Formulation and evaluation of fast dissolving sublingual films of Rizatriptan Benzoate

Bhyan Bhupinder*1, Jangra Sarita2
1Department of Pharmaceutical Sciences, Lovely Professional University, Jalandhar-Delhi G.T. Road (NH-1), Phagwara. Punjab, India.
2Seedling College of Pharmacy, Jaipur National University, Jaipur-302025, Rajasthan, India.

Abstract
Rizatriptan Benzoate, a serotonin 5-HT1 receptor agonist is a new generation antimigraine drug which has oral bioavailability of 47% due to hepatic first pass metabolism. The present study investigated the possibility of developing Rizatriptan benzoate fast dissolving sublingual films allowing fast, reproducible drug dissolution in the oral cavity, thus bypassing first pass metabolism to provide rapid onset of action of the drug. The fast dissolving films were prepared by solvent casting method. Low viscosity grade of hydroxylpropyl methylcellulose (HPMC E 15) and maltodextrin were used in combination as film forming polymer, due to their hydrophilic nature and palatable taste. To decrease the disintegration time of formulations sodium starch glycolate was used as disintegrating agent. Glycerol, mannitol, aspartame and sodium lauryl sulphate were used as a cooling agent, sweetening agent and oral penetration enhancer respectively. All the films formulations (F1-F8) was evaluated for their thickness, weight variations, tensile strength, percentage elongation, folding endurance, surface pH, in-vitro disintegration, drug content, in-vitro drug release and ex-vivo permeation. Disintegration time showed by the formulations was found to be in range of 25-50 sec. Formulations F1 and F2 showed 90% in-vitro drug release within 7 min and 61% ex-vivo drug permeation within16 min. The film showed an excellent stability at least for 4 weeks when stored at 40°C and 75% in humidity.

Key words:

How to Cite this Paper:

Copyright © 2010 IJDDR, Bhyan Bhupinder et al. This is an open access paper distributed under the copyright agreement with Serials Publication, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

INTRODUCTION
There has been increased demand for the novel dosage form to gain more patient compliance. Fast dissolving films recently have acquired great importance in the pharmaceutical industry due to their unique properties and specific advantages like no need of water for disintegration, accurate dosing,
rapid onset of action, ease of transportability, ease of
handling, pleasant taste and improved patient
compliance [1]. Fast dissolving film is a type of drug
delivery system, which when placed in the oral cavity
it rapidly disintegrates and dissolves to release the
medication for oromucosal and intragastric
absorption, without chewing and intake of water [2].
This technology evolved over the past few years from
the confection and oral care markets in the form of
breath strips and became a novel and widely accepted
form by consumers. These films have a potential to
deliver the drug systemically through intragastric,
sublingual or buccal route of administration and also
has been used for local action [3, 4]. This type of
technology offer a convenient way of dosing
medication, not to special population groups like
pediatric, geriatric, bedridden patients, mentally ill
patients, but also to the general population. The
sublingual mucosa is relatively permeable due to thin
membrane and large veins. It gives rapid absorption
and instant bioavailability of drugs due to high blood
flow [5, 6]. As the fast-dissolving film is taken through
the sublingual route, rapid absorption of drug is
possible, which finally leads to quick onset of drug
action and prevent the first pass-metabolism of the
drug.
Migraine is one of the ten most disabling disorders
worldwide, and despite recent developments in the
management of migraine, it remains underdiagnosed
and undertreated [7]. Disability due to migraine
headache and associated symptoms has been
estimated to cost American employers $US 13 billion
per year, due to missed work days and impaired work
performance. Epidemiological studies in migraine
reveal that the vast majority of patients (>90%) have
experienced nausea during a migraine attack.
Similarly, most (almost 70%) have vomited at some
time during an attack so they avoid intake of excess
of liquid [8]. Also the migraine sufferers have marked
reduction in their functional abilities so they would
be benefited from the acute treatment that help them
to resume their functional abilities as quick as possible. The new generation anti-migraine drug,
Rizatriptan benzoate is an orally active serotonin 5-
HT1receptor agonist that potently and selectively
binds to 5-HT1B/1D subtypes. Chemically it is N,N-
dimethyl-5-(1H-1,2,4-triazol-1-ylmethyl)-1H-indole-
3-ethanamine monobenzoate. The initial gut
absorption of Rizatriptan is high (90%); however, the
compound undergoes moderate first-pass
metabolism, which limits the bioavailability to 47%
[9]. So orally fast dissolving sublingual films of
Rizatriptan prevents its first-pass metabolism and
eliminates the need of intake of water by the patient
during the migraine attack and provide fast onset of
action which would be beneficial to migraine
sufferers in resuming their functional abilities as
soon as possible.

