectra of levocetirizine diHCl in 0.1N HCl (Fig 4.8), the peaks of Levocetirizine diHCl were observed at 231nm and do not change in the complexes indicates no interaction between the drug and BCD and same was observed with Mannitol solid dispersion. The same results were observed in simulated saliva solution as well.

b. Cefixime complexes

UV overlay spectra of Cefixime and its complexes in 0.1N HCl (Fig 4.9), the peaks were identically observed at 288nm and do not change in the complexes indicate no interaction in complexes.
4. Preliminary Studies

Fig. 4.9 UV Overlay Spectra of Cefixime, Cefixime BCD Complex and Cefixime Mannitol Solid Dispersion in 0.1N HCl and in Simulated saliva

4.6.3.2 Differential Scanning Calorimetry (DSC)

Fig. 4.10 DSC Thermogram of Levocetirizine diHCl pure drug in comparison to BCD Complex
The thermal behavior of levocetirizine diHCl and its BCD complex was studied using DSC thermogram (Fig 4.10). The DSC thermogram of levocetirizine and BCD showed an endothermic peak at 222.06°C and 229.27°C corresponding to their melting point. The DSC thermogram of Levocetirizine BCD complex showed endothermic peak at 217.15°C indicating no change in drug melting point and can be explained in terms of the reduction in the crystallinity of the drug and the inclusion of drug into the hydrophobic cavity of the β-cyclodextrin.

Fig. 4.11 DSC Thermogram of Levocetirizine diHCl pure drug in comparison to Mannitol Solid Dispersion

The DSC thermogram of mannitol showed sharp endothermic peak at 171.12°C and levocetirizine mannitol solid dispersion shows two endothermic peaks corresponding to the melting point of drug and mannitol indicating no chemical interaction between them.
4.6.3.3 Powder X-ray Diffraction Studies

Fig. 4.12 XRD Spectra of Levocetirizine (A), BCD (B), Levocetirizine BCD Complex (C)

The XRD pattern of levocetirizine showed intense and sharp peaks, indicating its crystalline nature. The diffraction patterns of levocetirizine and BCD complex (Fig. 4.12) showed peaks of levocetirizine and β-Cyclodextrin with little decrease in the peak intensity of levocetirizine due to its 1:1w/w ratio and the broadening of peaks indicating reduction in crystallinity of the drug. In levocetirizine BCD complex (Fig. 4.12 C) Levocetirizine peaks are shielded in BCD complex showing inclusion type complex formed by β-Cyclodextrin.
4. Preliminary Studies

In XRD spectra of levocetirizine mannitol solid dispersion (Fig. 4.13 C) showed peaks of mannitol as well as levocetirizine and some peaks of levocetirizine are absent in mannitol solid dispersion XRD spectra showing hindrance of the levocetirizine by the mannitol thus justified the mechanism of its taste masking.

![XRD Spectra](image)

*Fig. 4.13 XRD Spectra of Levocetirizine (A), Mannitol (B), Levocetirizine Mannitol S.D. (C)*
4. Preliminary Studies

4.6.3.4 Scanning Electron Microscopy (SEM)

The SEM photographs describes that levocetirizine are small crystalline structure but its complex with BCD is totally amorphous and no sign of crystallinity was observed in SEM photographs (4.14 C) indicating that the levocetirizine crystals were entrapped in the BCD cavity producing inclusion type complex as justified by the XRD spectra.

Fig. 4.15 SEM Photograph of Levocetirizine (A), Mannitol (B), Levocetirizine Mannitol Solid Dispersion (C)

From SEM (fig. 4.15), Mannitol was observed as crystalline with large elongated crystals (Fig. 4.15 B) and levocetirizine observed as small crystalline drug. In levocetirizine mannitol solid dispersion (Figure No. 4.15 C), the elongated crystals of mannitol changes to small crystals with increment in surface area and porosity which will allows faster water absorption into the complex.
4. Preliminary Studies

4.6.4 Results of taste masking of levocetirizine diHCl

a. Using Ion exchange Resins complex

Levocetirizine resin complex at 1:2 w/w ratio showed that the complex was palatable but at 1:3 w/w ratio it was tasteless which was reported by 90% volunteers and at 1:4 and 1:5 w/w ratio 100% volunteers reported that the complete taste masking was achieved.

