Formulation and Evaluation of Immediate Release Tablets of Zaltoprofen

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Abstract: Zaltoprofen is a nonsteroidal anti-inflammatory drug (NSAIDs) with powerful analgesic action on inflammatory pain. The purpose of this research work was to formulate an immediate release tablet of Zaltoprofen for the treatment of pain and inflammation, by using superdisintegrant such as Croscarmellose sodium and different grades of microcrystalline cellulose. Immediate release tablets of Zaltoprofen were prepared by direct compression method using superdisintegrant such as Croscarmellose sodium and different grades of microcrystalline cellulose in different ratios. Sodium starch glycolate was added to aid disintegration. Tablets were subjected to physicochemical characterization such as thickness, hardness, friability, weight uniformity, drug content, disintegration time, in vitro drug release, and stability study. Tablets were found to be satisfactory when evaluated for thickness, hardness, friability, weight uniformity, drug content, disintegration time and in vitro drug release. The tablet disintegration time was less than one minute for all the tablet formulations. The in vitro drug release in optimized formulation F14 was found to be 98.89 % in 45 min. The optimized formulation F14 also showed satisfactory hardness (5.83±0.556 kg/cm²), friability (0.425%±0.0029), drug content (98.29%±0.0657), weight variation (270.21±0.2184 mg), disintegration time (25.02±0.0028seconds) and stability.

Keywords: Pain and inflammation, Immediate release tablets, Superdisintegrants, NSAIDs.

INTRODUCTION
This research work is concerned with design and characterization of oral immediate release tablets of Zaltoprofen, in order to provide immediate relief from pain and inflammation. Immediate release drug delivery systems are designed to provide immediate drug levels in short period of time. Immediate release drug delivery is desirable for drugs having long biological half life, high bioavailability, lower clearance and lower elimination half life. But main criterion for immediate release dosage form is poor solubility of the drug and the need of immediate action of drug to treat unwanted defect or disease [1]. The tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness and ease in manufacturing. In pharmaceutical industries, manufacturers of generic tablets are usually focussed on the optimization of the excipient mixture to obtain a product that meets established standards [2, 3].

Zaltoprofen, 2-(10, 11-dehydro – 10 – oxodibenzo [b, f] thiepin – 2 - yl) pro-pionic acid is a potent nonsteroidal anti-inflammatory drug (NSAID) [4]. Zaltoprofen is a nonsteroidal anti-inflammatory drug (NSAIDs) with powerful analgesic action on inflammatory pain [5, 6]. It is a preferential cyclooxygenase (COX)-2 inhibitor [7].

NSAIDs are classified according to their chemical structure or their selective inhibition of COX-1 and COX-2. Zaltoprofen is a preferential COX-2 inhibitor [8] and selectively inhibits prostaglandin E2 (PGE2) production at inflammatory sites [9-13]. Zaltoprofen has a unique action in inhibiting bradykinin (BK)– induced nociceptive responses more potently than do other NSAIDs [5, 14].

MATERIALS
Zaltoprofen was obtained as a gift sample from Intas Pharmaceuticals Ltd., Ahmedabad, Gujarat, India. All other chemicals used were analytical grade and were used without purification. Double distilled water was used in the study.

METHOD
Immediate release tablets were prepared by the formula given in table 1. Direct compression method was employed using a combination of different grades of microcrystalline cellulose [15-25, 31, 33, 37]. Different grades of microcrystalline cellulose like Avicel pH 102 and Avicel pH 200 were sifted through sieve number 40 along with diluent directly compressible lactose. Sifted drug and disintegrants sodium starch glycolate and ac-di-sol were added and mixed thoroughly [26]. Sodium lauryl Sulphate was added to aid release. The prepared powder blend was
evaluated for various parameters like bulk density, tapped density, angle of repose, compressibility index and Hausner’s ratio [27, 28]. This blend was then compressed using a rotary compression machine (Cadmach, Ahmedabad, India) using magnesium stearate as lubricant and colloidal silicon dioxide as glidant.