MATERIALS AND METHODS
Rizatriptan benzoate was received as gift samples
from SMS pharmaceuticals Ltd., Hyderabad, India.
Hydroxypropyl methyl cellulose (E-15) was procured
from The Dow chemicals, China. Maltodextrin,
sodium starch glycolate and sodiumlaurylsulphate
was obtained from Loba Chemie, Mumbai, India.
Glycerine was obtained from Qualikems Fine Chem,
Vadodara, India. Mannitol and aspartame was
purchased from Central Drug House, New Delhi.

Drug polymer compatibility studies
Drug polymer compatibility studies were carried out
using FTIR. The sample was dispersed in KBr powder
and analyzed. Spectra were obtained by powder
diffuse reflectance on a FT-IR spectrophotometer
type FT-IR Shimadzu 8400S, Shimadzu Ltd, USA.

UV Spectrum Analysis of Rizatriptan
Benzoate
The solution was scanned in the range of 200 to 400
nm to fix the maximum wave length and UV
spectrum was obtained.
Standard plot of Rizatriptan Benzoate in pH 6.8 Phosphate buffer
The standard plot of Rizatriptan Benzoate was prepared in pH 6.8 phosphate buffer. 50 mg of drug was weighed accurately and dissolved in 50 ml of phosphate buffer. Appropriate dilutions were made with buffer to obtain test solutions ranging from 2 µg/ml to 8 µg/ml. The absorbance of the drug in the buffer was then measured on a double beam UV-visible spectrophotometer at $\lambda_{\text{max}}$ of 226 nm against the respective blank.

Standard plot of Rizatriptan Benzoate in pH 7.4 Phosphate buffer
The standard plot of Rizatriptan Benzoate was prepared in pH 7.4 phosphate buffer. 50 mg of drug was weighed accurately and dissolved in 50 ml of phosphate buffer. Appropriate dilutions were made with buffer to obtain test solutions ranging from 1 µg/ml to 6 µg/ml. The absorbance of the drug in the buffer was measured on a double beam UV-visible spectrophotometer at $\lambda_{\text{max}}$ of 226 nm against the respective blank.

Method of preparation of fast dissolving sublingual film of Rizatriptan Benzoate.
Fast-dissolving film of rizatriptan benzoate was prepared by the solvent-casting method \[11\]. Aqueous solution I was prepared by dissolving the polymer and glycerine in specific proportion-in distilled water and was allowed to stir for 4 hours and kept for 1 hour to remove all the air bubbles entrapped. Aqueous solution II was prepared by dissolving the rizatriptan benzoate, mannitol, and strawberry flavor in specific proportion, in distilled water. Both aqueous solutions I and II were mixed and stirred for 1 hour. Then the mixture solution was casted onto a plastic petri dish and it was dried in the oven at 50°C for 24 hour. The film was carefully removed from the petri dish, checked for any imperfections, and cut according to the size required for testing (square film: 2 cm length, 2 cm width). The samples were stored in a glass container maintained at a temperature of 30°C±1°C and relative humidity 60±5% until further analysis.

EVALUATION

Thickness
The thickness of the patch was measured using digital Vernier Calliper with a least count of 0.01 mm at different spots of the film. The thickness was measured at three different spots of the patch and average was taken and SD was calculated.

