FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLET OF LORNOXICAM

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ABSTRACT
The object of the present study was to develop sustained release matrix tablets of Lornoxicam drug using different polymers viz. Hydroxy Propyl methyl cellulose K100M (HPMC K100M) and Ethyl cellulose. The tablets were evaluated for physical characteristic like friability, weight variation, hardness and drug content. In-vitro release of drug substance was performed in 0.1 N HCl solution (pH-1.2) for two hours & phosphate buffer solution (PBS) pH 6.8 for the rest of the period. Compatibility of Lornoxicam drug with different excipient (drug: excipient in the ratio 1:1) was carried out using Fourier Transform Infra Red Spectroscopy (FTIR) and TLC methods. These physical mixtures were subjected for accelerated stability study as per ICH guidelines (40±2OC at 75±5% RH) for three months period. For sustaining the release of Lornoxicam drug it is necessary to develop a suitable extended release formulation, hence by using the compatible polymers sustained release tablets were formulated and subjected for various types of evaluation parameters like friability, hardness, drug content and dissolution behaviour. Tablet containing HPMC and Ethyl Cellulose (3:1 ratio) as a matrix former showed maximum release (96.26%) and was found to be more stable under accelerated stability conditions.

KEYWORDS: Lornoxicam, Sustained Release Tablets, HPMC K100M polymer, Ethyl Cellulose polymer.

INTRODUCTION
Lornoxicam is a Non Steroidal anti Inflammatory drug which is mainly used in treatment of “Arthritis” means joint Inflammation. Lornoxicam drug belongs to class of oxicam which inhibits the production of prostaglandins by inhibiting the action of cyclooxygeenase enzyme which regulates the conversion of arachidonic acid to prostaglandins pathway. Lornoxicam drug is absorbed rapidly and completely from gastro-intestinal tract after oral administration route. The absolute bioavailability of Lornoxicam drug is 90-100%[1]. The inhibition of cyclooxygenase enzyme is thought to be primarily responsible for the anti inflammatory effect and analgesic effect of Lornoxicam drug[2].

Previsously Senthil et. al. (2015)[3]worked on development of extended release matrix type tablets of lornoxicam drug using eudragit RS100, polyvinylpyrrolidone, ethyl cellulose, carbopol and pectin polymer as carriers substance in various concentrations. Their study showed to improve biological
efficiency of drug and better type patient compliance. Jadi et. al. (2015)[4] worked on design of extended release matrix tablets of lornoxicam drug using natural polymers like pectin, okra gum, locust bean gum, orange peel and xanthum gum. The formulation containing xanthan gum polymer as drug retarding polymer showed better extended effect for 12 hours period. Yadav et. al. (2014)[5] worked on development of once daily extended release matrix type tablets of lornoxicam drug using polymers such as HPMC K 15M, xanthum gum, guar gum, ethyl cellulose as carriers used in various concentrations showed greater level retarding of drug.

Efforts have been done to develop a stable tablet with a controlled release for 24 h period using biocompatible hydrophilic and hydrophobic polymers. HPMC polymer upon contact with dissolution fluid hydrate slowly, swells and forms a thick gel at the surface of the tablet which is basic responsible for controlling drug release rate. In this present study it was aimed to Design, Develop and Evaluate a sustained release matrix tablet of Lornoxicam using HPMC K 100M and Ethyl Cellulose polymers

MATERIAL AND METHODS

Lornoxicam drug, pharmaceutical excipients and different chemicals was used of Pharma grade or Laboratory grade and supplied from different chemical and Pharma companies/suppliers as listed below.

