7 EXPERIMANTAL

7.1 FORMULATION OF CORE TABLET

The core tablet was prepared by wet granulation method. The different batches prepared and their composition formulae are mentioned in the table 7.1, 7.2 & 7.3.

Table 7.1: Designed composition details of different Eterocoxib EOP tablet batches.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>INGREDIENTS (Mg/tablet)</th>
<th>01a</th>
<th>02a</th>
<th>03a</th>
<th>04a</th>
<th>05a</th>
<th>06a</th>
<th>07a</th>
<th>08a</th>
<th>09a</th>
<th>10a</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>Eterocoxib</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>02</td>
<td>MCC</td>
<td>187</td>
<td>187</td>
<td>187</td>
<td>187</td>
<td>157</td>
<td>147</td>
<td>137</td>
<td>157</td>
<td>147</td>
<td>122</td>
</tr>
<tr>
<td>03</td>
<td>Nacl</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>30</td>
<td>40</td>
<td>50</td>
<td>----</td>
<td>----</td>
<td>40</td>
</tr>
<tr>
<td>04</td>
<td>Kcl</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>30</td>
<td>40</td>
<td>----</td>
<td></td>
</tr>
<tr>
<td>05</td>
<td>NaHCO3</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>25</td>
</tr>
<tr>
<td>06</td>
<td>SLS</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>07</td>
<td>Talc</td>
<td>03</td>
<td>03</td>
<td>03</td>
<td>03</td>
<td>03</td>
<td>03</td>
<td>03</td>
<td>03</td>
<td>03</td>
<td>03</td>
</tr>
<tr>
<td>08</td>
<td>Mg Stearate</td>
<td>03</td>
<td>03</td>
<td>03</td>
<td>03</td>
<td>03</td>
<td>03</td>
<td>03</td>
<td>03</td>
<td>03</td>
<td>03</td>
</tr>
<tr>
<td>09</td>
<td>PVP</td>
<td>05</td>
<td>05</td>
<td>05</td>
<td>05</td>
<td>05</td>
<td>05</td>
<td>05</td>
<td>05</td>
<td>05</td>
<td>05</td>
</tr>
</tbody>
</table>

*MCC-Microcrystalline cellulose, Nacl-Sodium chloride, Kcl-Potassium chloride, NaHCo3-Sodium bicarbonate, SLS-Sodium lauryl sulphate, PVP-Polyvinyl pyrrolidine.*
Table 7.2: Designed composition details of different celecoxib EOP tablet batches

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>INGREDIENTS (Mg/tablet)</th>
<th>BATCH CODE:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>01b</td>
</tr>
<tr>
<td>01</td>
<td>Celecoxib</td>
<td>100</td>
</tr>
<tr>
<td>02</td>
<td>MCC</td>
<td>177</td>
</tr>
<tr>
<td>03</td>
<td>NaCl</td>
<td>----</td>
</tr>
<tr>
<td>04</td>
<td>Kcl</td>
<td>----</td>
</tr>
<tr>
<td>05</td>
<td>NaHCO3</td>
<td>----</td>
</tr>
<tr>
<td>06</td>
<td>SLS</td>
<td>12</td>
</tr>
<tr>
<td>07</td>
<td>Tale</td>
<td>03</td>
</tr>
<tr>
<td>08</td>
<td>Mg Stearate</td>
<td>03</td>
</tr>
<tr>
<td>09</td>
<td>PVP</td>
<td>05</td>
</tr>
</tbody>
</table>

MCC-Microcrystalline cellulose, NaCl-Sodium chloride, Kcl-Potassium chloride, NaHCO3-Sodium bicarbonate, SLS-Sodium lauryl sulphate, PVP-Polyvinyl pyrrolidine

Table 7.3: Designed composition details of different Lornoxicam EOP tablet batches