Table 4.1 Observation for taste evaluation of Levocetirizine diHCl Resin Complex

<table>
<thead>
<tr>
<th>Drug : Resin (w/w)</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:0.5</td>
<td>-</td>
</tr>
<tr>
<td>1:1</td>
<td>+</td>
</tr>
<tr>
<td>1:2</td>
<td>++</td>
</tr>
<tr>
<td>1:3</td>
<td>+++</td>
</tr>
<tr>
<td>1:4</td>
<td>+++</td>
</tr>
<tr>
<td>1:5</td>
<td>+++</td>
</tr>
</tbody>
</table>

- Bitter, + slightly bitter but not Palatable
  ++ Palatable formulation
  +++ Completely taste masked (Tasteless)

Entrapment Efficiency: Calculated from unbound drug (levocetirizine) (table 4.2) and was found more than 90% in 1:4 w/w and 1:5 w/w ratio.

Table 4.2 Entrapped efficiency of levocetirizine in complexes

<table>
<thead>
<tr>
<th>Drug : Resin (w/w)</th>
<th>Conc. of Sol. (mcg/ml)</th>
<th>Unbound Drug (%)</th>
<th>Entrapment Efficiency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:0.5</td>
<td>28.26</td>
<td>71.99</td>
<td>28.01</td>
</tr>
<tr>
<td>1:1</td>
<td>19.23</td>
<td>48.98</td>
<td>51.02</td>
</tr>
<tr>
<td>1:2</td>
<td>12.13</td>
<td>30.89</td>
<td>69.11</td>
</tr>
<tr>
<td>1:3</td>
<td>7.98</td>
<td>20.34</td>
<td>79.66</td>
</tr>
<tr>
<td>1:4</td>
<td>3.40</td>
<td>8.66</td>
<td>91.34</td>
</tr>
<tr>
<td>1:5</td>
<td>0.33</td>
<td>0.84</td>
<td>99.16</td>
</tr>
</tbody>
</table>
Drug Release from Complex: carried out using USP I Dissolution apparatus in two different environments (in simulated saliva and in simulated gastric fluid).

**Table 4.3 Cumulative percentage drug release from complexes in simulated saliva**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>1:0.5</th>
<th>1:1</th>
<th>1:2</th>
<th>1:3</th>
<th>1:4</th>
<th>1:5</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>2.12±0.1</td>
<td>3.12±0.7</td>
<td>3.10±0.5</td>
<td>4.23±0.7</td>
<td>5.11±0.5</td>
<td>5.34±0.5</td>
</tr>
<tr>
<td>5</td>
<td>5.10±0.6</td>
<td>8.10±0.6</td>
<td>9.11±0.9</td>
<td>10.15±0.8</td>
<td>9.99±0.8</td>
<td>8.23±0.9</td>
</tr>
<tr>
<td>10</td>
<td>7.12±0.7</td>
<td>10.11±0.7</td>
<td>12.10±0.8</td>
<td>11.90±0.9</td>
<td>12.67±1.1</td>
<td>13.25±0.7</td>
</tr>
<tr>
<td>20</td>
<td>10.11±0.6</td>
<td>13.12±0.9</td>
<td>14.11±1.2</td>
<td>15.20±1.1</td>
<td>16.20±1.2</td>
<td>15.20±0.9</td>
</tr>
<tr>
<td>40</td>
<td>13.12±1.1</td>
<td>16.20±1.2</td>
<td>16.90±1.3</td>
<td>17.45±1.4</td>
<td>18.20±1.1</td>
<td>17.20±1.3</td>
</tr>
<tr>
<td>60</td>
<td>14.10±0.9</td>
<td>18.20±1.1</td>
<td>19.10±1.3</td>
<td>20.13±1.2</td>
<td>22.34±1.5</td>
<td>23.20±1.2</td>
</tr>
<tr>
<td>90</td>
<td>17.20±0.8</td>
<td>20.12±1.3</td>
<td>22.10±1.4</td>
<td>25.10±1.1</td>
<td>26.10±1.1</td>
<td>27.12±1.5</td>
</tr>
</tbody>
</table>