Table no.1: List of materials and suppliers

<table>
<thead>
<tr>
<th>Materials</th>
<th>Supplier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lornoxicam drug</td>
<td>Glenmark Pharmaceutical Ltd, Himachal pradesh.</td>
</tr>
<tr>
<td>Hydroxy propyl methyl cellulose</td>
<td>Arihant trading company, Mumbai.</td>
</tr>
<tr>
<td>K100M</td>
<td></td>
</tr>
<tr>
<td>Ethyl cellulose</td>
<td>Elegant drugs Pvt.Ltd, Mumbai.</td>
</tr>
<tr>
<td>PVP K-30</td>
<td>S.D. fine chem Ltd., Mumbai.</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>Famy care Ltd., Mumbai.</td>
</tr>
<tr>
<td>Lactose</td>
<td>Ranbaxy chemicals, Mumbai.</td>
</tr>
<tr>
<td>Talc</td>
<td>S.D. Fine chem Ltd., Mumbai.</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>S.D. Fine chem Ltd., Mumbai.</td>
</tr>
<tr>
<td>Potassium dihydrogen phosphate</td>
<td>S.D. Fine chem Ltd., Mumbai.</td>
</tr>
<tr>
<td>Disodium hydrogen ortho phosphate</td>
<td>S.D. Fine Chem Ltd., Mumbai</td>
</tr>
<tr>
<td>Potassium chloride</td>
<td>S.D. Fine chem Ltd., Mumbai.</td>
</tr>
<tr>
<td>Potassium bromide</td>
<td>S.D. Fine chem Ltd., Mumbai.</td>
</tr>
</tbody>
</table>
Procedure for formulation of Sustained release matrix tablet

All the ingredients were weighed accurately and mixed well in double cone blender Lornoxicam drug was first mixed with the polymer, PVP K30 and directly compressible lactose for 10 min to obtain uniform mixture. Then the mixture was passed through 60#. Finally the mixture was blended with talc and magnesium stearate. 100 mg tablets were punched by direct compression in compression machine. Further these tablets were subjected for the different evaluation parameters.

Table no.2: Composition for sustained release matrix tablet of lornoxicam formulation design

<table>
<thead>
<tr>
<th>Ingredient (in mg)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lornoxicam</td>
<td>16</td>
<td>16</td>
<td>16</td>
<td>16</td>
<td>16</td>
<td>16</td>
<td>16</td>
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<td>16</td>
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<tr>
<td>HPMC K100M</td>
<td>16</td>
<td>32</td>
<td>48</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>24</td>
<td>16</td>
<td>08</td>
</tr>
<tr>
<td>Ethyl Cellulose</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>16</td>
<td>32</td>
<td>48</td>
<td>08</td>
<td>16</td>
<td>24</td>
</tr>
<tr>
<td>PVP K 30</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Lactose</td>
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<td>16</td>
<td>56</td>
<td>24</td>
<td>16</td>
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<td>12</td>
<td>08</td>
<td>-</td>
<td>16</td>
<td>08</td>
<td>08</td>
<td>-</td>
<td>16</td>
</tr>
<tr>
<td>Magnesium Stearat</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Talc</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Pre-formulation parameters:

1) Infrared absorption:

IR spectrum of drug substance was measured in the solid state as potassium bromide dispersion. The sample was previously ground and well mixed thoroughly with potassium bromide at 1:100 ratio (sample: KBr) respectively. The KBr substance discs were prepared by compressing the powders under high force of 12 tonnes for 5 min in a hydraulic press. Infrared spectrum of pure drug substance sample of Lornoxicam was concordant with reference spectrum of Lornoxicam drug.

2) UV Spectra:

Accurately weighed about 100 mg of Lornoxicam drug and dissolved in phosphate buffer solution (pH 6.8). Diluted the solution to 100 ml with phosphate buffer (pH 6.8). Further 10 ml of this solution type was diluted to 100 ml with phosphate buffer solution (pH 6.8). The resultant solution
of the drug was scanned for absorption maxima (λmax) spectrophotometrically between 200nm and 400nm range. The solution of the drug was shown absorption maxima at 376nm.

