CHAPTER-4

FORMULATION AND EVALUATION OF RIZATRIPTAN SUBLINGUAL TABLETS

4.1 EXPERIMENTAL METHODS

4.1.1 Preparation of standard graph of rizatriptan in water at 282nm

16.3mg of rizatriptan benzoate was taken in a standard flask and dissolved and volume be made up to 100 ml with water. From this 5ml, 10ml, 15ml and 20ml of solutions were taken and diluted to 50ml to get 11.2µg/ml, 22.4µg/ml, 33.6µg/ml and 65.2µg/ml of rizatriptan solution respectively. The absorbance of the above was determined at 282nm on a UV-VIS spectrophotometer (Schimadzu UV-1601) against water as blank. A standard graph of concentration v/s absorbance was plotted (Figure-4.1).

4.1.2 Standard graph of rizatriptan benzoate in mixture of buffer (pH3.5) and acetonitrile (80:20)

4.1.2.1 Preparation of the standard and sample drug solutions

About 50 mg of rizatriptan benzoate working standard was weighed and taken into a 50ml volumetric flask, about 25ml of mixture of buffer (pH3.5) and acetonitrile (80:20) were added and sonicated for dissolving the drug and it was diluted with mobile phase i.e. mixture of buffer (pH3.5) and acetonitrile (80:20). From this, 5ml of solution was taken into 50ml standard flask and it was made up to 50ml using mobile phase. From this, 20 ml of solution was transferred in 100ml standard flask and the volume was made up to 100ml with mobile phase.
20 tablets each containing equivalent to 10 milligrams of rizatriptan benzoate were taken and powdered in a mortar. The powder quantity equivalent to 10 mg of rizatriptan benzoate was weighed and transferred to the 50 ml volumetric flask. This was dissolved in mobile phase, sonicated for few min and diluted to the mark. This was then filtered. From this 5 ml of the above solution was taken into the 50 ml volumetric flask and the volume was made 50 ml with the same mobile phase.

4.1.2.2 \( \lambda_{\text{max}} \) determination

From standard dilution 10 µg/ml solution was taken and scanned between 200 nm-400 nm using UV-VIS spectrophotometer (Schimadzu UV-1601). Based on the maximum absorption of the drug, the \( \lambda_{\text{max}} \) was found to be at 225 nm.

4.1.2.3 Preparation of Mobile Phase

Mixture of buffer (pH 3.5) and acetonitrile in the ratio 80:20.

4.1.2.4 Preparation of Buffer

About 2.76 g of sodium dihydrogen orthophosphate monohydrate was dissolved in 1000 ml of water. 2 ml of triethylamine was added and solution was adjusted to 3.5±0.05 pH with orthophosphoric acid and filtered by 0.45 µm nylon membrane filter and was degassed with the help of bath sonicator.

4.1.2.5 Preparation of standard graph.

The working standard solutions were prepared using 50 mg of rizatriptan benzoate in 50 ml standard flask and volume was made to 50 ml using the mobile phase. From this 10 ml of solution was taken and made to
100 ml to get 100µg/ml. 5ml, 10ml, 15ml, 20ml and 25ml of the stock solution was taken which was further diluted to 100ml to get 5, 10, 15, 20 and 25µg/ml respectively. The calibration graph was plotted between 5µg/ml to 25µg/ml. A 10µl of the drug solution was injected at a flow rate of 1.0ml/min into the column. The detection wavelength was monitored at 225nm. The column temperature was maintained at 30°C. Each solution was injected for six times and corresponding chromatograms were obtained. The graph was plotted between concentrations in µg/ml versus peak area (Figure-4.3).

4.2 PREPARATION OF SUBLINGUAL TABLETS USING DIRECT COMPRESSION TECHNIQUE

In present study direct compression technique was used for the preparation of fast disintegrating sublingual tablets of rizatriptan benzoate using superdisintegrants like sodium starch glycollate, croscarmellose sodium and crospovidone (Shangraw et al., 1989). The excipients such as mannitol (100mg) and avicel pH102 (between16% to 21%) were selected as diluents (Debord et al., 1987). Aspartame (0.5%) was used as sweetening agent (Rameshwari et al., 2009) and magnesium stearate (1.0%) was selected as lubricant in this study (Gohel et al., 2005).

Based on the preparations availability in market, tablet weight was fixed. The excipients details were collected from USFDA recommended guidelines. Most widely used superdisintegrants like sodium starch glycollate, croscarmellose sodium and crospovidone were used and optimised their concentrations to get better wetting and disintegration of tablets.
Accurately weighed 14.5mg of rizatriptan benzoate. After passing through sieve number 60 (standard sieve test) all excipients were homogenously mixed using geometric dilution. Finally magnesium stearate of 1.5mg was added for lubrication and triturated well (Biradar et al., 2006). Total nine formulations were prepared. In all the formulations, the superdisintegrant concentration varied between 2-6%. In first three formulations sodium starch glycollate was present as 2%, 4% and 6%, second three formulations had croscarmellose sodium as 2%, 4% and 6% and last three formulations had cros povidone as 2%, 4% and 6%. Different concentrations of excipients were used to prepare various formulations of sublingual tablets. The blended material was compressed on 8mm standard concave punch using a minipress tablet punching machine (RIMEK, India). The total weight of tablet was made up to 150 mg (Keny et al., 2010) (Table-4.). The punched tablets contain 14.5 mg of rizatriptan benzoate i.e., 10mg (equivalent) of rizatriptan. The taste masking of the rizatriptan tablets was done by using aspartame as sweetener.
Table-4.1: Composition of the rizatriptan sublingual formulations.