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>INGREDIENTS (Mg/tablet)</th>
<th>BATCH CODE:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>01c</td>
</tr>
<tr>
<td>01</td>
<td>Lornoxicam</td>
<td>08</td>
</tr>
<tr>
<td>02</td>
<td>MCC</td>
<td>119</td>
</tr>
<tr>
<td>03</td>
<td>NaCl</td>
<td>----</td>
</tr>
<tr>
<td>04</td>
<td>Kcl</td>
<td>----</td>
</tr>
<tr>
<td>05</td>
<td>NaHCO3</td>
<td>----</td>
</tr>
<tr>
<td>06</td>
<td>SLS</td>
<td>12</td>
</tr>
<tr>
<td>07</td>
<td>Tale</td>
<td>03</td>
</tr>
<tr>
<td>08</td>
<td>Mg Stearate</td>
<td>03</td>
</tr>
<tr>
<td>09</td>
<td>PVP</td>
<td>05</td>
</tr>
</tbody>
</table>

MCC-Microcrystalline cellulose, NaCl-Sodium chloride, Kcl-Potassium chloride, NaHCO3-Sodium bicarbonate, SLS-Sodium lauryl sulphate, PVP-Polyvinyl pyrrolidine
7.2 PREFORMULATION STUDY OF POWDER BLEND

Preformulation studies are the first step in the development of dosage form of a drug substance. Preformulation investigations are designed to identify those physicochemical properties and excipient that may influence the formulation design, method of manufacture, and pharmacokinetic-biopharmaceutical properties of the resulting product. Followings are the test performed for the preformulation study.

1) Identification of drug by UV
2) Drug-Excipient interaction study
3) Bulk density
4) Tapped density
5) Flow property (Angle of Repose)
6) Carr’s index & Hausner’s ratio

7.2.1 Identification of drug by UV
A solution of 100ug/mL concentration was prepared by dissolving 10mg of drug in 100mL of saline phosphate buffer pH-7.4 and scanned between respective ranges in nm.

7.2.2 Drug and excipient interaction study
To detect any incompatibility of drug with excipient, the IR spectroscopic analysis is carried out.

7.2.3 Determination of bulk density
Weighed quantity of the granules (W) was taken in a graduated measuring cylinder and volume (V₀) was measured and bulk density was calculated using formula

\[ \text{Bulk density} = \frac{\text{Weight of powder}}{\text{Bulk volume}} \]

7.2.4 Determination of Tapped density
Take weighed quantity of granules and transferred in 100 mL graduated cylinder of tapped density apparatus. And density was calculated using formula

\[ \text{Tapped density} = \frac{\text{Weight of powder}}{\text{Tapped volume of packing}} \]
7.2.5 Carr’s Compressibility index & Hausner’s Ratio

The compressibility index and Hausner ratio are measures of the propensity of powder to be compressed. Carr’s compressibility index and Hausner’s ratio can be calculated as follows:\textsuperscript{118}

\[
\text{Carr’s index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100
\]

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

<table>
<thead>
<tr>
<th>Compressibility Index (%)</th>
<th>Flow Character</th>
<th>Hausner Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>\leq 10</td>
<td>Excellent</td>
<td>1.00–1.11</td>
</tr>
<tr>
<td>11–15</td>
<td>Good</td>
<td>1.12–1.18</td>
</tr>
<tr>
<td>16–20</td>
<td>Fair</td>
<td>1.19–1.25</td>
</tr>
<tr>
<td>21–25</td>
<td>Passable</td>
<td>1.26–1.34</td>
</tr>
<tr>
<td>26–31</td>
<td>Poor</td>
<td>1.35–1.45</td>
</tr>
<tr>
<td>32–37</td>
<td>Very poor</td>
<td>1.46–1.59</td>
</tr>
<tr>
<td>&gt;38</td>
<td>Very, very poor</td>
<td>&gt;1.60</td>
</tr>
</tbody>
</table>

7.2.6 Determination of flow property

The frictional force in the powder can be measured by the angle of repose. Angle of repose was calculated by fixed funnel method. Angle of repose can be calculated by using following formula

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

Where, \( h = \) Height of heap in cm,

\[
\text{and } r = \text{Radius of heap base in cm.}
\]
Table 7.5: Correlations between Angle of Repose & Flow Property