Weight variation
Four centimeter square of the film was cut at three different places from the casted film. The weight of each film was taken and weight variation was calculated.

Folding endurance
Folding endurance was determined by repeated folding of the film at the same place till the strip breaks \[10\]. The number of times the film is folded without breaking was computed as the folding endurance value.

Tensile strength
Tensile testing was conducted using a texture analyzer AG/MC1 (Acquati, Italy), equipped with a 5 N load cell. The film was cut into 30 × 20 mm strips. Tensile tests were performed according to ASTM International Test Method for Thin Plastic Sheeting (D 882-02). Each test strip was placed in tensile grips on the texture analyzer. Initial grip separation was 20 mm and crosshead speed was 1 inch/min. The test was considered concluded when the film breaks. Tensile strength, was computed with help of load require to break the film and cross sectional area to evaluate tensile properties of the films. Tensile strength (TS) Tensile strength is the maximum stress applied to a point at which the film specimen breaks.
and can be calculated by dividing the maximum load by the original cross-sectional area of the specimen and it was expressed in force per unit area (MPa)\[^{12}\].

\[
\text{Tensile Strength} = \frac{\text{Force at break (N)}}{\text{Cross sectional area (mm}^2)}
\]

**Percentage elongation**

For the determination of percentage elongation of the film formulations, the distance between the tensile grips of the tensile strength testing machine was measured before and after the fracture of the film. Then the percentage elongation of the films was computed with the help of the formula given below:-

\[
\%E = \frac{D_f - D_0}{D_0} \times 100
\]

Where:-

\%E = Percentage elongation

\(D_0\) = Distance between the tensile grips before the fracture of the film.

\(D_f\) = Distance between the tensile grips after the fracture of the film

**Surface pH**

The surface pH of fast dissolving film was determined in order to investigate the possibility of any side effect in vivo. As an acidic or alkaline pH may cause irritation of the oral mucosa, it was determined to keep the surface pH as close to neutral as possible. A combined pH electrode was used for this purpose. Oral film was slightly wet with the help of water. The pH was measured by bringing the electrode in contact with the surface of the oral film\[^{13}\]. The procedure was performed in triplicate and average with standard deviation was reported.

**Disintegration**

*In vitro* disintegration time was determined visually in a petri dish containing 25 ml of pH 6.8 phosphate buffer with swirling every 10 sec. The disintegration time is the time when the film starts to break or disintegrates.

**Drug Content**

Drug content determination of the film was carried out by dissolving the film of 4 cm\(^2\) in 100 ml of pH 6.8 phosphate buffer using magnetic stirrer for 1 hour. The drug concentration was then evaluated spectrophotometrically at \(\lambda_{\text{max}}\) of 226 nm. The determination was carried out in triplicate for all the formulations and average with standard deviation was recorded.

**In-vitro dissolution**

The dissolution study was carried out using USP Type I (Basket type) dissolution apparatus. The dissolution was carried out in 900 ml of pH 6.8 phosphate buffer maintained at 37 ± 0.5°C at 50 rpm. 10 ml aliquots of samples were taken at various time intervals which were replaced with same volume of fresh pH 6.8 phosphate buffer maintained at 37 ± 0.5°C. Rizatriptan Benzoate in the samples was then determined spectrophotometrically at \(\lambda_{\text{max}}\) of 226 nm. The results were expressed as mean of three determinations.