<table>
<thead>
<tr>
<th>Ingredients(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>Rizatriptan benzoate</td>
<td>14.5</td>
<td>14.5</td>
<td>14.5</td>
<td>14.5</td>
<td>14.5</td>
<td>14.5</td>
<td>14.5</td>
<td>14.5</td>
<td>14.5</td>
</tr>
<tr>
<td>Sodium starch glycollate</td>
<td>3</td>
<td>6</td>
<td>9</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Croscarmellose Sodium</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>Crospovidone</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>Aspartame</td>
<td>0.75</td>
<td>0.75</td>
<td>0.75</td>
<td>0.75</td>
<td>0.75</td>
<td>0.75</td>
<td>0.75</td>
<td>0.75</td>
<td>0.75</td>
</tr>
<tr>
<td>Mannitol</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>
<tr>
<td>Magnesium stearate</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</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>

Each tablet contains equivalent to 10mg of rizatriptan.
4.3 Evaluation of fast disintegrating sublingual rizatriptan benzoate tablets

4.3.1 Evaluation of blends

The flow properties of the powder were very important in handling and processing operations. Hence the following Micromeritic properties were studied on the rizatriptan benzoate powder formulations.

4.3.1.1 Angle of repose (θ)

It is described as the maximum possible angle possible among the surface piles of powder to the horizontal plane (Lachmann et al., 1998).

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

\[ \theta = \tan^{-1}(h/r) \]

\( \theta \) - Repose angle

\( h \) - Height in cm

\( r \) - radius in cm

The angle of repose was measured by means of conventional fixed funnel method. 100 gm of the drug powder was flown through funnel which was fixed to the stand at a fixed height (h). Then radius and the height of the powder bed were measured.

4.3.1.2 Bulk density \((D_b)\)

This is defined as the ratio of mass of the total powder to the bulk volume of powder. It was determined by placing 100 gm of powder material into the measuring cylinder and noted the initial volume of the powder. This is called as a bulk volume. Through this bulk volume, bulk density was measured by using the following formula.
Where $M$ is powder mass.

$V_b$ is powder bulk volume.

$D_b$ is bulk density.

### 4.3.1.3 Tapped density ($D_t$)

It is defined as the ratio of the total powder mass to the tapped volume of powder. This was determined by tapping the 100 gm of the powder for 750 times and noted the volume using tap density tester USP (Tap density tester, Electro lab ETD-1020). The tapping is further continued till the differences between two successive volumes is <2% and is expressed in gm/ml, given by

$$D_t = \frac{M}{V_t}$$

Where $M$ is powder mass

$V_t$ is tapped volume of powder.
Table-4.2 Powder flow properties and angle of repose

<table>
<thead>
<tr>
<th>Flow property</th>
<th>Angle of Repose (degrees)</th>
<th>Compressibility Index (%)</th>
<th>Hausner's Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>25-30</td>
<td>≤10</td>
<td>1.00-1.11</td>
</tr>
<tr>
<td>Good</td>
<td>31-35</td>
<td>11-15</td>
<td>1.12-1.18</td>
</tr>
<tr>
<td>Fair-aid not needed</td>
<td>36-40</td>
<td>16-20</td>
<td>1.19-1.25</td>
</tr>
<tr>
<td>Passable-may hang up</td>
<td>41-45</td>
<td>21-25</td>
<td>1.26-1.34</td>
</tr>
<tr>
<td>Poor-must agitate, vibrate</td>
<td>46-55</td>
<td>26-31</td>
<td>1.35-1.45</td>
</tr>
<tr>
<td>Very poor</td>
<td>56-65</td>
<td>32-37</td>
<td>1.46-1.59</td>
</tr>
<tr>
<td>Very, very poor</td>
<td>&gt;66</td>
<td>&gt;38</td>
<td>&gt;1.60</td>
</tr>
</tbody>
</table>

4.3.1.4 Carr’s Index (Compressibility percentage)

It can be calculated from bulk and tapped density.

Which shows powder flow properties and is expressed as

\[
I = \frac{D_t - D_b}{D_t} \times 100
\]

Where \( D_t \) - tapped density of the powder and \( D_b \) - bulk density of the powder.

4.3.1.5 Hausner’s Ratio

It is an indirect index of easy of powder flow and is measured from the bulk and tapped density of rizatriptan sublingual powder formulation, it is expressed as (Aulton et al., 1988)
Hausner’s ratio = \frac{D_t}{D_b}

Where \(D_t\) is powder tapped density and \(D_b\) is powder bulk density.

4.3.2 Determination of physical properties of tablets

The tablets from each formulation were subjected to the following tests

4.3.2.1 Appearance

General appearance of tablet, overall elegance and visual identity is very much needed for consumer acceptance.

4.3.2.2 Tablet thickness and diameter

Thickness and diameter of tablet is very important characteristic in reproducing appearance. Some filling equipment utilizes the counting mechanism to get uniform thickness. Randomly 20 tablets were taken from each formulation and the thickness and diameter was determined with a vernier caliper (Mututoyo, Japan). The size of the tablet should be described, monitored and controlled.