<table>
<thead>
<tr>
<th>Angle of Repose (θ)</th>
<th>Predicted Flow Property</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-30</td>
<td>Excellent</td>
</tr>
<tr>
<td>31-35</td>
<td>Good</td>
</tr>
<tr>
<td>36-40</td>
<td>Fair (Aid not needed)</td>
</tr>
<tr>
<td>41-45</td>
<td>Passable (May Hang up)</td>
</tr>
<tr>
<td>46-55</td>
<td>Poor (Must agitate or vibrate)</td>
</tr>
<tr>
<td>56-65</td>
<td>Very poor</td>
</tr>
<tr>
<td>&gt;66</td>
<td>Very, Very Poor</td>
</tr>
</tbody>
</table>

7.3 CONSTRUCTION OF CALIBRATION CURVE FOR ETEROCOXIB

7.3.1 Calibration curve of Etercoxib in saline phosphate buffer pH 7.4

a) Preparation of standard stock solution

About 10 mg of Etercoxib was dissolved in 100 mL of phosphate buffer pH 7.4 to give concentration of 100μg/mL.

b) Preparation of working standards solution

From standard stock solution 1mL of solution was taken in a volumetric flask and volume made up to 100mL with buffer to get solution of concentration 1μg/mL. In this manner, solutions of concentration 2μg/mL, 3μg/mL up to 10μg/mL were prepared. Same procedure was followed for calibration curve of Etoricoxib in hydrochloric acid pH 1.2.

c) Preparation of saline phosphate buffer pH 7.4

About 2.38g of sodium hydrogen phosphate, 0.19g of potassium dihydrogen phosphate and 8.0gm of sodium chloride were dissolved in sufficient water to produce 1000mL.

d) Preparation of hydrochloric acid pH 1.2

About 50mL of 0.2M potassium chloride was taken in 200mL volumetric flask to which was added 85mL of 0.2M hydrochloric acid and sufficient purified water to make up the volume.
7.4 CONSTRUCTION OF CALIBRATION CURVE FOR CELECOXIB

7.4.1 Preparation Standard stock solution for both Calibration curve

A stock solution of celecoxib was prepared by dissolving 10mg of drug in 100mL of 1.2 pH hydrochloric acid Buffer to get a final concentration of 100μg/mL. From the stock solution remove 1mL stock solution in 100mL volumetric flask and make volume up to 100mL, it will give concentration of 1μg/mL in these way various dilutions were made to obtain solutions of 1, 2, 3, 4 up to 10μg/mL, and absorbance was measured for each dilution.

1 Standard calibration curve for Celecoxib in Hcl Buffer pH-1.2

Place 50mL of 0.2M potassium chloride in 200ml volumetric flask, add 85ml of 0.2M hydrochloric acid and then add water to volume.

2 Standard curve for Celecoxib in saline phosphate buffer pH-7.4

Dissolve 2.38g of sodium hydrogen phosphate, 0.19g of potassium di hydrogen phosphate and 8g of sodium chloride in sufficient water to produce 1000mL.

Note- As the drug is slightly soluble in buffer, 2% of sodium lauryl sulphate is added to increase solubility of drug.

7.5 CONSTRUCTION OF CALIBRATION CURVE FOR LORNOXICAM

7.5.1 Construction of calibration curve for lornoxicam in Phosphate Buffer

a) Preparation of 7.4 pH phosphate buffer solution

Dissolve 2.38g of disodium hydrogen phosphate, 0.19g of potassium di hydrogen phosphate and 8gm of sodium chloride in sufficient water to produce 1000mL. Adjust the pH if necessary.

b) Preparation of solvent phase (100mL)

Mix 50mL of Phosphate buffer 7.4 and 50mL of Methanol to made solvent phase of Phosphate buffer: methanol in ratio 50:50.

c) Preparation of standard stock solution

Standard stock solution was prepared by dissolving 50mg of lornoxicam in 50mL of solvent phase to get concentration of 1mg/mL.
d) Preparation of working standard solution and construction of calibration curve

The prepared stock solution was further diluted with solvent phase to get working standard solution of 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10μg of Lornoxicam to construct Beer’s law plot for the pure drug, the absorbance was measured at λ max at 380nm, against solvent phase as blank. The standard graph was plotted by taking concentration of drug on X-axis and absorbance on Y-axis in the concentration range of 1-10μg.