Mean ± S.D for six readings

**Table 4.4 Cumulative percentage drug release from complexes in 0.1N HCl**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>1:0.5</th>
<th>1:1</th>
<th>1:2</th>
<th>1:3</th>
<th>1:4</th>
<th>1:5</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>39.80±0.4</td>
<td>57.57±0.9</td>
<td>39.20±0.6</td>
<td>28.31±1.1</td>
<td>30.59±0.8</td>
<td>40.55±0.7</td>
</tr>
<tr>
<td>5</td>
<td>62.64±0.9</td>
<td>72.67±1.4</td>
<td>68.41±1.3</td>
<td>67.90±1.2</td>
<td>68.44±1.1</td>
<td>59.55±1.1</td>
</tr>
<tr>
<td>10</td>
<td>76.56±1.2</td>
<td>88.76±1.3</td>
<td>81.23±1.5</td>
<td>86.83±1.5</td>
<td>85.58±1.4</td>
<td>84.43±1.1</td>
</tr>
<tr>
<td>20</td>
<td>87.94±1.4</td>
<td>95.31±2.5</td>
<td>93.14±1.8</td>
<td>95.02±1.2</td>
<td>93.87±1.6</td>
<td>89.82±1.7</td>
</tr>
<tr>
<td>40</td>
<td>93.88±1.3</td>
<td>97.20±2.1</td>
<td>94.84±1.5</td>
<td>97.09±1.4</td>
<td>96.65±1.2</td>
<td>93.61±1.8</td>
</tr>
<tr>
<td>60</td>
<td>97.53±1.8</td>
<td>98.75±2.1</td>
<td>97.71±1.6</td>
<td>98.11±2.1</td>
<td>98.30±1.1</td>
<td>97.38±2.2</td>
</tr>
<tr>
<td>90</td>
<td>99.59±1.9</td>
<td>99.37±1.8</td>
<td>99.77±1.3</td>
<td>99.12±2.3</td>
<td>99.95±1.7</td>
<td>99.66±2.3</td>
</tr>
</tbody>
</table>

Mean ± S.D for six readings
4. Preliminary Studies

In simulated saliva, the resin complex does not release the drug and thus the drug become unavailable to taste bud (masked the bitter taste of drug) due to decreased solubility of levocetirizine at saliva pH but release the drug in acidic pH 1.2 (0.1N HCl) (table 4.4).

Fig. 4.16 Drug release profile from the resin complex in saliva and gastric fluid

b. Inclusion complex method

100% volunteers reported that BCD inclusion complex of levocetirizine at ratio 1:2w/w was palatable (table 4.5); 1:3 ratio was tasteless and completely taste masked at higher ratios.

Table 4.5 Observation for taste evaluation of Levocetirizine diHCl BCD Complex

<table>
<thead>
<tr>
<th>Drug : Resin (w/w)</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:0.5</td>
<td>-</td>
</tr>
<tr>
<td>1:1</td>
<td>+</td>
</tr>
<tr>
<td>1:2</td>
<td>++</td>
</tr>
<tr>
<td>1:3</td>
<td>++</td>
</tr>
<tr>
<td>1:4</td>
<td>+++</td>
</tr>
<tr>
<td>1:5</td>
<td>+++</td>
</tr>
</tbody>
</table>

- Bitter, + slightly bitter but not Palatable
++ Palatable formulation
+++ Completely taste masked (Tasteless)
Taste masking of levocetirizine diHCl with BCD was due to hindrance of the drug by forming inclusion complex thus unpleasant tastes or odors was hidden from the sensory receptors by encapsulating them within the BCD cavity.

c. **Solid dispersion method using sugar derivative**

With sugar derivatives (Mannitol), physical mixture fails to mask the bitter taste of the levocetirizine and give slight palatable mixture at ratio 1:5 w/w (table 4.6) whereas solid dispersion of Mannitol at 1:3 ratio was palatable; 1:4 ratio was tasteless (>90% volunteers reported). In solid dispersion, levocetirizine and mannitol dispersion was at molecular level and creates a hydrated coating around the drug molecule therefore prevent attachment with taste bud receptor on the tongue in the mouth cavity thus have no or little taste or odor and are much more acceptable to the patient.