4.3.2.3 Weight variation

A group of 20 tablets were taken from each formulation randomly and weighed using an electronic balance (Mettler-Toledo, PB303-S/FACT, Switzerland) and measured the average weight. The individual tablet weights are compared with average weight (Gohel et al., 2004).
Table-4.3 Uniformity of weight

<table>
<thead>
<tr>
<th>Tablet average weight</th>
<th>Percentage difference allowed</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤80</td>
<td>±10</td>
</tr>
<tr>
<td>Between 80 and 250</td>
<td>±7.5</td>
</tr>
<tr>
<td>&gt;250</td>
<td>±5</td>
</tr>
</tbody>
</table>

4.3.2.4 Tablet hardness

Strength of the tablet is defined as tensile strength (N: Newton). Tablet crushing load is defined as the force necessary to fracture a tablet into 2 halves by applying compression. The hardness of tablet was measured by tablet hardness tester (Tab machines, India). Six tablets randomly selected from each formulation and noted the average hardness (Gohel et al., 2004).

4.3.2.5 Friability

It is a measurement of mechanical strength of tablet. The friability test was done to evaluate the effects of rubbing and shocks which may frequently cause tablet to damage, cap or rupture. For this purpose Friabilator (Electro lab, India) was used. A pre-weighed group of 20 tablets was located in the Friabilator and rotated for 100 times (USP/NF., 2003). The dusted tablets were then reweighed. The compressed tablets must not drop more than 1% of their weight.

The friability (F) is expressed by

\[ F = \frac{W_{\text{initial}} - W_{\text{final}}}{W_{\text{initial}}} \times 100 \]

4.3.2.6 Wetting time
Wetting time related with contact angle which is significant parameter required for fast dissolving tablets. The tablets with lower wetting time have faster disintegration (Ishikawa et al., 2001). The tablet wetting time was performed using simple procedure and it was done by placing the tablet on tissue paper which was located in a Petri-dish having 10ml of water at room temperature. The complete wetting time of the tablet was recorded (Honey et al., 2008).

4.3.2.7 Disintegration time in vitro

The tablets disintegration time was one of the important factors which are supposed to be optimized in improvement of the sublingual tablets. This test is carried out on six tablets by means of Disintegration tester USP (Electro lab, ED-2AL, India), in distilled water at 37°C ±2°C was used as disintegration medium (USP/NF, 2003). The complete disintegration of tablets without leaving palpable mass on the surface of mesh screen of basket assembly was noted.

4.3.2.8 Disintegration time in vivo

The in vivo disintegration time was carried out by introduction of a tablet in the floor of the mouth of the volunteer (n=6). The time required for total disintegration was noted until the tablet had completely disappeared in the volunteer’s mouth (Najib et al., 1986).

4.3.2.9 Water absorption ratio

6ml of water was located in a Petri-dish and above this water a small tissue paper bend twice was located. The previously weighed tablet was placed gently on it and time taken for total wetting was noted. The weight of wetted tablet was noted.
Wa-Wb
Water absorption ratio (R) =-----------------------x100
Wb

Where Wa and Wb were weights of the tablets after and before absorption of water

4.3.2.10 Dissolution in vitro

For all the formulations the *In vitro* dissolution were studied (Andries et al., 2003); with the help of a USP dissolution test apparatus II i.e., paddle method (Lab India, DS 14000, India) at a speed of 50 RPM according to US FDA recommended guidelines (Toshihiro et al., 2003). Freshly collected 900ml of water was placed in dissolution vessels of dissolution apparatus (USP, apparatus II paddle method). The tablets containing equivalent to 10mg of rizatriptan was placed in a dissolution media at 37±0.5°C temperature and the paddles were rotated at a speed of 50 RPM. 10ml of samples were collected and filtered using a 0.45µm pore size PVDF filter. Sample volume was immediately replaced in vessels with same volume of freshly collected distilled water. The samples were collected at fixed times like 5min, 10min, 15min, 20min, 30min, 45min and 60 min, diluted and analysed for drug substance with a UV-Visible spectrophotometer (Schimadzu, model UV1601, Japan) set at 282nm (Acharjya et al.,2010). The amount of the drug release from the tablets at definite at definite intervals was calculated by using standard graph of rizatriptan in water at 282nm.
4.3.2.11 Uniformity of content

20 tablets were arbitrarily selected and weighed and the average weight of the tablet was calculated. The tablets were then powdered in a glass mortar. Drug content uniformity (USP/NF., 2003) was determined by dissolving the crushed tablets powder equivalent to 10mg of rizatriptan in mobile phase i.e., (80:20 %( v/v)) mixture of buffer (pH 3.5) and acetonitrile respectively and filtered through 0.45µm membrane filter which was degassed. It was made necessary dilutions and analysed by using High Performance Liquid Chromatography (HPLC -Agilent 1100 series, USA) at the wavelength of 225nm. The liquid chromatography equipped with UV detector and column Zorbax SB phenyl, 5µm (250mmx4.6mm) was used. Isocratic elution was down at a flow rate 1.0 ml per min. The volume of injection was 10µl and the temperature of the column was 30°C. The system was equilibrated for at least 30minutes until a steady base line was obtained.

4.3.3 Characterisation of rizatriptan sublingual tablets

4.3.3.1 Scanning Electron Microscopy (SEM) studies

Surface characteristics of the rizatriptan sublingual tablets and standard rizatriptan were examined using Scanning Electron Microscope (SEM) (Scanning Electron Microscopy, JEOL 5400, Japan). The samples were attached on a brass stub by using a two sided adhesive tape (Rahul et al., 2009) and it was made electrically conductive by coating it 5-6 times and formed a layer of gold on it. Then SEM images were measured at an acceleration voltage of 5 kv.
4.3.3.2 **Differential Scanning Calorimetry (DSC) studies**

Molecular state of the drug was measured by performing DSC analysis of placebo (tablet), physical mixture with drug, sublingual rizatriptan formulation and standard rizatriptan using differential scanning calorimeter, (DSC 6, Perkin Elmer, USA) the samples curves were obtained. The samples were heated using hermetically sealed aluminium fans at a temperature range of 35° C - 350° C at a rate of 10.0° C per minute using nitrogen purge at 20ml/minute.