7.5.2 Construction of calibration curve for lornoxicam in HCl pH 1.2

a) Preparation of 0.1N HCl pH 1.2

About 8.5mL of concentrated HCl was placed in a 1000mL volumetric flask. Then volume was adjusted to 1000mL with distilled water. The prepared solution was tested using pH meter. The pH of solution was adjusted to 1.2. The prepared solution was freshly prepared for all the experimental procedures.

b) Preparation of stock solution of Lornoxicam

About 10mg of Lornoxicam was weighed accurately and it was dissolved in 100mL of pH 1.2 buffer solution. The strength of solution was found to be 0.1mg/mL respective dilutions were prepared using stock solution.

c) Preparation of working standard solution and construction of calibration curve

The prepared stock solution was further diluted with solvent phase to get working standard solution of 2, 4, 6, 8, and 10μg of Lornoxicam to construct Beer’s law plot for the pure drug, the absorbance was measured at λ max at 380nm, against solvent phase as blank. The standard graph was plotted by taking concentration of drug on X-axis and absorbance on Y-axis in the concentration range of 2-10μg.

7.6 PREAPRATION OF ELEMENTRY OSMATIC PUMP TABLET\textsuperscript{123}

7.4.1 Formulation of core tablet

Accurately weighed quantities of ingredients mentioned in formula were passed through sieve No. 85 (aperture size 180 micron, British standard). All the ingredient,
except (lubricant-magnesium stearate, glidant-talc and binder -polyvinylpyrrolidone (PVP)), were manually blended homogeneously in a mortar by way of geometric dilution. The mixture was moistened with aqueous solution of 10% (m/v) PVP, and granulated through sieve No.18 (aperture size 1003 micron, US standard) and dried in a hot air oven at 60⁰C for sufficient time so that the moisture of the granules reached 2-4 %. The dried granules were passed through sieve No.25 (aperture size 710 micron, US standard) and blended with talc and magnesium stearate. The homogeneous blend was then compressed into tablets (300 mg) using 10mm diameter, deep concave punches. The compression force was adjusted to give tablet with approximately 7-8 kg/cm² hardness on a Monsanto tablet hardness tester.

### 7.4.2 Coating of core tablet:

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>COATING FORMULATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>01.</td>
<td>Cellulose acetate 2% w/v</td>
</tr>
<tr>
<td>02.</td>
<td>Castor oil or Polyethylene glycol(400) 20% of total solid polymer 10%v/v</td>
</tr>
<tr>
<td>03.</td>
<td>Isopropyl alcohol 10% v/v</td>
</tr>
<tr>
<td>04.</td>
<td>Acetone q.s.to 100% v/v</td>
</tr>
</tbody>
</table>

The coating operation was performed on 40-tablet batch in a conventional laboratory model of stainless steel, 20 cm diameter pear shaped, baffled coating pan. Baffled were three in number to allow free tumbling of tablet. The pan speed was 30 rpm and the coating solution was sprayed on tumbling bed of tablet with the help of spray gun manually. The inlet air temperature was 40-45⁰C and the manually coating procedure used was intermittent spraying and drying technique. The coat weight and thus was coating thickness was controlled by the volume of coating solution consumed in the coating process. Coated tablet were allowed to dry completely in a hot air oven at 60⁰C. An appropriate orifice was drilled on one face of the tablet through the membrane by mechanical microdrill.
7.5 EVALUATION OF UNCOATED TABLET

7.5.1 Weight variation \(^{124}\)

Twenty tablets were randomly selected from each batch and individually weigh. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation. If not more than 2 of the individual tablet weight deviates from the average weight. Weight variation of uncoated tablet was performed by taking random sample of 20 tablets. All the tablets were individually weigh to calculate average weight and to verify the weight of the same.

7.5.2 Friability \(^{125}\)

20 uncoated tablets were weighed and placed in the Roche friability test apparatus. The tablets were exposed to rolling and repeated shocks resulting from free fall tablet in the apparatus. Apparatus speed was maintained at 25rpm/min. The test was carried for 4 min. (total 100 revolution) Then the tablet were dedusted and reweighed. The friability was determined as the percent loss in weight of the tablets.

7.5.3 Hardness \(^{126}\)

Monsanto hardness tester was used to test the hardness of the tablets. Tablet was kept diagonally between the two plungers and a pressure was applied to it until the tablets are broken down and scale reading was noted down.