**Ex-vivo permeation studies**

Ex vivo permeation studies through porcine oral mucosa (ventral surface of tongue) was carried out using the Franz diffusion cell of internal diameter of 2.5 cm. The buccal mucosa was excised and trimmed evenly from the sides, washed in isotonic phosphate buffer of pH 6.8 and used immediately. The membrane was stabilized before mounting to remove the soluble components. The mucosa was mounted between the donor and receptor compartments. The receptor compartment was filled with 15 ml of isotonic phosphate buffer of pH 7.4 which was maintained at 37± 0.2°C and hydrodynamics were maintained using magnetic stirrer. One film of dimension 2 cm × 2 cm was previously moistened.
with a few drops of pH 6.8 phosphate buffer and placed in donor compartment. The donor compartment was filled with 1 ml of pH 6.8 phosphate buffer. 1 ml samples from receptor compartment were withdrawn at suitable time interval which was then replaced with 1 ml of pH 7.4 phosphate buffer [14]. The percentage of Rizatriptan Benzoate permeated was determined by measuring the absorbance in UV-Visible spectrophotometer at $\lambda_{\text{max}}$ of 226 nm.

### Stability study

Stability study was carried out at two different storage conditions, one was normal room conditions and other was 40°C/75% RH for 4 weeks. Each piece of the films of formulation F1 and F2 was packed in butter paper followed by aluminum foil and plastic tape. After 4 weeks, the films were evaluated for the physical appearance, surface pH, drug content and in vitro drug release.

### RESULTS AND DISCUSSION

#### UV Spectrum Analysis of Rizatriptan Benzoate

**Figure 1:** Scan of Rizatriptan Benzoate

**Table 1:** Standard curve of Rizatriptan Benzoate in pH 6.8 phosphate buffer at $\lambda_{\text{max}}$ 226 nm

<table>
<thead>
<tr>
<th>S. No</th>
<th>Concentration (µg/ml)</th>
<th>Absorbance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>0.261±0.002</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>0.534±0.016</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>0.793±0.018</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>0.977±0.005</td>
</tr>
</tbody>
</table>

**Figure 2:** Standard curve of Rizatriptan Benzoate in pH 6.8 Phosphate Buffer

**Table 2:** Standard curve of Rizatriptan Benzoate in pH 7.4 phosphate buffer at $\lambda_{\text{max}}$ 226 nm

<table>
<thead>
<tr>
<th>S. No</th>
<th>Concentration (µg/ml)</th>
<th>Absorbance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>0.168±0.041</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>0.314±0.063</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>0.448±0.018</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>0.570±0.005</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>0.718±0.007</td>
</tr>
<tr>
<td>7</td>
<td>6</td>
<td>0.850±0.011</td>
</tr>
</tbody>
</table>

**Figure 2:** Standard curve of Rizatriptan Benzoate in pH 7.4 Phosphate Buffer
Figure 11: FTIR spectra of (a) Pure Rizatriptan Benzoate (b) Physical mixture of Rizatriptan Benzoate and HPMC E-15 (c) Physical mixture of Rizatriptan Benzoate and Maltodextrin (d) Physical mixture of Rizatriptan Benzoate and Mannitol (e) Physical mixture of Rizatriptan Benzoate and Aspartame (f) Physical mixture of Rizatriptan Benzoate and Sodium starch glycolate.
Table 3: Composition of Rizatriptan Benzoate fast dissolving films