**4.3.3.3 Powder X-Ray Diffractometry (PXRD) studies**

The Physical mixture with drug, sublingual rizatriptan formulation and standard rizatriptan were measured using X-Ray powder diffract meter (XRD x’ pert PRO MPD PANalytical, USA). The diffraction pattern was measured using Ni filtered Cu Kα (45kV/40mA) radiation (Takao et al., 2005). The samples were measured between the angular range of 2°-50°(2θ) using 0.017° steps and 10 s counting time per step.
4.3.3.4 Fourier Transform Infrared Spectroscopy (FT-IR) studies

A composite group of tablets were crushed in a mortar. From this, ten parts of the tablet powder was mixed with hundred parts of KBr and compressed into pellet using KBr pellet press. This pellet was kept in a sample holder of FTIR and the spectrum was obtained. This spectrum was compared with standard rizatriptan spectrum which is obtained by mixing one part of drug with hundred parts of KBr and a pellet is made using KBr pellet press. Both the spectra’s of sample and standard were compared for possible deviations. Infrared spectrum peaks of placebo (tablets), physical mixture without drug, physical mixture with drug and rizatriptan sublingual formulation was compared with rizatriptan standard by means of FT-IR spectrophotometer (Perkin Elmer Spectrum one series, USA) by KBr pellet method. The scanning range was between 400 to 4000 cm\(^{-1}\) and 1 cm\(^{-1}\) resolution.

4.4 STABILITY STUDIES

Optimized formulation (F9) was subjected to stability studies by keeping the tablets in the stability chamber (Thermo lab, USA) at 40±2\(^{\circ}\)C/75±5% RH up to 3 months. The tablets were analyzed at a time interval of 30 days for drug content, hardness, friability, wetting time, and disintegration time \textit{in vitro}. 
4.5 RESULTS AND DISCUSSION

4.5.1 Calibration curves of rizatriptan

4.5.1.1 Preparation of calibration curve of rizatriptan

Rizatriptan has maximum absorbance at 282nm in water. The standard graph of rizatriptan in water was plotted by taking concentration range from 11.2µg/ml to 65.2µg/ml. The calibration curve for rizatriptan in water was found to be linear from 11.2-65.2µg per ml with R²>0.999 (Figure 4.1).

**Table-4.4 Standard graph of rizatriptan in water at 282nm**

<table>
<thead>
<tr>
<th>Concentration(µg/ml)</th>
<th>Absorbance</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.2</td>
<td>0.242</td>
</tr>
<tr>
<td>22.4</td>
<td>0.38</td>
</tr>
<tr>
<td>33.3</td>
<td>0.52</td>
</tr>
<tr>
<td>65.2</td>
<td>0.931</td>
</tr>
</tbody>
</table>

**Figure-4.1 Standard graph of rizatriptan in water at 282nm**

\[ y = 0.012x + 0.095 \]

\[ R^2 = 0.999 \]
4.5.1.2 Calibration curve of rizatriptan benzoate in mixture of buffer (pH3.5) and acetonitrile (80:20)

Mobile phase consists of mixture of buffer (pH3.5) and acetonitrile in the ratio of 80:20 that retained a good symmetric peak at 3.847 and 4.3 respectively. A typical chromatogram was shown in Figure-4.2.

**Figure-4.2 Typical chromatogram of rizatriptan benzoate in mixture of buffer (3.5) and acetonitrile.**

A calibration curve was plotted with concentration versus peak area as shown in the figure-4.3. The linear regression showed good linearity at a concentration range (n=6) of 5-25μg/ml and the $R^2$ of >0.99 was obtained.
Table-4.5 Calibration curve of rizatriptan benzoate in mixture of buffer (pH3.5) and acetronitrile (80:20)

<table>
<thead>
<tr>
<th>Concentration(µg/ml)</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>415.2</td>
</tr>
<tr>
<td>10</td>
<td>771.1</td>
</tr>
<tr>
<td>15</td>
<td>1168.7</td>
</tr>
<tr>
<td>20</td>
<td>1539.2</td>
</tr>
<tr>
<td>25</td>
<td>1924.5</td>
</tr>
</tbody>
</table>

Figure-4.3 Calibration curve of rizatriptan benzoate in mix. buffer (pH3.5) and acetronitrile (80:20)
Table-4.6 Rizatriptan benzoate method validation parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retention time(min)</td>
<td>3.85 and 4.3</td>
</tr>
<tr>
<td>Linearity</td>
<td>5-25 µg/ml</td>
</tr>
<tr>
<td>Correlation coefficient</td>
<td>0.999</td>
</tr>
<tr>
<td>LOD</td>
<td>0.11 µg/ml</td>
</tr>
<tr>
<td>LOQ</td>
<td>0.33 µg/ml</td>
</tr>
<tr>
<td>Precision intraday(%RSD)</td>
<td>1.7</td>
</tr>
<tr>
<td>Precision interday(%RSD)</td>
<td>1.5</td>
</tr>
<tr>
<td>No of theoretical plates</td>
<td>4,330</td>
</tr>
<tr>
<td>Tailing factor</td>
<td>1.3, 1.8</td>
</tr>
<tr>
<td>Recovery</td>
<td>97.62%-102.7%</td>
</tr>
</tbody>
</table>
4.5.2 Evaluation of rizatriptan sublingual Tablets