7.6 EVALUATION OF COATED TABLET \(^{127}\)

7.6.1 Uniformity of Coating

The uniformity of coating among the tablet was estimated by determining the weight, thickness, and diameter of tablet before and after coating using 20 individual tablets, and the corresponding average values, standard deviation (SD) and coefficient of variation (CV) were calculated.

7.6.2 Coat weight and Thickness

The coat weight and thickness were determined (n=20) using a standard analytical balance and screw gauge, respectively, and their corresponding S.D. values were calculated.
7.6.3 Orifice Diameter

The average orifice diameter of the coated tablet was determined microscopically (n=20) using a recalibrated ocular microscope.

7.6.4 In-vitro release

In vitro releases of Celecoxib from various OPTs were investigated using the standard USP dissolution apparatus II at 100rpm. One tablet was placed in 900mL of dissolution media equilibrated to 37 ± 0.1 °C. Then 5mL sample were withdrawn, from the point halfway between the surface of the dissolution medium and the top of the paddle, with pipette at different time interval, replacing with an equal volume of pre-warmed (37±0.1°C.) fresh dissolution medium and analyzed spectro photometerically at 254nm after suitable dilution. Each study was done in triplicate and the mean values are reported.

7.6.5 Drug Release as a Function of Agitation Intensity

To study the effect of agitation intensity, drug release studies were performed at a relatively high (100 rpm) and low (50 rpm) agitation intensity and at static condition using the USP dissolution apparatus in saline phosphate buffer pH-7.4, similarity as described above. Under static conditions, samples at different times were taken after uniform mixing of the medium to preclude any possible sampling error.

7.6.6 Effect of pH of the Dissolution medium on Release rate

Release rates of Celecoxib from OPTs in saline phosphate buffer of pH 7.4 and in 0.1 N HCl of pH 1.2 were compared using USP dissolution apparatus at 100rpm, similarly as described above.

7.7 KINETIC MODEL FITTING STUDY\textsuperscript{128}

Kinetics release studies

For determination of drug release kinetics from osmotic tablet, \textit{in-vitro} release data were analyzed by zero order, first order, Higuchi, and Korsmeyer and Peppas model.
Zero order release kinetics
To study the zero order release kinetics, the release data were fitted into the equation no and the graph is plotted percentage cumulative drug release vs. time.

\[ Q_t = K_0 t \] \quad \text{(7.1)}

Where,
- \( Q \): amount of drug release
- \( K_0 \): Zero order release rate constant
- \( t \): release time

First order release kinetics
To study the first order release kinetics release data were fitted into the equation no. and the graph is plotted log % CDR remaining Vs time.

\[ Q_t = Q_0 (1 - e^{-kt}) \] \quad \text{(7.2)}

Where,
- \( Q \): Fraction of drug release
- \( K \): first order 1 release rate constant
- \( t \): release time

Higuchi Release model
To study the Higuchi Release model the release rate data were fitted into the equation no and The graph is plotted log % CDR Vs square root of time

\[ Q_t = K_h \sqrt{t} \] \quad \text{(7.3)}

Where,
- \( Q \): Fraction of drug
- \( K_h \): release rate constant
- \( t \): release time

Korsmeyer and Peppas kinetics
To study the Korsmeyer and Peppas kinetics the release rate data were fitted into the following equation. The graph is plotted log % CDR Vs log time
\[ \frac{Q_t}{Q_\infty} = Kp t^n \] \hspace{1cm} (7.4)

Where,

\[ \frac{Mt}{M_\infty} \] - fraction of drug release,

K - kp release rate constant, t - release time

n - Diffusion exponent related to mechanism of drug release

**Hixson-Crowell cube root law**

To study Hixson-Crowell cube root law the kinetics of release rate data were fitted into the following equation.

\[ 3\sqrt[3]{Q_t} - 3\sqrt[3]{Q_\infty} = Khct \] \hspace{1cm} (7.5)

**7.8 DRILLING OF ORIFICE IN EOP TABLET**

The drilling of different sizes of orifice was done by with the help of mechanical microdrill as shown in figure 10 & 11.

![Figure 7.1: Mechanical microdrill & different size of rods](image)

Figure 7.1: Mechanical microdrill & different size of rods
Figure 7.2: Drilling of orifice in EOP tablet with microdrill