**Preparation of standard solution:**

100 mg of Lornoxicam drug was accurately weighed and dissolved into small volume of phosphate buffer solution (pH 6.8) in 100 ml volumetric flask then shake well and sonicated and made up the volume with the phosphate buffer solution (pH 6.8) to get a concentration of 1000μ g/ml (SS-I). The stock solution-I 10 ml was diluted to 100 ml with phosphate buffer solution (pH 6.8). Solution to get a concentration of 100μ g/ml

3) **Compatibility studies of drug and Excipients:**

Compatibility studies of the Lornoxicam drug was performed by visual observation and Fourier transform Infrared spectroscopy (FTIR).

**Sample preparation for compatibility study:**

Physical mixture of drug substance and different tablet excipients were prepared in the ratio of 1:1 (25mg of each). After mixing filled and then sterile vials in an aseptic environment. These vials were sealed with aluminium caps type. These vials of sample were then stored in stability chamber under controlled condition as mentioned in ICH guidelines. In this study samples were stored at 40 ± 2OC and 75 ± 5% relative humidity for twenty-one days and evaluated for visual observation and FTIR.

4) **Determination of drug content:**

Accurately weighted about 5mg of the mixture from each vial and dissolved in phosphate buffer solution (pH 6.8). Different dilutions were made to get the concentration within beers law range. Absorbance of each sample was measured by using UV spectrophotometer at 376nm. Drug content was calculated using equation below.

**Drug content = absorbance/slope x dilution factor**

5) **Fourier Transform Infrared Spectroscopy**

After twenty-one days the samples were removed from stability chamber and were pressed into pellets with KBr substance. These pellets were scanned between 500 to 4000 cm⁻¹ wave number. The sample was previously ground stage and mixed thoroughly with potassium bromide substance at 1:100 ratio (sample:KBr) respectively. Preparation of KBr substance pellets: 5 mg of the physical mixture was taken in a small glass mortar substance and mixed with little quantity of KBr substance powder and mix well type. Finally thin pellets formed were compressed and used for FTIR scanning.
Evaluation of Pre-compression Parameters:

a. Bulk density:
The loose bulk density (LBD) and tapped bulk density (TBD) both were determined. An amount of the powder blend was introduced in a 100 ml measuring cylinder then the weight of powder blend was determined tared type method. The cylinder was allowed to fall onto a hard surface or plate from a height of 2.5 cm at 2 sec intervals. The tapping was continued on tab densitometer till no volume change of cylinder was noted. LBD and TBD both were calculated by using following formulas:

\[ LBD = \frac{\text{weight of the powder}}{\text{volume before tapping}} \]
\[ TBD = \frac{\text{weight of the powder}}{\text{tapped volume of the packing}} \]

b. Carr’s Compressibility Index:
A significant measure that can be simple obtained from the bulk density determinations is percent (%) compressibility C, % Carr’s Index parameter can be basically calculated by using the following formula-

\[ \text{Carr’s index percentage} = \frac{\text{tapped bulk density (TBD)} - \text{loose bulk density (LBD)}}{\text{tapped bulk density (TBD)}} \times 100 \]

c. Hausner’s ratio:
Hausner ratio is an indirect type index for measuring the powder flow character. It is widely used for calculated by this following formula

\[ \text{Hausner ratio’s ratio} = \frac{\text{tapped density (TD)}}{\text{bulk density (BD)}} \]

Lower hausner ratio are (<1.25) indicates better flow properties character.

d. Angle of repose:
The angle of repose of the powder blend was determined by using the funnel method. The accurately weighed or quantity of the powder was taken in a funnel. The height of the funnel which was more adjusted in such a way that the tip of the funnel is just touched the apex of the heap of the powder material. The diameter of the powder material cone formed was measured and the angle of repose was calculated by using the below formula  \( \tan \theta = \frac{h}{r} \)

Where h and r are indicate for the height of pile and radius of the base of pile.