4.5.2.1 Evaluation of blend

The Micromeritic properties of the rizatriptan benzoate powder formulations are essential in handling operations because the uniformity of the dose and ease of filling the powder into the container is detected by its flow properties. The powder flow properties can be accessed from angle of repose, Hausner’s ratio and Carr’s index. The results for powder formulations were represented in Table-4.7. Results indicate angle of repose <33° assuring that the flow properties were good for all formulations. Apart from this, Carr’s index and Hausner’s ratio were ≤15 and ≤1.18 respectively for all nine formulations and showed good mixing, flow ability and compressibility.
Table-4.7 Powder flow properties of the rizatriptan benzoate formulations.

<table>
<thead>
<tr>
<th>Code</th>
<th>Angle of repose(θ)</th>
<th>Bulk density (gm/cm³)</th>
<th>Tapped density (gm/cm³)</th>
<th>Compressibility index (I)</th>
<th>Hausner's Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>32.6±0.10</td>
<td>0.22±0.01</td>
<td>0.26±0.01</td>
<td>14.87±0.98</td>
<td>1.18±0.01</td>
</tr>
<tr>
<td>F2</td>
<td>32.1±0.12</td>
<td>0.30±0.01</td>
<td>0.34±0.01</td>
<td>11.64±0.21</td>
<td>1.13±0.00</td>
</tr>
<tr>
<td>F3</td>
<td>31.6±0.13</td>
<td>0.22±0.01</td>
<td>0.25±0.01</td>
<td>12.01±0.48</td>
<td>1.14±0.01</td>
</tr>
<tr>
<td>F4</td>
<td>31.0±0.12</td>
<td>0.25±0.01</td>
<td>0.29±0.01</td>
<td>13.64±0.27</td>
<td>1.16±0.01</td>
</tr>
<tr>
<td>F5</td>
<td>30.9±0.13</td>
<td>0.25±0.01</td>
<td>0.28±0.01</td>
<td>10.59±0.21</td>
<td>1.13±0.00</td>
</tr>
<tr>
<td>F6</td>
<td>30.4±0.13</td>
<td>0.25±0.01</td>
<td>0.28±0.01</td>
<td>10.59±0.21</td>
<td>1.13±0.02</td>
</tr>
<tr>
<td>F7</td>
<td>29.8±0.12</td>
<td>0.26±0.00</td>
<td>0.30±0.01</td>
<td>13.48±0.27</td>
<td>1.15±0.02</td>
</tr>
<tr>
<td>F8</td>
<td>30.3±0.13</td>
<td>0.25±0.01</td>
<td>0.28±0.01</td>
<td>10.84±0.23</td>
<td>1.12±0.01</td>
</tr>
<tr>
<td>F9</td>
<td>29.7±0.13</td>
<td>0.26±0.01</td>
<td>0.29±0.01</td>
<td>10.46±0.21</td>
<td>1.12±0.00</td>
</tr>
</tbody>
</table>

Data is indicated as Mean ± SD. (n=3).

4.5.2.2 Evaluation of prepared rizatriptan sublingual tablets

The prepared tablets from each formulation are small white circular, biconcave and odourless tablets. These tablets were subjected for evaluation tests as shown in table-4.8, table-4.9, table-4.10 and table-4.11. The diameter and thickness of all the formulations were ranged from 8.03±0.0mm to 8.07±0.06 mm and from 3.09±0.01 mm to 3.2±0.01 mm respectively. The average weight of the tablet in all formulations ranged from 147.96± 0.06mg to 153.5 ± 0.25mg. All the formulations of tablets indicated good mechanical
strength (4-5 kg/cm²) during compression. The friability in all formulations showed less than 0.5%, indicating the friability was within the acceptable limits (USP 31) and are not brittle and can handle without difficulty.

The wetting time was measured for all the prepared formulations which were very important parameter in fast disintegrating tablets. The wetting time for all the formulations was 65.33±0.58s to 5.33±0.58s which shows the highly permeable nature of the tablets. For the optimized formulation (F9) it was found to be 5.33±0.58s which indicates quicker disintegration of the tablets. The percentage water absorption for all the formulations was between 156.73±0.0% and 94.17±0.0%.