*Table 4.6 Observation for taste evaluation of Levocetirizine diHCl by Mannitol*

<table>
<thead>
<tr>
<th>Drug : Polymer (w/w)</th>
<th>Physical Mixture (using mannitol)</th>
<th>Solid Dispersion (using mannitol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:0.5</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>1:1</td>
<td>--</td>
<td>-</td>
</tr>
<tr>
<td>1:2</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>1:3</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>1:4</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>1:5</td>
<td>+</td>
<td>+++</td>
</tr>
</tbody>
</table>

- Bitter, + slightly bitter but not Palatable
++ Palatable formulation
+++ Completely taste masked (Tasteless)
4.6.5 Phase Solubility Study

The solubility of pure drug (Cefixime) was found to be 352±14 mcg/ml at gastric pH (in 0.1N HCl) and 321±25 mcg/ml in simulated saliva solution (table 4.8). By forming inclusion complex with BCD in different ratios, the solubility was enhanced linearly with increased concentration of BCD and also independent of the physiological pH at higher concentration (4204±42 mcg/ml at gastric pH, 4153±78 mcg/ml at saliva pH).

Table 4.7 Phase solubility studies of Cefixime and its complexes at gastric pH

<table>
<thead>
<tr>
<th>Drug: Polymer (w/w)</th>
<th>Inclusion Complex (with BCD)</th>
<th>Physical Mixture (using mannitol)</th>
<th>Solid Dispersion (using mannitol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:0</td>
<td>352±14</td>
<td>352±14</td>
<td>352±14</td>
</tr>
<tr>
<td>1:1</td>
<td>1005±25</td>
<td>403±15</td>
<td>806±12</td>
</tr>
<tr>
<td>1:2</td>
<td>2122±43</td>
<td>485±18</td>
<td>1561±23</td>
</tr>
<tr>
<td>1:3</td>
<td>3449±36</td>
<td>694±17</td>
<td>2633±32</td>
</tr>
<tr>
<td>1:4</td>
<td>4204±42</td>
<td>816±19</td>
<td>3485±23</td>
</tr>
</tbody>
</table>

n = 6, ± Standard Deviation

Fig. 4.17 Phase solubility study of Cefixime complex at gastric pH
By using sugar derivatives, mannitol fails to increase the solubility of Cefixime in physical mixture (816±19mcg/ml in gastric pH, 755±76mcg/ml at pH 6.2 in ratio 1:5) but by preparing solid dispersion of the cefixime with mannitol, solubility increases linearly with mannitol concentration (3485±23mcg/ml in gastric pH, 3403±56mcg/ml at pH 6.2 in ratio 1:5). This was due to the mannitol solid dispersion at molecular level and creates hydrated environment around the Cefixime thus increases its solubility.

Table 4.8 Phase solubility studies of Cefixime and its complexes at pH 6.2

<table>
<thead>
<tr>
<th>Drug: Polymer (w/w)</th>
<th>Solubility at pH 6.2 (mcg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inclusion Complex (with BCD)</td>
</tr>
<tr>
<td>1:0</td>
<td>321±25</td>
</tr>
<tr>
<td>1:1</td>
<td>1036±78</td>
</tr>
<tr>
<td>1:2</td>
<td>2092±63</td>
</tr>
<tr>
<td>1:3</td>
<td>3255±121</td>
</tr>
<tr>
<td>1:4</td>
<td>4153±78</td>
</tr>
</tbody>
</table>

n = 6, ± Standard Deviation

Fig. 4.18 Phase solubility study of Cefixime complex at pH 6.2