Development and Assessment of Trandolapril Immediate Release Tablets Employing Various Super-disintegrating Agents

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ABSTRACT

Trandolapril is a powerful prodrug that does not contain sulfur and is converted into its active form, trandolaprilat, in the liver. Trandolapril has demonstrated efficacy and safety in treating mild-to-moderate essential hypertension in obese persons. The half-life of trandolapril and trandolaprilate is roughly 6 hours and 16-24 hours, respectively. This refers to the duration it takes for the concentration of these compounds to reduce by half due to elimination mechanisms. The aim of this study is to improve the composition of the Trandolapril immediate release tablet by integrating various types of supersintegrants. The optimization procedure utilized Crospovidone, sodium starch glycolate, and croscarmellose sodium as superdisintegrating agents. These agents were used at concentrations of 2%, 4%, and 6%. Nine formulations (IRTR 1 to IRTR 9) were created using the direct compression approach. The pre-compression parameters of all batches were assessed in relation to the set thresholds, and it was concluded that the powder blend had outstanding flow and compressibility characteristics. The tablets were assessed for post-compression properties, including hardness, drug content, and Disintegration Time (DT). A drug dissolution test was performed in a laboratory setting using 900 ml of hydrochloric acid (HCl) with a concentration of 0.1N. The test was completed at a controlled temperature of 37 ± 0.5°C. When formulating IRTR1-IRTR9, the disintegration time varied between 30.23 and 71.67 seconds. Additionally, over 70% of the medication was released during a 30-minute period. Therefore, after assessing many characteristics, it was concluded that the formulation of immediate release tablets of Trandolapril was successfully developed. The tablet designated IRTR3 demonstrated a disintegration time of 30.23, which is the shortest time it took to break down. Additionally, it achieved a drug release of 90.56% within a 30-minute period.

Keywords: Cytotoxicity, Gene delivery, Nanoparticles, Targeted therapy, Clinical trials, Ligand.

INTRODUCTION

Trandolapril, a non-sulfhydryl prodrug, is a highly effective angiotensin-converting enzyme (ACE) inhibitor that undergoes rapid hydrolysis in the liver to form the active diacid molecule known as trandolaprilat.[1-2] The compound is classified as belonging to Biopharmaceutics Classification System (BCS) Class II and Biopharmaceutics Drug Disposition Classification System (BDDCS) Class II.[3] Clinically, it is utilized for the management of patients diagnosed with congestive heart failure and myocardial infarction.[1-2] In the case of individuals who are overweight and have mild-to-moderate essential hypertension, trandolapril has been found to be both effective and safe.[3] Because of its robust affinity for ACE and high lipophilicity index, it exhibits superior efficacy in comparison to alternative ACE (Angiotensin Converting Enzyme) inhibitors. The user's text is already technical and does not need to be rewritten. The elimination half-life of Transdolapril is approximately 6 hours.[4-5] The trandolaprilat has an effective half-life of 16 to 24 hours at steady state. Therefore, it is a suitable candidate for an immediate release dosage form. An
immediate release dosage form refers to a type of medication where at least 85% of the labeled amount dissolves within 30 minutes.\textsuperscript{[6]} The tablet formulation primarily utilizes superdisintegrants such as croscarmellose, sodium starch glycolate, and crospovidone. These superdisintegrants facilitate rapid disintegration of the tablet upon ingestion in the gastric environment. Therefore, reducing the disintegration time, which subsequently improves the drug dissolution rate.\textsuperscript{[7]}

Immediate release drug delivery is advantageous for medications with extended biological half-life. This study focuses on the design and characterization of oral immediate release tablets containing Trandolapril. The objective is to develop a formulation that can effectively manage high blood pressure by providing immediate release of the medication. Immediate release drug delivery systems are developed by incorporating superdisintegrants to achieve rapid drug release within a short timeframe. In this study, we evaluated the performance of immediate release tablets containing Trandolapril.

**MATERIALS**

Trandolapril was acquired as a complimentary sample from Mylan Laboratories Limited, Hyderabad. All other chemicals utilized in the experiment were of analytical grade.

**METHODS**

The Trandolapril immediate release tablets were manufactured according to the composition specified in Table 1. Various superdisintegrating agents, including crospovidone, sodium starch glycolate, and croscarmellose sodium, were employed alongside a consistent quantity of microcrystalline cellulose (MCC) and produced using the direct compression technique.\textsuperscript{[8-11]} MCC with a pH of 102 and diluent directly compressible lactose were both subjected to filtration using sieve number 40. The drug was prepared by employing the geometric dilution technique, in which it was combined with a pre-sieved excipient mixture and different disintegrants. The prepared powder blend underwent testing to determine various parameters, such as the density of the blend (both bulk and tapped), Hausner's ratio, compressibility index, and angle of repose. The mixtures underwent pre-mixing with talc and magnesium stearate before being compressed using the Rimek Mini Press-II MT Rotary tableting 12 station Machin.