Table 4.8 Evaluation tests of sublingual tablets rizatriptan

<table>
<thead>
<tr>
<th>Formulations Code</th>
<th>Diameter(mm)***</th>
<th>Thickness(mm)***</th>
<th>Average weight(mg)***</th>
<th>Hardness (Kg/cm²)***</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>8.03±0.0</td>
<td>3.2±0.01</td>
<td>153.5±0.25</td>
<td>4.33±0.58</td>
</tr>
<tr>
<td>F2</td>
<td>8.03±0.06</td>
<td>3.10±0.0</td>
<td>151.33±0.06</td>
<td>4.33±0.58</td>
</tr>
<tr>
<td>F3</td>
<td>8.05±0.06</td>
<td>3.15±0.01</td>
<td>150.07±0.06</td>
<td>4.33±0.58</td>
</tr>
<tr>
<td>F4</td>
<td>8.03±0.06</td>
<td>3.18±0.01</td>
<td>153.27±0.06</td>
<td>4.66±0.58</td>
</tr>
<tr>
<td>F5</td>
<td>8.03±0.06</td>
<td>3.10±0.0</td>
<td>147.96±0.06</td>
<td>4.33±0.29</td>
</tr>
<tr>
<td>F6</td>
<td>8.07±0.06</td>
<td>3.09±0.01</td>
<td>150.60±0.0</td>
<td>4.16±0.29</td>
</tr>
<tr>
<td>F7</td>
<td>8.07±0.06</td>
<td>3.18±0.01</td>
<td>151.46±0.10</td>
<td>4.16±0.29</td>
</tr>
<tr>
<td>F8</td>
<td>8.07±0.06</td>
<td>3.20±0.01</td>
<td>151.72±0.02</td>
<td>4.5±0.50</td>
</tr>
<tr>
<td>F9</td>
<td>8.07±0.06</td>
<td>3.10±0.00</td>
<td>152.34±0.03</td>
<td>4.33±0.29</td>
</tr>
</tbody>
</table>

*** All values show mean ± standard deviation (SD) n=20

** All values show mean ± standard deviation (SD) n=6
**Table-4.9 Evaluation tests of sublingual tablets rizatriptan**

<table>
<thead>
<tr>
<th>Formulations code</th>
<th>Friability (%) ***</th>
<th>Wetting time (seconds)*</th>
<th>Water absorption ratio (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.29±0.0</td>
<td>65.33±0.58</td>
<td>156.73±0.0</td>
</tr>
<tr>
<td>F2</td>
<td>0.30±0.0</td>
<td>53.67±0.58</td>
<td>147.36±0.01</td>
</tr>
<tr>
<td>F3</td>
<td>0.25±0.0</td>
<td>42.33±0.58</td>
<td>141.55±0.00</td>
</tr>
<tr>
<td>F4</td>
<td>0.25±0.0</td>
<td>15.33±0.58</td>
<td>129.07±0.0</td>
</tr>
<tr>
<td>F5</td>
<td>0.30±0.0</td>
<td>14.33±0.58</td>
<td>121.36±0.0</td>
</tr>
<tr>
<td>F6</td>
<td>0.32±0.0</td>
<td>12.33±0.58</td>
<td>118.20±0.01</td>
</tr>
<tr>
<td>F7</td>
<td>0.29±0.0</td>
<td>9.33±0.58</td>
<td>109.58±0.0</td>
</tr>
<tr>
<td>F8</td>
<td>0.37±0.0</td>
<td>7.33±0.58</td>
<td>105.73±0.0</td>
</tr>
<tr>
<td>F9</td>
<td>0.35±0.0</td>
<td>5.33±0.58</td>
<td>94.17±0.0</td>
</tr>
</tbody>
</table>

*** All values show mean ± standard deviation (SD) n=20  
* All values show mean ± standard deviation (SD) n=3

The tablet in vitro disintegration time of is an important parameter which is supposed to be optimized for the improvement of sublingual tablets. The tablet disintegration was effected by the wicking, swelling of the disintegrant (Jinichi et al., 2006). The crospovidone containing tablets quickly wicks the saliva into the tablet and generates expansion of the volume and hydrostatic pressure which provides rapid disintegration in mouth (Rudnic et al., 1980). Mainly the crospovidone as super disintegrant uses a combination of swelling and wicking principle and wicking of liquid into the tablet and particles to generate rapid disintegration. Crospovidone swells rapidly in
water without getting gel formation due to its high cross link density (Mohanchandran et al., 2011).

All the tablets from each formulation were disintegrated in the range varied from 80.33±0.58s to 7.33±0.58s. From the results formulations containing crospovidone had shown less disintegration time compared with other superdisintegrants. The reason for delayed disintegration time of sodium starch glycollate and croscarmellose sodium might be due to their tendency to get gel from more when compared with crospovidone. The crospovidone, croscarmellose sodium and sodium starch glycollate was optimized at 6% concentration. After these concentrations of superdisintegrants there was no much change in the disintegration time.

The in vivo disintegration time for each formulation were found to be in the range of 110.33±0.51s to 13.67±0.51s. The in vivo disintegration time for formulation nine (F9) was found to be 13.67±0.51s. The in vitro disintegration time was lower as compared to the in vivo disintegration time. This is mainly due to the mechanical stress applied to the tablets during in vitro disintegration experiment.

All the formulations were checked for content uniformity. The uniformity in drug was good amid various batches of tablets and the % of drug content was greater than 95.5%. The results also proved satisfactory and uniform distribution of drug in all tablets (Table-4.10).
Table-4.10 Evaluation tests of sublingual tablets rizatriptan.