Evaluation of Physicochemical Parameters

a. Hardness:
Tablet requires certain amount of mechanical strength or stress or hardness which was measured by Monsanto Hardness Tester. Ten tablets which were randomly picked from each
formulation of drug batch and evaluated for hardness during manufacturing and which expressed in Kg/cm². For each single batch five tablets were used.

b. **Friability:**

The Friability was performed by using Roche Friabilator. Twenty tablets of lornoxicam formulation were previously weighed (Initial weight-W) and placed in the plastic chamber of friabilator. This was then operated for 100 revolutions for 4 min time at 25 rpm. Tablets were dropped from a distance of six inches with each revolution of friabilator. Tablets were dedusted and reweighted (final weight-Wt). Friability of the tablets of lornoxicam formulation should be less than 1%.

\[
\text{Friability} = \left[ 1 - \left( \frac{W_t}{W} \right) \right] \times 100
\]

c. **Weight variation:**

Twenty tablets were selected randomly from each types of the formulation and weighed individually to check or analysis for the weight variation. Average weight was calculated and compared to the individual tablet weight to the average weight. The US Pharmacopoeia allows a very little variation in the weight of a tablet formulation.

d. **Drug content uniformity:**

Thirty tablets of the formulation were weighed and powdered. The quantity equivalent to 100 mg of the lornoxicam drug was weighed accurately and taken in 100 ml of the volumetric flask. The volume was made up to 100 ml with the phosphate buffer solution (pH 6.8) and filtered. 10ml of the filtrate solution was diluted into 100 ml of the volumetric flask and the volume was made with the phosphate buffer solution (pH 6.8). From this solution 1.2 ml solution were pipetted out into 10ml volumetric flasks and the volume made with phosphate buffer solution (pH 6.8). The absorbance of drug was measured at the 376 nm. The drug content uniformity was calculated.

e. **In-vitro dissolution studies:**

In-vitro dissolution studies were carried out using the USP XXIII dissolution apparatus type II at 50 rpm using 0.1N HCl (pH 1.2) solution (900 ml) as a dissolution medium at 37 ± 0.5°C for the first 2 hr interval and phosphate buffer (pH 6.8) solution (900 ml) for the rest of the time period. 5 ml of drug sample was withdrawn at the predetermined time interval of 1 hr up to 24 hr and replaced with the same volume of fresh dissolution medium. The withdrawn drug samples were filtered and analyzed by UV spectrophotometer at 376 nm using pH 6.8 solution as a blank. The Percentage cumulative drug release was calculated.
Kinetics Modelling of Drug

To analyze the mechanism of drug release and release rate kinetics of the dosage form and the data obtained were fitted into Zero order kinetic, First order kinetic, Higuchi matrix and Hixon Crowell model. Based on the ‘R’-value and the best-fit model was more selected.

- **Zero order kinetics:**
  \[ Q_t = Q_0 + K_0 \cdot t \]
  Where,
  \( Q_t \) = amount of the drug substance dissolved in time \( t \)
  \( Q_0 \) = initial amount of the drug substance in the solution
  \( K_0 \) = zero order kinetic release constant.

- **First order kinetics:**
  \[ \log_Q t = \log_Q o + K_1 \cdot \frac{t}{2.303} \]
  Where,
  \( Q_t \) = amount of the drug substance released in time \( t \)
  \( Q_0 \) = initial amount of the drug substance in the solution and
  \( K_1 \) = first order kinetic release constant.

- **Higuchi model:**
  \[ Q_t = K_H \cdot t^{1/2} \]
  Where,
  \( Q_t \) = amount of the drug substance released in time \( t \)
  \( K_H \) = Higuchi dissolution rate constant.