**Table 1: Formulation composition of Immediate release tablets of Trandolapril**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>IRTR1</th>
<th>IRTR2</th>
<th>IRTR3</th>
<th>IRTR4</th>
<th>IRTR5</th>
<th>IRTR6</th>
<th>IRTR7</th>
<th>IRTR8</th>
<th>IRTR9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trandolapril</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>CP</td>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>6</td>
<td>9</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SSG</td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>CCS</td>
<td></td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MCC (PH 102)</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
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<td>50</td>
</tr>
<tr>
<td>Anhydrous Lactose</td>
<td>91</td>
<td>88</td>
<td>85</td>
<td>91</td>
<td>88</td>
<td>85</td>
<td>91</td>
<td>88</td>
<td>85</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Talc</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>Total weight (mg)</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
</tr>
</tbody>
</table>

CP: Crospovidone, SSG: Sodium starch glycolate, CCS: Croscramellose sodium, MCC: Microcrystalline cellulose.

**Pre-compression evaluation of Powder Blend**

*Drug–Excipient Interaction Study by FTI*\textsuperscript{[12-13]}
The drug and drug-excipient mixture (1:1) were subjected to characterization using infrared (IR) spectroscopy. The Fourier-transform infrared (FTIR) spectrophotometer (Bruker Alpha Model _Absorbance Mode)[7] was employed for this purpose.[12-13] The KBr disc method was utilized to obtain spectra within the wavelength range of 4000–400 cm\(^{-1}\).

**Drug–Excipient Interaction Study by XRD [12-13]**

The X-ray diffraction (XRD) experiments were performed using a D8 Advance XRD instrument equipped with a 2.2 kW sealed X-ray tube operating at a wavelength of Cu-K\(\alpha\). A scanning rate of 10°/min was employed to collect X-ray powder diffraction patterns over a 2θ angular range of 5–80°, with an increment of 0.05°.

**Bulk Density [14-15]**

The bulk density of the powder was determined using 20g of powder was weighed and then poured into a graduated cylinder through a large funnel. The resulting volume was measured using Equation 1. The tapped density was assessed by repeatedly tapping the graduated cylinder for 200 times and volume was observed. The volume of the sample after tapping was then measured using Equation 2.

\[
\text{Bulk density} = \frac{M}{V_0} \quad \text{Eq.1}
\]

Where, \(M\) = Mass of the powder, \(V_0\) = Bulk volume of the powder

\[
\text{Tapped Density (TD) = Weight of powder/ Tapped volume} \quad \text{Eq.2}
\]

**Hausner’s ratio and Carr’s index [14-15]**

The Hausner’s ratio Eq. 3 is used to know the flow property of powder or granular material.[9]

\[
H = \frac{TD}{BD} \quad \text{Eq.3}
\]

Where, \(BD\) is the Bulk density of the powder, and \(TD\) is the Tapped density of the powder.

**Carr’s Index (CI)** is an indication of the compressibility and flow property of a powder. It is calculated by Eq. [4]:

\[
CI = \left\{ \frac{(TD-BD)}{TD} \right\} \times 100 \quad \text{Eq.4}
\]

Where, \(BD\) is the Bulk density of the powder, and \(TD\) is the Tapped density of the powder.

**Angle of repose (\(\theta\)) [14-15]**

The maximum angle that can be formed between the surface of the powder pile and the horizontal plane is referred to as the greatest angle. The fixed funnel method was the prevailing technique that was frequently employed. An orthogonal coordinate system was established on a level plane, onto which a grid paper was placed. A funnel was affixed to the surface with its apex positioned at a designated vertical distance, \(h\). The apex of the conical pile was carefully filled by pouring it through a funnel until it made contact with the tip of the funnel (Eq 5).[8]

\[
\text{Angle of repose (\(\theta\)) = tan}^{-1}(h/r) \quad \text{Eq. 5}
\]

**Post Compression Characterization of Tablets**

**Thickness [10]**

The tablet thickness was measured using a Vernier caliper. A total of ten tablets were selected from each batch, and the average values were recorded.