<table>
<thead>
<tr>
<th>Formulations</th>
<th>RTB (mg)</th>
<th>HPMC E-15 (mg)</th>
<th>MDX (mg)</th>
<th>GLY (mg)</th>
<th>SSG (mg)</th>
<th>SLS (mg)</th>
<th>MNT (mg)</th>
<th>ASP (mg)</th>
<th>Col. (ml)</th>
<th>Flv. (ml)</th>
<th>Water Upto (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>7.265</td>
<td>15</td>
<td>20</td>
<td>5</td>
<td>1</td>
<td>0.5</td>
<td>5</td>
<td>2</td>
<td>0.05</td>
<td>0.05</td>
<td>q.s</td>
</tr>
<tr>
<td>F2</td>
<td>7.265</td>
<td>15</td>
<td>20</td>
<td>10</td>
<td>1</td>
<td>0.5</td>
<td>5</td>
<td>2</td>
<td>0.05</td>
<td>0.05</td>
<td>q.s</td>
</tr>
<tr>
<td>F3</td>
<td>7.265</td>
<td>20</td>
<td>20</td>
<td>5</td>
<td>1</td>
<td>0.5</td>
<td>5</td>
<td>2</td>
<td>0.05</td>
<td>0.05</td>
<td>q.s</td>
</tr>
<tr>
<td>F4</td>
<td>7.265</td>
<td>20</td>
<td>20</td>
<td>10</td>
<td>1</td>
<td>0.5</td>
<td>5</td>
<td>2</td>
<td>0.05</td>
<td>0.05</td>
<td>q.s</td>
</tr>
<tr>
<td>F5</td>
<td>7.265</td>
<td>25</td>
<td>20</td>
<td>5</td>
<td>1</td>
<td>0.5</td>
<td>5</td>
<td>2</td>
<td>0.05</td>
<td>0.05</td>
<td>q.s</td>
</tr>
<tr>
<td>F6</td>
<td>7.265</td>
<td>25</td>
<td>20</td>
<td>10</td>
<td>1</td>
<td>0.5</td>
<td>5</td>
<td>2</td>
<td>0.05</td>
<td>0.05</td>
<td>q.s</td>
</tr>
<tr>
<td>F7</td>
<td>7.265</td>
<td>30</td>
<td>20</td>
<td>5</td>
<td>1</td>
<td>0.5</td>
<td>5</td>
<td>2</td>
<td>0.05</td>
<td>0.05</td>
<td>q.s</td>
</tr>
<tr>
<td>F8</td>
<td>7.265</td>
<td>30</td>
<td>20</td>
<td>10</td>
<td>1</td>
<td>0.5</td>
<td>5</td>
<td>2</td>
<td>0.05</td>
<td>0.05</td>
<td>q.s</td>
</tr>
</tbody>
</table>

Table 4: Evaluation of physicomechanical parameters of fast dissolving film of rizatriptan benzoate

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Thickness (mm)</th>
<th>Weight (mg) per 4 cm²</th>
<th>Tensile strength (MPa)</th>
<th>Percentage elongation</th>
<th>Folding endurance (no. of folds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.05 ± 0.004</td>
<td>49.00 ± 1.000</td>
<td>1.82</td>
<td>5</td>
<td>145.3 ± 9.451</td>
</tr>
<tr>
<td>F2</td>
<td>0.06 ± 0.004</td>
<td>52.66 ± 0.577</td>
<td>1.53</td>
<td>5</td>
<td>195.0 ± 13.453</td>
</tr>
<tr>
<td>F3</td>
<td>0.08 ± 0.008</td>
<td>51.66 ± 0.577</td>
<td>2.95</td>
<td>5</td>
<td>171.3 ± 6.110</td>
</tr>
<tr>
<td>F4</td>
<td>0.08 ± 0.004</td>
<td>58.00 ± 1.000</td>
<td>2.71</td>
<td>10</td>
<td>185.3 ± 12.013</td>
</tr>
<tr>
<td>F5</td>
<td>0.10 ± 0.006</td>
<td>58.33 ± 0.577</td>
<td>3.55</td>
<td>10</td>
<td>142.6 ± 11.372</td>
</tr>
<tr>
<td>F6</td>
<td>0.10 ± 0.014</td>
<td>62.00 ± 1.000</td>
<td>3.10</td>
<td>15</td>
<td>183.6 ± 9.073</td>
</tr>
<tr>
<td>F7</td>
<td>0.13 ± 0.008</td>
<td>63.33 ± 0.577</td>
<td>4.01</td>
<td>10</td>
<td>155.3 ± 8.504</td>
</tr>
<tr>
<td>F8</td>
<td>0.15 ± 0.008</td>
<td>68.66 ± 0.577</td>
<td>3.85</td>
<td>20</td>
<td>184.6 ± 10.692</td>
</tr>
</tbody>
</table>

Table 5: Surface pH, disintegration time and drug content of fast dissolving films loaded with rizatriptan benzoate