**Accelerated stability studies of the optimized formulation.**

According to the ICH guidelines, Accelerated stability studies are testing at 40 °C ± 2 °C / 75 % RH ± 5 % for a specific time period or interval up to 3 months and long term the stability studies are testing at 25 °C ± 2 °C / 60 % RH ± 5 % for a specific time period or interval up to 12 months.
RESULTS AND DISCUSSION

Table no.3: Evaluation of Pre-compression parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loose bulk density (LBD)</td>
<td>0.400</td>
<td>0.385</td>
<td>0.324</td>
<td>0.331</td>
<td>0.338</td>
<td>0.254</td>
<td>0.305</td>
<td>0.317</td>
<td>0.302</td>
</tr>
<tr>
<td>Tapped density (TBD)</td>
<td>0.465</td>
<td>0.451</td>
<td>0.371</td>
<td>0.383</td>
<td>0.399</td>
<td>0.284</td>
<td>0.365</td>
<td>0.379</td>
<td>0.348</td>
</tr>
<tr>
<td>Compressibility index</td>
<td>13.97</td>
<td>14.63</td>
<td>12.66</td>
<td>13.57</td>
<td>15.28</td>
<td>10.56</td>
<td>16.43</td>
<td>16.35</td>
<td>13.21</td>
</tr>
<tr>
<td>Hausner ratio</td>
<td>1.16</td>
<td>1.17</td>
<td>1.14</td>
<td>1.15</td>
<td>1.18</td>
<td>1.11</td>
<td>1.19</td>
<td>1.19</td>
<td>1.16</td>
</tr>
<tr>
<td>Angle of repose (θ)</td>
<td>25.54</td>
<td>25.25</td>
<td>25.18</td>
<td>25.22</td>
<td>24.87</td>
<td>24.85</td>
<td>25.28</td>
<td>26.95</td>
<td>26.11</td>
</tr>
</tbody>
</table>

The Powder of Lornoxicam was tested for to determine the flow properties of powder. The Angle of repose was found in the range of 24.85 -26.11, which indicated a good flow property. The hausner ratio was found within a range of 1.11-1.18 indirectly indicating a good flow property. The compressibility index was found to be in the range of 10.56-16.43%. All the findings of Pre-compression studies indicated a good flowability of the powder formulation. Thus making the powder liable for direct compression.

Infrared Spectrum:

The IR spectrum was measured in the solid state as potassium bromide salt dispersion. The IR spectrum of lornoxicam drug is presented in Figure 1. Observed peaks are similar to reported peaks of lornoxicam drug.

**Figure no.1:** IR spectra of pure lornoxicam

UV spectra of Lornoxicam:

A UV spectrum of 10ug/ml of Lornoxicam drug substance was taken using phosphate buffers (pH 6.8) solution. The UV spectra was showed at \( \lambda_{max} \) at 376 nm. The standard calibration
curve of lornoxicam drug was prepared using concentration range between 5-30 µg/ml in phosphate buffer solution of 6.8 pH. The Graph of Absorbance vs. Concentration was plotted and found to be linear with \( R^2 = 0.999 \)

![Figure no.2: Standard calibration curve of lornoxicam in phosphate buffer (pH 6.8)](image)

**FTIR Spectra of pure drug, Excipients and their physical mixture.**

The Compatibility studies were also carried out by using FTIR spectra of pure drug, polymer and their physical mixtures. From the results, it was found that there was no interference of the type of functional group as the principle peaks of the lornoxicam drug was found to be unaltered in the drug-excipient physical mixtures and which indicates they were more chemically compatible

![Figure no. 3: FTIR spectra of pure lornoxicam](image)
The tablet thickness of various formulations from F1 –F7 varied from 2.44±0.02 to 2.61± 0.02. The average thickness was found to be within the range of ± 0.17%, which is minimum variation. The hardness of tablet formulations ranged from 5.15.1 ± 0.5 to 7.2 ± 0.2 indicating a good mechanical strength and satisfying the parameter for sustained release. The maximum weight variation of
formulations from F1 to F7 was found to be ± 1.80% which was within the limits as per IP. The drug content in different tablet formulations was highly uniform and in the range of 97.21 ± 0.83% to 101.25 ± 1.31%. The % friability for various formulations was found within the IP limits with the range of 0.29± 0.03% to 0.38 ± 0.08%.