EVALUATION OF POWDER BLEND

Particle size distribution [29, 30]

The measurement of particle size distribution was performed by sieving method using vibration sieve apparatus. A sieve stack with six sieves in aperture progression was loaded with powder on to the coarsest sieve of the assembled stack and nest is subjected to mechanical vibration. After 10 min, the particles are considered to be retained on the sieve mesh; then weighed the powder retained in the sieves and the respective parameters were calculated.

Drug–Excipient Interaction Study [30-33]

The drug, polymer and other formulation ingredients were characterized by IR spectroscopy using a FTIR 8400S (Shimadzu, Japan). The spectra were taken by KBr discs method in the range of 4700–400 cm–1.

Bulk density [30-33]

It is a ratio of mass of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantity of powder was carefully poured in to graduated measuring cylinder through large funnel and volume was measured, which is called initial bulk volume. It is expressed in gm/ml and is given by the formula

\[
\text{Bulk density} = \frac{M}{V_0}
\]

Where, \(M\) = mass of the powder
\(V_0\) = bulk volume of the powder

Tapped density [30-33]

Ten gram of powder was introduced into a clean, dry 100 ml measuring cylinder. The cylinder was then tapped 100 times from a constant height and the tapped volume was read. It is expressed in gm/ml and is given by

\[
\text{Tapped density} = \frac{M}{V_t}
\]

Where, \(M\) = mass of the powder
\(V_t\) = final tapping volume of the powder

Angle of repose (\(\theta\)) [30-33]

It is defined as the maximum angle possible between the surface of the pile of the powder and the horizontal plane. Fixed funnel method was used. A funnel was fixed with its tip at a given height ‘\(h\)’, above a flat horizontal surface to which a graph paper was placed. Powder was carefully poured through a funnel till the apex of the conical pile just touches the tip of the funnel. The angle of repose was then calculated using following equation

\[
\text{Angle of repose} \ (\theta) = \tan^{-1}\left(\frac{h}{r}\right)
\]

Where, \(h\) = height of the pile
\(r\) = radius of the pile

Compressibility index (Carr’s index) [30-33]

Compressibility index is used as an important parameter to determine the flow behaviour of the powder. It is indirectly related to the relative flow property rate, cohesiveness and particle size. It is simple, fast and popular method for predicting flow characteristics. Carr’s index can be represented by Equation

\[
\text{Carr’s index} \ (\%) = \left(\frac{\text{Tapped density}}{\text{Bulk density}}\right) \times 100
\]

Hausner’s ratio [30-33]

Hausner’s ratio is used to predict the flowability of the powders. This method is similar to compressibility index. Hausner’s ratio can be represented by Equation

\[
\text{Hausner’s Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}
\]

EVALUATION OF TABLETS [34-36]

All the tablets were evaluated for different parameters as thickness, hardness, friability, uniformity of weight, disintegration time, drug content and in vitro dissolution study.

Dimensional Analysis

The thickness and diameter of tablets was determined using vernier caliper. Twenty tablets from each batch were used and average values were calculated.

Hardness

The Monsanto hardness tester was used to determine the tablet hardness. The tablet was held between affixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of the hardness of the tablet. It is expressed in kg/cm². For each formulation, the hardness of six tablets was determined and average value was calculated.

Weight variation

Randomly selected twenty tablets were weighed individually and together in a single pan balance. The average weight was noted and standard deviation calculated. The tablets pass the test if not more than two tablets fall outside the percentage limit and none of the tablet differs by more than double percentage limit. IP limit for weight variation in case of tablets weighing up to 120 mg is ± 10%, 120 mg to 300 mg is ± 7.5% and more than 300 mg is ± 5%.

\[
\text{PD} = \left[\left(\frac{W_{\text{avg}} - W_{\text{initial}}}{W_{\text{avg}}}\right)\right] \times 100
\]

Where, \(PD\) = Percentage deviation,
\(W_{\text{avg}}\) = Average weight of tablet,
\(W_{\text{initial}}\) = Individual weight of tablet.
Drug content

Tablets were crushed and the powder equivalent to 100mg of drug were accurately weighed and transferred to 50ml volumetric flask. To this flask, sufficient amount of distilled water was added to dissolve the tablets completely. Then, the volume of flask was made up to the mark with same solvent. From this solution, 1ml of the sample was pipetted out and transferred to 10 ml volumetric flask. The volume in the second flask was made up to the mark with distilled water. From this 0.6ml, 0.8ml, and 1ml samples were withdrawn and volume was made up to 10ml to maintain concentration within the beer’s range. This final diluted solution was estimated UV spectrophotometrically at 340 nm.