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Surface pH of films</th>
<th>Disintegration time in Sec (Starts)</th>
<th>Drug content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>6.67 ± 0.050</td>
<td>25.6 ± 1.154</td>
<td>93.6±1.040</td>
</tr>
<tr>
<td>F2</td>
<td>6.76 ± 0.078</td>
<td>29.3 ± 1.527</td>
<td>92.5±1.044</td>
</tr>
<tr>
<td>F3</td>
<td>6.81 ± 0.045</td>
<td>31.3 ± 2.309</td>
<td>93.6±0.700</td>
</tr>
<tr>
<td>F4</td>
<td>6.82 ± 0.036</td>
<td>28.6 ± 3.785</td>
<td>93.4±0.871</td>
</tr>
<tr>
<td>F5</td>
<td>6.74 ± 0.025</td>
<td>34.6 ± 3.511</td>
<td>93.9±0.360</td>
</tr>
<tr>
<td>F6</td>
<td>6.90 ± 0.030</td>
<td>33.3 ± 4.509</td>
<td>93.7±1.001</td>
</tr>
<tr>
<td>F7</td>
<td>6.82 ± 0.030</td>
<td>45.0 ± 3.000</td>
<td>94.6±0.700</td>
</tr>
<tr>
<td>F8</td>
<td>6.93 ± 0.015</td>
<td>49.3 ± 2.081</td>
<td>94.4±0.300</td>
</tr>
</tbody>
</table>

All values are mean of 3 readings ± standard deviation

Table 6: Comparative *in vitro* dissolution of formulations in pH 6.8 phosphate buffer

<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>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>44.4±0.893</td>
<td>42.1±0.489</td>
<td>35.2±1.204</td>
<td>36.4±0.384</td>
<td>32.8±0.941</td>
<td>33.2±1.054</td>
<td>28.6±0.705</td>
<td>27.2±0.847</td>
</tr>
<tr>
<td>2</td>
<td>67.1±1.294</td>
<td>68.9±0.571</td>
<td>62.4±0.030</td>
<td>60.6±0.592</td>
<td>53.5±0.553</td>
<td>53.8±0.223</td>
<td>47.7±0.552</td>
<td>49.3±1.390</td>
</tr>
<tr>
<td>4</td>
<td>88.7±0.992</td>
<td>89.0±0.623</td>
<td>79.5±0.468</td>
<td>79.7±0.837</td>
<td>66.7±0.438</td>
<td>71.0±0.725</td>
<td>61.5±0.622</td>
<td>52.9±0.547</td>
</tr>
<tr>
<td>6</td>
<td>91.8±0.537</td>
<td>92.5±0.839</td>
<td>89.9±0.936</td>
<td>88.1±1.088</td>
<td>78.9±0.691</td>
<td>79.1±0.269</td>
<td>74.3±0.832</td>
<td>75.0±0.684</td>
</tr>
<tr>
<td>8</td>
<td>92.8±0.348</td>
<td>92.7±0.759</td>
<td>91.2±0.773</td>
<td>91.6±0.457</td>
<td>85.4±0.283</td>
<td>86.2±0.393</td>
<td>80.5±0.480</td>
<td>81.3±2.034</td>
</tr>
<tr>
<td>10</td>
<td>93.3±0.429</td>
<td>92.8±0.845</td>
<td>92.1±0.403</td>
<td>93.0±0.248</td>
<td>90.7±0.772</td>
<td>91.4±0.772</td>
<td>87.5±0.296</td>
<td>86.2±0.166</td>
</tr>
<tr>
<td>15</td>
<td>93.9±0.532</td>
<td>93.2±0.134</td>
<td>93.8±0.631</td>
<td>93.6±0.740</td>
<td>93.4±0.499</td>
<td>94.3±0.579</td>
<td>93.2±0.188</td>
<td>94.5±0.257</td>
</tr>
</tbody>
</table>
Table 7: Comparative ex vivo permeation of different formulations of fast dissolving films