**Weight variation [16]**

An electronic balance (Shimadzu, AUX 220, Japan) was employed to accurately measure the weight of the twenty randomly selected tablets. The weight variation limit specified by the Indian Pharmacopoeia for tablets weighing 80 mg or less is ± 10%. For tablets weighing more than 80 mg but less than 250 mg, the limit is ± 7.5%. Tablets weighing 250 mg or more must have a weight variation within ± 5%.[10]

\[
\text{PD} = \left\{ \frac{(W_{avg} – Wind)}{W_{avg}} \right\} \times 100 \quad \text{Eq.6}
\]

Where, \(PD\) = Percentage deviation, \(W_{avg}\) = Average weight of tablet, \(Wind\) = Individual weight of tablet

**Hardness [10]**

The tablet’s hardness was evaluated using the Monsanto hardness instrument. The tablet was secured using a dynamic jaw and a static jaw. The scale of the hardness tester was calibrated to zero, and then the load was incrementally increased until
the tablet experienced fracture. The pressure exerted on the tablet is directly proportional to its hardness, allowing for a quantitative measurement. A total of six tablets from each formulation were subjected to hardness testing, and the resulting values were used to calculate the average hardness.

**Drug content** [16]

The tablets were pulverized and the resulting powder, which contained 10mg of the drug, was precisely measured and transferred into a 50ml volumetric flask. The drug was extracted and filtered, and after the necessary dilution, the solution was estimated using UV spectrophotometry at a wavelength of $\lambda_{\text{max}}$ 223nm.

**Disintegration test** [16]

The disintegration test measures the duration needed for the tablet to completely break down, ensuring that the drug substance is fully accessible for dissolution and absorption in the gastrointestinal tract. The disintegration test was conducted using a tablet disintegration test apparatus (Electrolab, India) with distilled water as the media at a temperature of 37±2°C.

**In-vitro drug release** [15-16]

An in vitro dissolution study was conducted using the USP type II Dissolution apparatus manufactured by Electrolab in Mumbai, India. The dissolution medium employed was a solution of 900 ml of 0.1 N hydrochloric acid (pH 1.2) at a temperature of 37±0.5°C. The rotational speed of the paddle was maintained at 50 revolutions per minute (rpm). Pre-weighed Trandolapril tablets were placed into the dissolution basket. 5 mL aliquots were extracted at time intervals of 5, 10, 20, and 30 minutes and substituted with 5 mL of new dissolution media. The collected samples underwent filtration using Whatman filter paper. Subsequently, the samples were analyzed after appropriate dilution, if necessary. The absorbance of the samples was measured at a wavelength of 223 nm using a UV-visible spectrophotometer. A blank solution consisting of 0.1N HCl (pH 1.2) was used as a reference.

**RESULTS AND DISCUSSION**

An immediate release tablet of Trandolapril was successfully prepared using the direct compression method. Superdisintegrants such as Crospovidone (IRTR1 to IRTR3), Sodium starch glycolate (IRTR4 to IRTR6), and Croscarmellose sodium (IRTR7 to IRTR9) were used according to the formulation described in Table 1.

**Drug-Excipient compatibility study by FTIR**

The FTIR spectra of the pure drug trandoalpril were analyzed, and the following spectral peaks were observed: 3280.70 cm$^{-1}$ (N-H stretching vibration of the amine group), 2879.87 cm$^{-1}$ (C-H stretching vibration), 1735.83 cm$^{-1}$ and 1653.67 cm$^{-1}$ (C-O stretching vibration in the ester and amide groups), and 1193.29 cm$^{-1}$ (C-O-C stretching vibration). When comparing these peaks to those of the drug and excipient mixture, minor differences were found: 3280.32 cm$^{-1}$, 2877.79 cm$^{-1}$, 1735.83 cm$^{-1}$ and 1653.67 cm$^{-1}$, 1654.07 cm$^{-1}$, and 1193.06 cm$^{-1}$. These differences confirmed that there was no chemical interaction between the drug and excipients. The Fourier Transform Infrared (FTIR) spectra of the pure drug and the drug with excipient mixture are presented in Fig. 1 and Fig. 2, respectively.

![Fig. 1: FTIR Spectrum of Pure Trandolapril](image-url)
Fig. 2: FTIR Spectrum of Trandolapril and Excipient mixture (1:1)

Drug-Excipient compatibility study by XRPD

The presence of similar peaks with higher intensity, as depicted in Figure 3, for both the pure drug (Trandolapril) and the Drug-excipient (1:1) mixture, with only minimal differences, indicates that the drug is compatible with all the excipients utilized in the formulation.