Friability

Twenty tablets samples were weighed accurately and placed in friabilator (Roche friabilator). After the given specification (4 min at 25 rpm), loose dust was removed from the tablets. Finally tablets were weighed. The loss in weight indicates the ability of the tablets to withstand this type of wear. The % friability was then calculated by

\[ \text{Firmability} = \left( \frac{W_{\text{avg}} - W_{\text{initial}}}{W_{\text{avg}}} \right) \times 100 \]

Disintegration test

Disintegration is evaluated to ensure that the drug substance is fully available for dissolution and absorption from the gastrointestinal tract. Disintegration test was carried out using tablet disintegration test apparatus (Electrolab, India) using distilled water without disk at room temperature (37±2°C).

In-vitro drug release

In vitro dissolution studies for all the tablets were carried out using USP type II Dissolution apparatus (Electrolab, Mumbai, India). The dissolution medium used was 900 ml, mixture of phosphate buffer solution pH 6.8 and water (1:1) used as dissolution medium. The tablets containing 80 mg of zaltoprofen were weighed and then introduced into the dissolution medium. 1 ml aliquots were withdrawn at every 1 hour and replaced by 1 ml of fresh dissolution media (37ºC). The medium was stirred at 50 rpm using paddle at 37±0.5°C. The samples were collected, filtered through Whatman filter paper (0.45um) and analyzed after suitable dilution (if required) at 340 nm using UV-visible spectrophotometer against phosphate buffer (pH 6.8) as blank.

Stability studies

The stability studies were conducted by storing the optimized formulation tablets at 40 ± 2°C/75 ± 5% RH in stability chamber for 45 days. The samples were withdrawn after 45 days and analyzed for various physical tests and drug release study.

RESULTS AND DISSCUSSION

Immediate release tablet of Zaltoprofen were successfully prepared by direct compression method using superdisintegrant like croscarmellose sodium and varying the grades of microcrystalline cellulose, as per formulation table (Table no. 1).

Table 1: Formulations of Immediate Release Tablet of Zaltoprofen

<table>
<thead>
<tr>
<th>Ingredients</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>
<th>F10</th>
<th>F11</th>
<th>F12</th>
<th>F13</th>
<th>F14</th>
<th>F15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zaltoprofen</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>80</td>
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<td>80</td>
</tr>
<tr>
<td>Directly Compressible Lactose</td>
<td>160</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>80</td>
<td>-</td>
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</tr>
<tr>
<td>Microcrystalline cellulose (Avicel pH 102)</td>
<td>-</td>
<td>-</td>
<td>60</td>
<td>30</td>
<td>40</td>
<td>-</td>
<td>160</td>
<td>80</td>
<td>100</td>
<td>97.3</td>
<td>94.6</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Microcrystalline cellulose (Avicel pH 200)</td>
<td>-</td>
<td>60</td>
<td>-</td>
<td>30</td>
<td>40</td>
<td>160</td>
<td>-</td>
<td>80</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>100</td>
<td>97.3</td>
<td>94.6</td>
<td>91.9</td>
</tr>
<tr>
<td>Ac – di – sol (Crosscarmellose Sodium)</td>
<td>15</td>
<td>15</td>
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<tr>
<td>Sodium starch glycolate</td>
<td>6</td>
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<tr>
<td>Colloidal silicon dioxide (Aerosil 200)</td>
<td>6</td>
<td>6</td>
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<tr>
<td>Magnesium Stearate</td>
<td>3</td>
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</tr>
<tr>
<td>Sodium Lauryl Sulphate</td>
<td>-</td>
<td>-</td>
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<td>-</td>
<td>2.7</td>
</tr>
</tbody>
</table>

Compatibility study

The FTIR spectral analysis showed that there was no change in any characteristic peaks of pure drug and excipients, which confirmed the absence of chemical interaction between drug and excipients. The FTIR spectra of pure drug and drug with excipients are given in Figure 1 and 2 respectively.
Mass-volume relationship

The characterizations of different formulation were done for determination of mass-volume relationship parameters. The evaluated parameters are bulk density, tapped density, compressibility index, and angle of repose, Carr’s index shown in table 2.