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>F1A4</th>
<th>F1B4</th>
<th>F2A4</th>
<th>F2B4</th>
<th>F3A4</th>
<th>F3B4</th>
<th>F4A4</th>
<th>F4B4</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>3.3±0.204</td>
<td>3.0±0.276</td>
<td>1.8±0.533</td>
<td>2.7±0.760</td>
<td>2.9±0.441</td>
<td>3.0±0.745</td>
<td>1.9±0.612</td>
<td>1.8±0.195</td>
</tr>
<tr>
<td>4</td>
<td>7.5±0.489</td>
<td>7.0±0.765</td>
<td>5.4±1.381</td>
<td>4.9±0.921</td>
<td>5.2±0.755</td>
<td>4.4±0.299</td>
<td>2.7±0.504</td>
<td>2.0±0.865</td>
</tr>
<tr>
<td>6</td>
<td>16.0±1.250</td>
<td>15.9±0.990</td>
<td>10.2±1.095</td>
<td>8.5±0.974</td>
<td>7.8±1.023</td>
<td>9.1±0.536</td>
<td>5.1±0.941</td>
<td>4.3±1.107</td>
</tr>
<tr>
<td>8</td>
<td>28.7±2.096</td>
<td>25.9±0.625</td>
<td>17.1±2.507</td>
<td>16.6±1.93</td>
<td>12.8±0.997</td>
<td>11.9±0.847</td>
<td>7.6±1.079</td>
<td>8.5±1.479</td>
</tr>
<tr>
<td>10</td>
<td>39.1±0.853</td>
<td>36.7±1.430</td>
<td>26.7±1.466</td>
<td>27.1±2.224</td>
<td>19.3±1.702</td>
<td>20.7±1.548</td>
<td>12.9±2.110</td>
<td>11.7±1.546</td>
</tr>
<tr>
<td>12</td>
<td>47.8±0.554</td>
<td>48.3±2.142</td>
<td>34.9±0.596</td>
<td>35.3±2.180</td>
<td>25.7±3.221</td>
<td>28.3±0.825</td>
<td>19.2±1.047</td>
<td>19.5±0.877</td>
</tr>
<tr>
<td>14</td>
<td>55.2±0.803</td>
<td>58.4±1.538</td>
<td>43.6±0.914</td>
<td>43.9±0.839</td>
<td>33.5±1.692</td>
<td>34.6±0.491</td>
<td>25.4±2.721</td>
<td>25.9±1.231</td>
</tr>
<tr>
<td>16</td>
<td>61.2±0.371</td>
<td>64.5±0.801</td>
<td>51.7±0.758</td>
<td>50.7±1.631</td>
<td>40.3±0.759</td>
<td>40.4±2.056</td>
<td>31.7±1.866</td>
<td>33.0±0.822</td>
</tr>
<tr>
<td>18</td>
<td>66.8±0.509</td>
<td>69.0±1.573</td>
<td>55.5±2.356</td>
<td>57.5±1.097</td>
<td>45.6±2.733</td>
<td>47.0±2.638</td>
<td>36.7±1.324</td>
<td>37.5±2.476</td>
</tr>
<tr>
<td>20</td>
<td>71.0±1.029</td>
<td>72.9±0.836</td>
<td>59.4±1.431</td>
<td>60.9±1.543</td>
<td>49.7±1.317</td>
<td>48.5±1.504</td>
<td>42.5±0.945</td>
<td>40.6±1.349</td>
</tr>
</tbody>
</table>

Figure 17: Plot of in vitro release of Rizatriptan Benzoate from the films containing 5 mg of glycerine

Figure 18: Plot of in vitro release of Rizatriptan Benzoate from the films containing 10 mg of glycerine

Figure 19: Plot of ex vivo permeation of Rizatriptan Benzoate from the films containing 5 mg of glycerine
**DISCUSSION**

**Physical evaluation**

1) **Film thickness**

As all the formulations contain different amount of polymers, hence the thickness was gradually increases with the amount of polymers. All the film formulations were found to have thickness in the range of 0.05 mm to 0.15 mm. The results are given in the table 4 shows gradual increase in the thickness.