Fig. 3: XRPD pattern of Trandolapril and (1:1); Trandolapril-Excipient

Pre-compression characteristics

The powder blend underwent evaluation for pre-compression parameters including bulk density, tapped density, Hausner's ratio, compressibility index, and angle of repose. The results are presented in Table 2. The bulk density of the powder/s ranged from 0.421±0.012 to 0.435±0.023 gm/ml, while the tapped density ranged from 0.478±0.001 to 0.492 gm/ml. These values suggest that the powder was not voluminous. The Hausner's ratio values ranged from 1.11±0.020 to 1.15±0.017, indicating favorable powder flow characteristics. The Carr's index values were observed to range from 10.25±0.008 to 12.47±0.019, which suggests that the powder blend exhibits favorable compressibility. The measured angle of repose for the formulations ranged from 26.32º ±0.017 to 32.45º ±0.021, which suggests that the powder blend exhibits favorable flow behavior (Table 2).

Table 2: Evaluation of Pre-compressed Powdered Blend

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Bulk density (mean± SD)</th>
<th>Tapped density (mean± SD)</th>
<th>Hausner's ratio (mean±SD)</th>
<th>Carr's index (%) (mean± SD)</th>
<th>Angle of repose (°) (mean± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRTR 1</td>
<td>0.421±0.012</td>
<td>0.481±0.027</td>
<td>1.14±0.006</td>
<td>12.47±0.019</td>
<td>31.09±0.017</td>
</tr>
<tr>
<td>IRTR 2</td>
<td>0.422±0.014</td>
<td>0.485±0.018</td>
<td>1.15±0.017</td>
<td>12.99±0.013</td>
<td>32.45±0.021</td>
</tr>
<tr>
<td>IRTR 3</td>
<td>0.435±0.023</td>
<td>0.490±0.016</td>
<td>1.13±0.019</td>
<td>11.22±0.021</td>
<td>30.23±0.012</td>
</tr>
<tr>
<td>IRTR 4</td>
<td>0.431±0.021</td>
<td>0.492±0.013</td>
<td>1.14±0.026</td>
<td>12.40±0.012</td>
<td>31.54±0.016</td>
</tr>
<tr>
<td>IRTR 5</td>
<td>0.430±0.015</td>
<td>0.488±0.024</td>
<td>1.13±0.014</td>
<td>11.89±0.014</td>
<td>30.67±0.023</td>
</tr>
<tr>
<td>IRTR 6</td>
<td>0.427±0.027</td>
<td>0.484±0.016</td>
<td>1.13±0.033</td>
<td>11.78±0.007</td>
<td>30.23±0.014</td>
</tr>
<tr>
<td>IRTR 7</td>
<td>0.428±0.018</td>
<td>0.489±0.015</td>
<td>1.14±0.012</td>
<td>12.47±0.016</td>
<td>31.07±0.026</td>
</tr>
<tr>
<td>IRTR 8</td>
<td>0.426±0.024</td>
<td>0.482±0.012</td>
<td>1.13±0.041</td>
<td>11.62±0.005</td>
<td>30.45±0.028</td>
</tr>
<tr>
<td>IRTR 9</td>
<td>0.429±0.019</td>
<td>0.478±0.011</td>
<td>1.11±0.020</td>
<td>10.25±0.008</td>
<td>26.32±0.017</td>
</tr>
</tbody>
</table>

Post-compression Characterization of Tablets

The results of post-compression evaluation are displayed in Table 3. The average weight of the tablets ranged from 150.21±0.026 mg to 153.10±0.041 mg, and all of the formulations successfully met the weight variation test criteria. The tablet thickness exhibited a range of 0.59±0.002 to 0.62±0.008. The hardness of the
material was consistently maintained and measured to be within the range of 4.3±0.026 to 5.2±0.021 kg/cm². The tablets from each batch exhibited rapid disintegration. The disintegration time ranged from 30.23±0.069 to 71.67±0.071 seconds. The formulation IRTR3, which contained 6% of crospovidone, exhibited the lowest level of disintegration. The tablets from all batches were analyzed for their drug content percentage, which ranged from 96.78±0.125 to 101.85±0.158. These values were determined to be within the acceptable limits.

The table 4 provides comparative cumulative percentage drug release data for all formulations. The dissolution profiles of formulations IRTR1 to IRTR3, IRTR4-IRTR6, and IRTR7 to IRTR9 are depicted in Figure 3, respectively. The drug release for various batches was determined to range from 71.09±0.275 to 90.56±0.736 within a 30-minute timeframe. The highest drug release was observed with Immediate Release Tablet Formulation 3 (IRTR3) containing crospovidone (90.56±0.736) among all formulations within a 30-minute timeframe.