<table>
<thead>
<tr>
<th>Formulations code</th>
<th>Disintegration time (seconds)**</th>
<th>In vivo disintegration time (seconds)**</th>
<th>Content uniformity (%)***</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>80.33±0.58</td>
<td>110.33±0.51</td>
<td>95.92±0.04</td>
</tr>
<tr>
<td>F2</td>
<td>58.33±0.58</td>
<td>100.33±0.51</td>
<td>95.80±0.03</td>
</tr>
<tr>
<td>F3</td>
<td>54.67±0.58</td>
<td>80.33±0.51</td>
<td>95.79±0.03</td>
</tr>
<tr>
<td>F4</td>
<td>20.0±0.0</td>
<td>38.33±0.51</td>
<td>96.14±0.04</td>
</tr>
<tr>
<td>F5</td>
<td>19.0±0.0</td>
<td>35.67±0.51</td>
<td>95.77±0.04</td>
</tr>
<tr>
<td>F6</td>
<td>14.33±0.58</td>
<td>29.33±0.51</td>
<td>95.81±0.03</td>
</tr>
<tr>
<td>F7</td>
<td>11.0±0.00</td>
<td>28.33±0.51</td>
<td>96.23±0.04</td>
</tr>
<tr>
<td>F8</td>
<td>9.33±0.58</td>
<td>20.33±0.51</td>
<td>95.98±0.01</td>
</tr>
<tr>
<td>F9</td>
<td>7.33±0.58</td>
<td>13.67±0.51</td>
<td>96.03±0.04</td>
</tr>
</tbody>
</table>

*** All values show mean ± standard deviation (SD) n=20

** All values show mean ± standard deviation (SD) n=6
### Table -4.11 *In vitro* drug release profiles of the rizatriptan benzoate tablet formulations

<table>
<thead>
<tr>
<th>Time (Min)/ Code</th>
<th>F-1</th>
<th>F-2</th>
<th>F-3</th>
<th>F-4</th>
<th>F-5</th>
<th>F-6</th>
<th>F-7</th>
<th>F-8</th>
<th>F-9</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>82.50±0.61</td>
<td>82.58±0.50</td>
<td>81.10±0.75</td>
<td>82.25±0.66</td>
<td>81.65±0.55</td>
<td>83.48±0.78</td>
<td>83.22±0.28</td>
<td>84.19±0.86</td>
<td>85.87±0.54</td>
</tr>
<tr>
<td>10</td>
<td>85.34±0.99</td>
<td>85.43±0.65</td>
<td>82.49±0.24</td>
<td>85.90±0.88</td>
<td>87.32±0.52</td>
<td>88.09±0.30</td>
<td>87.72±0.11</td>
<td>88.42±0.52</td>
<td>89.46±0.34</td>
</tr>
<tr>
<td>15</td>
<td>86.33±0.51</td>
<td>85.69±0.02</td>
<td>87.14±0.87</td>
<td>87.18±0.14</td>
<td>88.60±0.29</td>
<td>90.75±0.83</td>
<td>95.74±0.59</td>
<td>96.61±0.43</td>
<td>97.47±0.36</td>
</tr>
<tr>
<td>20</td>
<td>87.74±0.30</td>
<td>87.91±0.91</td>
<td>89.26±0.56</td>
<td>89.59±0.75</td>
<td>91.01±0.96</td>
<td>92.57±0.36</td>
<td>96.02±0.43</td>
<td>96.89±0.27</td>
<td>98.19±0.17</td>
</tr>
<tr>
<td>30</td>
<td>89.16±0.58</td>
<td>88.34±0.26</td>
<td>89.96±0.76</td>
<td>90.59±0.41</td>
<td>92.14±0.79</td>
<td>96.63±0.45</td>
<td>96.86±0.44</td>
<td>96.90±0.68</td>
<td>98.47±0.12</td>
</tr>
<tr>
<td>45</td>
<td>93.69±0.44</td>
<td>94.08±0.69</td>
<td>98.63±0.28</td>
<td>96.26±0.44</td>
<td>96.53±0.17</td>
<td>97.20±0.39</td>
<td>97.56±0.04</td>
<td>98.30±0.45</td>
<td>99.05±0.38</td>
</tr>
<tr>
<td>60</td>
<td>96.25±0.04</td>
<td>98.20±0.69</td>
<td>99.05±0.17</td>
<td>98.39±0.42</td>
<td>98.80±0.07</td>
<td>98.88±0.07</td>
<td>99.25±0.02</td>
<td>99.57±0.37</td>
<td>99.76±0.14</td>
</tr>
</tbody>
</table>

All values indicate mean ± standard deviation (SD) n=6
4.5.2.3 Comparison of dissolution profile for F1, F2 and F3 rizatriptan formulations containing 2%, 4% and 6% of sodium starch glycollate.

The *in vitro* dissolution study of formulations F1, F2 and F3 batches showed percentage drug release 86.33±0.51, 85.69±0.02 and 87.14±0.87 respectively within 15 minutes. The F3 batch showed good dissolution (Table-4.11) which contained 6% of sodium starch glycollate (Figure-4.4). The mechanism of disintegration of the tablets occurs by fast uptake of water and by rapid swelling.

**Figure 4.4** Comparison of dissolution of F1, F2 and F3 rizatriptan formulations containing 2%, 4% and 6% of sodium starch glycollate.
4.5.2.4 Comparison of dissolution of F4, F5 and F6 rizatriptan formulations containing 2%, 4% and 6% of croscarmellose sodium.

The in vitro dissolution study of formulations F4, F5 and F6 batches showed percentage drug release 87.18±0.14, 88.60±0.29 and 90.75±0.83 respectively within 15 minutes. The F6 batch showed good dissolution (Figure-4.5) which contained 6% of croscarmellose sodium (Table-4.11). The disintegration of tablets was mainly due to the swelling nature of croscarmellose sodium.

**Figure 4.5** Comparison of dissolution of F4, F5 and F6 rizatriptan formulations containing 2%, 4% and 6% of croscarmellose sodium.
4.5.2.5 Comparison of dissolution of F7, F8 and F9 rizatriptan formulations containing 2%, 4% and 6% of crospovidone.