2) **Weight variations**

Three films each of 4 cm² were cut at three different places from the casted film and weight variation was determined. Weight variation varies from 49.00 ± 1.000 to 68.66 ± 0.577 mg. The result of weight variation is shown in table 4.

**Evaluation of mechanical properties**

A suitable FDF requires moderate tensile strength, acceptable percentage elongation and folding endurance. Study of mechanical properties was undertaken for all the selected formulations. Table 4 shows the comparative mechanical properties of various formulations prepared during the study.

The tensile strength was found to increase with increase with concentration of HPMC E-15 whereas the increase in the concentration of glycerine leads in the decrease in the tensile strength. The tensile strength of formulation F7 was found maximum 4.01. The percentage elongation of all the batches ranges from 5-20. It increased upon increasing the amount of plasticizer and polymer as shown by the formulations. Formulation F8 had highest percentage elongation. Folding endurance increases with increase in the concentration of glycerine. The number of time the film fold until it broke is reported in the table 4.

**Surface pH**

The surface pH of the films was ranging from 6.67 ± 0.050 to 6.93 ± 0.015 as shown in table 5. Since the surface pH of the films was found to be around the neutral pH, there will not be any kind of irritation to the mucosal lining of the oral cavity.

**In vitro disintegration**

It was observed that in vitro disintegration time varies from 25 to 50 sec for all the formulations. In vitro disintegration time of OFDFs containing HPMC E-15 and maltodextin as polymer was affected
by the thickness of the film. In vitro disintegration time of the films was found to increased with increase in the amount of the polymer.

**Determination of drug content of the films**

The prepared film formulations were assayed for drug content. It was observed that all the formulations were satisfactory in uniformity of drug as given in table 5.

**In-Vitro drug release tests**

The in vitro drug release profiles of the formulations in pH 6.8 phosphate buffer show differences depending on their composition as given in table 6. A rapid dissolution of all the film preparations was observed by the dissolution test, in which approximately 90% of Rizatriptan Benzoate dissolved within 15 min. The formulations F1 and F2 showed approximately 90% drug release within 6 minutes. It was also observed that HPMC E-15 was able to modulate the Rizatriptan release as higher amount of HPMC E-15 resulted in release of drug at slower rate.

**Ex-vivo drug permeation**

Drug ex-vivo drug permeation it was found that the formulation F1 and F2 showed better drug permeation of 71.0% and 72.9% in 20 min respectively, when compared to other formulation as shown in table 7. The percentage amount of drug permeated was plotted against time to obtain permeation profile as shown in figure 19-20. It was observed that other film formulation took longer time probably due to higher content of HPMC E-15.

**Stability study**

The stability study of the formulation F1 and F2 was carried out at normal room conditions and 40°C/75% RH for a period of one month. The films does not show any change in appearance and flexibility. The drug content and surface pH was found almost constant for upto one month. The in vitro dissolution time of the films after the stability study was also not found to be affected.

**CONCLUSION**

The results of the present study indicated that HPMC E15 could be used as a film forming polymer for formulation of fast dissolving film containing rizatriptan benzoate. Acceptable mechanical properties were obtained for all the batches with in-vitro disintegration time of 30 s. On the basis of data obtained from in-vitro dissolution and ex-vivo permeation studies that F1 and F2 are promising formulation suitable for the immediate release of rizatriptan benzoate for the systemic use since they exhibited maximum drug release and permeation respectively. The formulation batch F1 and F2 was found to be stable for a period of one month at 40°C/75%RH.

**REFERENCES**


6) Keiko T, Yasuko O, Tsuneji N, Thorseinn L, Kozo T. Buccal absorption of ergotamine tartrate using the


12) Han HJ, Floros DJ, Casting antimicrobial packaging films and measuring their physical properties and antimicrobial activity. J. Plastic Film and Sheeting. 18, 287-298.