Table 2: Evaluation of Pre-compressed Powder Blend

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Bulk Density (gm/ml)</th>
<th>Tapped Density (gm/ml)</th>
<th>Angle of Repose (θ)</th>
<th>Carr’s Compressibility Index</th>
<th>Hausner’s Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.3525±0.0019</td>
<td>0.4840±0.0043</td>
<td>30.763±0.324</td>
<td>27.16±1.0438</td>
<td>1.3731±0.0196</td>
</tr>
<tr>
<td>F2</td>
<td>0.3279±0.0008</td>
<td>0.4709±0.0048</td>
<td>30.631±0.213</td>
<td>20.80±0.6574</td>
<td>1.2628±0.0105</td>
</tr>
<tr>
<td>F3</td>
<td>0.4355±0.0025</td>
<td>0.5782±0.0032</td>
<td>27.413±0.330</td>
<td>24.67±0.7104</td>
<td>1.3277±0.0125</td>
</tr>
<tr>
<td>F4</td>
<td>0.3661±0.0044</td>
<td>0.4805±0.0041</td>
<td>27.748±0.301</td>
<td>23.81±0.7456</td>
<td>1.3126±0.0128</td>
</tr>
<tr>
<td>F5</td>
<td>0.3852±0.0026</td>
<td>0.4991±0.0042</td>
<td>29.654±0.436</td>
<td>22.82±0.6827</td>
<td>1.2956±0.0114</td>
</tr>
<tr>
<td>F6</td>
<td>0.5039±0.0076</td>
<td>0.6380±0.0146</td>
<td>28.763±0.765</td>
<td>21.01±0.2798</td>
<td>1.2660±0.0045</td>
</tr>
<tr>
<td>F7</td>
<td>0.4923±0.0070</td>
<td>0.6052±0.0013</td>
<td>26.463±0.358</td>
<td>18.63±1.0889</td>
<td>1.292±0.0165</td>
</tr>
<tr>
<td>F8</td>
<td>0.5104±0.0069</td>
<td>0.6152±0.0121</td>
<td>26.763±0.314</td>
<td>17.01±0.8365</td>
<td>1.205±0.0122</td>
</tr>
<tr>
<td>F9</td>
<td>0.5159±0.0114</td>
<td>0.6772±0.0053</td>
<td>24.514±0.336</td>
<td>23.80±1.6335</td>
<td>1.3129±0.0284</td>
</tr>
<tr>
<td>F10</td>
<td>0.5116±0.0087</td>
<td>0.6207±0.0069</td>
<td>23.214±0.201</td>
<td>17.57±1.7219</td>
<td>1.2136±0.0251</td>
</tr>
<tr>
<td>F11</td>
<td>0.5040±0.0073</td>
<td>0.6068±0.0073</td>
<td>22.985±0.504</td>
<td>16.95±0.8713</td>
<td>1.204±0.0126</td>
</tr>
<tr>
<td>F12</td>
<td>0.4897±0.0065</td>
<td>0.5892±0.0024</td>
<td>22.645±0.225</td>
<td>16.88±1.3210</td>
<td>1.203±0.0189</td>
</tr>
<tr>
<td>F13</td>
<td>0.4874±0.0044</td>
<td>0.5686±0.0075</td>
<td>22.632±0.702</td>
<td>14.28±0.5358</td>
<td>1.166±0.0072</td>
</tr>
<tr>
<td>F14</td>
<td>0.4849±0.0057</td>
<td>0.5694±0.0019</td>
<td>22.225±0.452</td>
<td>14.82±1.2643</td>
<td>1.174±0.0017</td>
</tr>
<tr>
<td>F15</td>
<td>0.4940±0.0068</td>
<td>0.5856±0.0084</td>
<td>22.314±0.235</td>
<td>15.62±1.5644</td>
<td>1.185±0.0217</td>
</tr>
</tbody>
</table>