**In-vitro dissolution profile of final compressed tablet:**

The release of Lornoxicam from sustained release matrix tablets varied according to the types and proportion of matrix forming polymers. From *in vitro* drug dissolution profile of Lornoxicam matrix tablet, it was found that highest drug release of 14.41% was observed at 2 h from F1 formulation. From 2 to 8 h the marked percentage release was found to be 10-30%. After 8 h more than 60-80% of the drug was released. After 8 h the release rate slowed down slightly and a sustained release pattern was observed for a period of 24h. The hydrophilic HPMC polymer controlled the release of Lornoxicam effectively for 24 h. It was observed that formulation with the drug polymer ratio 1:1 (F1, F4, F8) showed high drug release rates in comparison with the other formulations. The rate of drug substance release for different formulations were found to be F1 > F4 > F8 as shown in table no.5

**Table no. 5: In-vitro dissolution profile of formulation 1-9.**

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>8.60</td>
<td>6.80</td>
<td>3.625</td>
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<td>2</td>
<td>14.41</td>
<td>12.46</td>
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<td>6.90</td>
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<td>3</td>
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<td>4</td>
<td>43.78</td>
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<td>5</td>
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<td>6</td>
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<td>7</td>
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<td>94.11</td>
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<td>98.47</td>
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<td>24</td>
<td>99.81</td>
<td>96.97</td>
<td>67.66</td>
<td>99.76</td>
<td>96.38</td>
<td>82.93</td>
<td>96.26</td>
<td>97.38</td>
<td>97.35</td>
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</tbody>
</table>
In-vitro drug release profile

![In-vitro drug release profile of sustain release matrix tablet F1- F9](image)

**Figure no.5:** In-vitro drug release profile of sustain release matrix tablet F1- F9

**Drug release kinetic data:**

The curve fitting results of the drug release rate profiles for the designed formulations were subjected for the data analysis. It was found that formulation 7 follows Higuchi model. HPMC matrix type tablet upon contact with dissolution fluid hydrate slowly, swells and forms a thick gel at the surface of the tablet which is basic responsible for controlling drug release rate. Overall curve fitting showed that the drug substance release from HPMC matrix type tablets followed non-fickian diffusion mechanism.

![Higuchi model of optimized formulation F7](image)

**Figure no.6:** Higuchi model of optimized formulation F7

**Stability studies**

Stability studies of the formulation were performed as per ICH guidelines. Physicochemical parameter determine at the interval of 30, 60, 90 days are shown in Table 25. It was found that the optimized tablets of batch F7 is more stable even at exaggerated condition of temperature and humidity. After 3 months time interval, when the optimized batch F7 was subjected for their
organoleptic properties, appearance, friability effect remains unaffected. The hardness after 3 months was found to be 5.0±0.6 kg/cm², drug content and drug release was found to be 99.29±0.68 and 96.25±0.7 % respectively.

CONCLUSION

The present investigation demonstrated that the use of hydrophilic and hydrophobic polymers could be more successfully employed for formulating sustained release matrix tablets of lornoxicam drug. Optimized formulation F7 containing HPMC K100M and Ethyl cellulose polymer at optimum ratio had successfully sustained the drug substance release for 24 h period. Matrix tablets of batch F7 had good in vitro drug substance release. F7 was selected as more optimized formulation and was further subjected or evaluated for stability study. Formulation F7 containing HPMC K100M and EC polymer in the ratio of 3:1 showed a maximum drug substance release of 96.26 % for 24 hours period. The optimized formulation was found to be more stable for a period of 3 months when subjected for the accelerated stability studies at 40 °C ± 2 °C and 75 % RH ±.5 % as per ICH guidelines. It was observed that the optimized matrix tablets of F7 batch followed the Higuchi model drug release profiles.

Thus, sustained release matrix tablets of Lornoxicam drug using biocompatible polymers like HPMC K100M and ethyl cellulose were successfully formulated, evaluated and found to be more suitable candidates in extending for sustaining the release of the drug substance from the matrix tablets.

REFERENCES