Table 3: Post Compession characteristics of Immediate Release Tablet of Trandolapril

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Thickness (mm)</th>
<th>Hardness (kg/cm²)</th>
<th>Tablet weight (mg)</th>
<th>Drug content (%)</th>
<th>Disintegration time (Sec.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRTR 1</td>
<td>0.59±0.002</td>
<td>4.6±0.049</td>
<td>150.21±0.054</td>
<td>98.27±0.034</td>
<td>60.13±0.081</td>
</tr>
<tr>
<td>IRTR 2</td>
<td>0.61±0.007</td>
<td>5.0±0.071</td>
<td>152.13±0.036</td>
<td>99.26±0.149</td>
<td>34.45±0.063</td>
</tr>
<tr>
<td>IRTR 3</td>
<td>0.62±0.004</td>
<td>4.8±0.085</td>
<td>153.10±0.041</td>
<td>100.05±0.126</td>
<td>30.23±0.069</td>
</tr>
<tr>
<td>IRTR 4</td>
<td>0.61±0.003</td>
<td>4.9±0.046</td>
<td>151.36±0.014</td>
<td>96.15±0.232</td>
<td>68.12±0.016</td>
</tr>
<tr>
<td>IRTR 5</td>
<td>0.62±0.002</td>
<td>4.5±0.055</td>
<td>153.11±0.083</td>
<td>98.52±0.014</td>
<td>48.26±0.094</td>
</tr>
<tr>
<td>IRTR 6</td>
<td>0.62±0.001</td>
<td>5.2±0.021</td>
<td>152.14±0.024</td>
<td>98.48±0.178</td>
<td>39.56±0.081</td>
</tr>
<tr>
<td>IRTR 7</td>
<td>0.61±0.012</td>
<td>4.6±0.045</td>
<td>151.32±0.048</td>
<td>96.78±0.015</td>
<td>71.09±0.071</td>
</tr>
<tr>
<td>IRTR 8</td>
<td>0.61±0.007</td>
<td>4.3±0.026</td>
<td>152.40±0.061</td>
<td>98.25±0.175</td>
<td>56.32±0.034</td>
</tr>
<tr>
<td>IRTR 9</td>
<td>0.62±0.008</td>
<td>4.7±0.087</td>
<td>153.09±0.067</td>
<td>101.85±0.158</td>
<td>51.45±0.081</td>
</tr>
</tbody>
</table>

The table 4 provides comparative cumulative drug release profiles of formulation

<table>
<thead>
<tr>
<th>Time min</th>
<th>Cumulative % release of trandolapril (mean±SD) (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IRT R 1</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>45.68±0.456</td>
</tr>
<tr>
<td>10</td>
<td>56.82±0.378</td>
</tr>
<tr>
<td>20</td>
<td>65.09±0.675</td>
</tr>
<tr>
<td>30</td>
<td>80.36±0.718</td>
</tr>
</tbody>
</table>

(a)

**Figure 3:** Comparative % Cumulative drug release profiles of formulation.
CONCLUSION

All formulations were determined to be acceptable based on evaluations of thickness, weight uniformity, hardness, drug content uniformity, and disintegration time. Based on the criteria of minimum disintegration time and maximum drug release (greater than 85%), the optimized formulation IRTR3 was chosen. The tablet disintegration time (30.23±0.069 seconds) was found to be the shortest for the IRTR3 formulation compared to all other tablet formulations. The measured in vitro drug release rate for IRTR3 was determined to be 90.56±0.736 in 30 minutes. The crospovidone, at a concentration of 6%, was determined to be the most effective superdisintegrating agent for formulating Immediate Release tablets of Trandolapril.

The successful preparation of a solid dispersion of repaglinide and PVP K30 (1:10) was concluded using the solvent evaporation method. Compared to the pure drug or its physical mixture, the solubility and dissolution of repaglinide from this dispersion system exhibited a notable increase. Experiments utilizing Differential Scanning Calorimetry and X-ray Diffraction techniques demonstrated that this particular system contained a pharmaceutical substance in an amorphous state. In this study, Polyvinylpyrrolidone K30 in a ratio of 1:10 was determined to be the optimal formula. This choice was based on the observation of a significant enhancement in the release of the drug after 30 minutes compared to pure drug.

Conflicts of Interest: The authors declare that there are no conflicts of interest.

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REFERENCES