All values are presented as Mean ±S.D.
Flow properties

The bulk density of the powder was in the range of 0.33 to 0.52 gm/ml; the tapped density was in the range of 0.47 to 0.67 gm/ml, which indicates that the powder was not bulky. The angle of repose of the formulations with lactose in larger quantity was in the range of 26° to 30°, which on increasing the quantity of microcrystalline cellulose decreased to the range of 22° to 24° which indicated good flow of the powder. The Carr’s index was found to be in the range of 17 to 23 with the formulations containing lactose indicating poor compressibility of the tablet blend. This compressibility index decreased to the range of 14 to 16 on increasing the quantity of microcrystalline cellulose and eliminating lactose which improved the compressibility pattern.

Weight variation

The weight variation was prominent in the formulations with more lactose because of poor flow properties of the powder mixture. It ranged from 268 mg to 271 mg with very high values of standard deviation. On increasing microcrystalline cellulose the weight variation was significantly reduced. The results are shown in table no. 3. All formulations pass the weight variation test.

Table 3: Evaluation of Immediate Release Tablets of Zaltoprofen

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Hardness (kg/cm²)</th>
<th>Friability (%)</th>
<th>Weight Variation (mg)</th>
<th>Content uniformity (%)</th>
<th>Thickness (cm)</th>
<th>Disintegration time (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>5.31±0.1495</td>
<td>0.463±0.1900</td>
<td>271.43±3.0130</td>
<td>98.06±0.1002</td>
<td>4.88±0.0251</td>
<td>30.58±1.932</td>
</tr>
<tr>
<td>F2</td>
<td>5.53±0.2666</td>
<td>0.431±0.0056</td>
<td>268.97±1.8593</td>
<td>97.21±0.0003</td>
<td>4.21±0.0051</td>
<td>29.10±0.485</td>
</tr>
<tr>
<td>F3</td>
<td>5.40±0.1557</td>
<td>0.470±0.0127</td>
<td>270.36±1.3376</td>
<td>98.23±0.1020</td>
<td>4.62±0.0003</td>
<td>27.08±0.023</td>
</tr>
<tr>
<td>F4</td>
<td>6.00±0.1026</td>
<td>0.476±0.0085</td>
<td>270.15±0.7823</td>
<td>98.41±0.1142</td>
<td>4.56±0.0506</td>
<td>29.23±0.0569</td>
</tr>
<tr>
<td>F5</td>
<td>5.46±0.6784</td>
<td>0.521±0.0210</td>
<td>270.30±0.8602</td>
<td>99.03±0.0305</td>
<td>4.33±0.0761</td>
<td>27.00±0.0147</td>
</tr>
<tr>
<td>F6</td>
<td>5.44±0.5148</td>
<td>0.445±0.0061</td>
<td>270.39±1.3497</td>
<td>100.23±0.0142</td>
<td>4.81±0.0032</td>
<td>28.61±0.0025</td>
</tr>
<tr>
<td>F7</td>
<td>5.63±0.6513</td>
<td>0.504±0.0146</td>
<td>269.95±0.3993</td>
<td>98.54±0.0651</td>
<td>4.44±0.0062</td>
<td>26.21±0.0124</td>
</tr>
<tr>
<td>F8</td>
<td>6.01±0.1159</td>
<td>0.698±0.5421</td>
<td>270.90±0.4420</td>
<td>99.63±0.5241</td>
<td>4.58±0.0910</td>
<td>27.36±0.0005</td>
</tr>
<tr>
<td>F9</td>
<td>5.69±0.1400</td>
<td>0.679±0.3451</td>
<td>270.43±0.9639</td>
<td>98.61±0.2142</td>
<td>4.31±0.1001</td>
<td>25.09±0.0054</td>
</tr>
<tr>
<td>F10</td>
<td>6.07±0.0602</td>
<td>0.580±0.0053</td>
<td>270.59±0.2523</td>
<td>97.65±0.0806</td>
<td>4.25±0.0147</td>
<td>25.87±0.0000</td>
</tr>
<tr>
<td>F11</td>
<td>6.03±0.0680</td>
<td>0.395±0.0315</td>
<td>270.88±0.3798</td>
<td>99.37±0.0547</td>
<td>4.61±0.0037</td>
<td>26.32±0.0052</td>
</tr>
<tr>
<td>F12</td>
<td>5.81±0.1692</td>
<td>0.401±0.0148</td>
<td>270.41±0.3255</td>
<td>98.72±0.0191</td>
<td>4.65±0.0154</td>
<td>27.43±0.0036</td>
</tr>
<tr>
<td>F13</td>
<td>6.17±0.5656</td>
<td>0.391±0.0159</td>
<td>270.93±0.2957</td>
<td>99.23±0.0140</td>
<td>4.70±0.0091</td>
<td>25.31±0.0001</td>
</tr>
<tr>
<td>F14</td>
<td>5.83±0.556</td>
<td>0.425±0.0029</td>
<td>270.21±0.2184</td>
<td>98.29±0.0657</td>
<td>4.62±0.0156</td>
<td>25.02±0.0028</td>
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<tr>
<td>F15</td>
<td>5.68±0.1184</td>
<td>0.437±0.0058</td>
<td>270.53±0.2332</td>
<td>97.88±0.0082</td>
<td>4.52±0.0213</td>
<td>25.64±0.0062</td>
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</table>