The in vitro dissolution study of formulations F7, F8 and F9 showed percentage drug release 95.74±0.59, 96.61±0.43 and 97.47±0.36 respectively within 15 minutes. The F9 batch showed good dissolution efficiency and less disintegration time (Figure-4.6) compared with all formulation which contained 6% of crospovidone (Table 4.11). Based on the above, this formulation (F9) was selected as optimised and subjected for characterisation.

**Figure 4.6 Comparison of dissolution of F7, F8 and F9 rizatriptan formulations containing 2%, 4% and 6% of crospovidone.**
4.5.2.6 Scanning Electron Microscopy (SEM) studies

Surface morphology of sublingual rizatriptan formulation and standard rizatriptan were examined by Scanning Electron Microscopy (Figure-4.7). The SEM micrographs reveal that there is no segregation or deposition of particles on the surface of sublingual tablets.

Figure-4.7 Scanning Electron Microscope images of a) Rizatriptan Standard b) Rizatriptan Sublingual Tablets.
4.5.2.7 Differential Scanning Calorimetry (DSC) studies

The DSC thermo grams of Placebo (tablet), Physical mixture with rizatriptan, Rizatriptan sublingual tablets (F9) and Rizatriptan standard were studied. The endothermic peaks of rizatriptan standard appear at 183°C and in the sublingual tablets, physical mixture was found at 179°C. The small size of peak is attributed to the fact that the amount of rizatriptan in tablets and physical mixture with drug was around 15%. It shows that drug exist in crystalline form in formulation without having polymorphic change which was shown in figure-4.8. The peak at 169°C in all the formulations except in standard rizatriptan was due to the presence of excipients.

Figure-4.8 DSC thermo grams of a) Placebo (tablet) b) Rizatriptan

Physical mixture with Drug c) Sublingual Rizatriptan tablets

d) Rizatriptan Standard.
4.5.2.8 Powder X-Ray Diffraction studies (PXRD)

The pure drug showed numerous distinctive high intensity diffraction peaks demonstrating the crystalline nature of rizatriptan. The more intensive peak was obtained at 18.84(2θ) for rizatriptan standard. Similarly in sublingual tablets and in physical mixture with drug a peak was present at about 18.74(2θ). The rizatriptan crystallinity was not changed in physical mixture with drug and in rizatriptan sublingual formulation which was shown in figure-4.9.

Figure-4.9 Powder X-ray diffraction patterns of a) Rizatriptan sublingual tablets b) Rizatriptan Physical mixture with Drug c) Rizatriptan Standard.
4.5.2.9 Fourier Transforms Infrared Spectroscopy (FTIR).

FT-IR spectra are of Placebo (tablet), Physical mixture without drug, Physical mixture with drug, Rizatriptan sublingual formulation and Standard rizatriptan (Figure 4.10). The pure rizatriptan benzoate exhibits characteristic peaks at 3120 cm$^{-1}$ (aromatic secondary amine N-H stretching), 2974 cm$^{-1}$ (aromatic C-H stretching), 1608 cm$^{-1}$ (C=O five member cyclic stretching) and 1270 cm$^{-1}$ (C-N aliphatic amine stretching) (Figure 4.10). All these peaks have appeared in rizatriptan sublingual formulation (F9) at 3291 cm$^{-1}$ (aromatic secondary amine N-H stretching), 2948 cm$^{-1}$ (aromatic C-H stretching), 1608 cm$^{-1}$ (C=O five member cyclic stretching) and 1281 cm$^{-1}$ (C-N aliphatic amine stretching).

Figure 4.10 FT-IR spectra of a) Placebo (tablet) b) Physical mixture without drug c) Physical mixture with drug d) Rizatriptan standard e) Sublingual rizatriptan tablets.
4.5.3 Evaluation of stability studies

The optimized formulation (F9) were subjected to stability studies by keeping the formulation in stability chambers (thermo lab, USA) at 40±2°C/75±5% and analyzed for every one month up to three months (Sunita et al., 2010). Drug content, friability, hardness, wetting time and *in vitro* disintegration time were evaluated. The optimized formulations are stable and did not show much variation in any of the parameters (Table-4.13).

Table-4.12 Effect of storage of formulation F9 at 40±2°C/75±5% RH

<table>
<thead>
<tr>
<th>Code/day</th>
<th>Drug content (%) **</th>
<th>Hardness (kg/cm²)**</th>
<th>Friability (%) ***</th>
<th>Wetting time (min)*</th>
<th>In vitro disintegration (min)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>F9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1St day</td>
<td>96.03±0.04</td>
<td>4.0±0.00</td>
<td>0.35±0.00</td>
<td>5.33±0.58</td>
<td>7.33±0.58</td>
</tr>
<tr>
<td>30th day</td>
<td>95.97±0.02</td>
<td>4.0±0.00</td>
<td>0.35±0.01</td>
<td>5.33±0.58</td>
<td>7.33±0.58</td>
</tr>
<tr>
<td>60th day</td>
<td>95.86±0.04</td>
<td>4.17±0.29</td>
<td>0.35±0.01</td>
<td>5.66±0.58</td>
<td>7.66±0.58</td>
</tr>
<tr>
<td>90th day</td>
<td>95.83±0.04</td>
<td>4.17±0.29</td>
<td>0.35±0.01</td>
<td>5.66±0.58</td>
<td>7.66±0.58</td>
</tr>
</tbody>
</table>

*** All values show mean ± standard deviation (SD) n=20

** All values show mean ± standard deviation (SD) n=6

* All values show mean ± standard deviation (SD) n=3