All values are presented as Mean ±S.D.

Tablet Thickness

Thickness of the formulations varied from 4.21±0.0051 to 4.88±0.0251 mm.

Hardness

The hardness was uniformly maintained and it was found to be within 5.31±0.1495 to 6.17±0.5656 kg/cm².

Friability

The values of friability were within the limits except the formulations F8 and F9 where high friability was noted. These high values may be due to the change in the grade of microcrystalline cellulose.

Disintegration test

Tablets from each batch show immediate disintegration. Disintegration time varied between 25 to 30 seconds. This rapid disintegration is due to the rapid uptake of water from the medium, swelling and burst effect of Crosscarmellose sodium.

Percentage drug content

The percentage drug content of tablets of all batches was found to be 97.21 % to 100.23 %, which was within the acceptable limits.

Drug release

Comparative cumulative percentage drug release data of all formulations are given in table no. 4. Dissolution profiles of formulations F1 to F8 and F9 to F15 are shown in Figure 3 and 4 respectively. Drug release for different batches was found to be 82.75 to 98.89 within 45 minute. The maximum drug release was observed in F14 among all formulations in 45 minute.
Table 4: Comparative % drug release profiles of formulation (F1-F15)

<table>
<thead>
<tr>
<th>Time (min)</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>
<th>F10</th>
<th>F11</th>
<th>F12</th>
<th>F13</th>
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<th>F15</th>
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Fig. 3: Dissolution profiles of formulations F1 to F8

Fig. 4: Dissolution profiles of formulations F9 to F15

CONCLUSION

All formulations were found to be satisfactory when evaluated for thickness, weight uniformity, hardness, friability, drug content uniformity, disintegration time and *in-vitro* drug release. The tablet disintegration time was less than one minute for all the tablet formulations. The *in vitro* drug release in optimized formulation F14 was found to be 98.89% in 45 min. The optimized formulation F14 also showed satisfactory hardness (5.83±0.556 kg/cm²), friability (0.425%±0.0029), drug content (98.29%±0.0657), weight variation (270.21±0.2184 mg), disintegration time (25.02±0.0028seconds) and stability.

REFERENCES

4. Ito A, Mori Y; Effect of a Novel Anti-Inflammatory Drug, 2-(10, 11-dihydro-10-oxo-dibenzo[b,f]-thiepin-2-yl)propionic acid (CN-100), on the Proteoglycan Biosynthesis in Articular Chondrocytes and Prostaglandin E2 Production in Synovial Fibroblasts. Res


