Biphasic release of Zolmitriptan through design of gastroretentive bilayer floating matrix tablets

N. Panda*, A.V. Reddy*, G.V.S. Reddyb, M.S. Ansari*

*Anwarul Uloom College of Pharmacy, Hyderabad, India & Department of Pharmaceutical Sciences, JNTUA, Anantapur, AP, India

bDepartment of Chemistry, JNTUA College of Engineering, Pulivendula, YSR (Kadapa), A.P

Article history:
Received: 23 June, 2015
Accepted: 02 July, 2015
Available online: 16 October, 2015

Keywords:
Bilayer tablet, Zolmitriptan, Gastroretensive drug delivery, Floating matrix tablet, Migraine

Corresponding Author:
Panda N.*
Associate Professor
Email: niranjanpharma82 (at) gmail (dot) com

A.V Reddy
Principal and Professor

G.V.S Reddy
Professor and Vice-Principal

M.S Ansari
Asst. Professor

Abstract
The objectives of the present study was to develop a bilayer floating sustained release matrix tablet of Zolmitriptan with biphasic release that increase the residence time in gastric fluid and improves its bioavailability. Floating bilayer tablets having one immediate release layer and another sustained release layer were prepared using direct compression technique. Among all the IR layer formulations, ZIRF10 showed highest $f_2$ value (57.84) and lowest $f_1$ value (10.72) was considered as best formulation. Dry powder blends of all the formulations were evaluated for precompression parameters like angle of repose, Carr’s index and Hausner’s ratio and the results comply with pharmacopoeia specification. The formulated tablet were characterized by weight variation, friability, hardness, swelling studies, in vitro release studies, in vitro release kinetic and FTIR and DSC analysis. DSC and FTIR analysis ensured compatibility between the drug and polymers used for formulations. The floating lag time, floating duration and swelling index of ZBFTF10 (optimized formulation) found as 21 second, 13 hour and 101.29 respectively. Out of all the formulation developed, formulation ZBFTF10 containing 23% of HPMC K100M and 10% of ethyl cellulose showed optimum in vitro drug release upto 99% at the end of 12 h. The kinetic of in vitro drug release profile of ZBFTF10 followed Pappas kinetic model ($R^2=0.995$) having drug release mechanism as anomalous diffusion coupled with erosion ($n=0.706$). Accelerated stability studies of optimized formulation (ZBFTF10) showed a little change in physicochemical properties as well as drug release profiles at the end of 90 days indicating the stability of formulations. The results of the current study clearly indicated a promising potential of the Zolmitriptan bilayer floating system as an alternative to the conventional dosage form as it released an initial loading dose that can be useful for acute migraine followed by maintenance dose as sustained release manner for better therapeutic benefits. However, further clinical studies are needed to assess the utility of this system for patients suffering from migraine.

Citation:

All Rights Reserved with Photon.
Photon Ignitor: ISJN82377516D803316102015

1. Introduction

The bilayer tablet concept containing single drug has long been utilized to formulate biphasic release of drugs (Patel et al., 2008). Such a bilayer tablet contains an immediate release layer and a sustained release layer. The immediate release layer leads to rapid release of the drug, so as to reach high plasma concentration above minimum effective concentration in a short period of time that is called as loading dose. The sustained release layer of the bilayer tablet releases the drug for prolonged period of time to maintain the effective concentration of drug within the therapeutic index (Patel et al., 2009).

Gastroretensive drug delivery systems were designed to prolong the residence time of drug in
the GIT and this approaches can be utilised for preparation of bilayer tablet containing an immediate release layer and a sustained release layer. Gastric retention can be prolonged by using floating, mucoadhesive, swelling and high density systems. These systems release the drug in gastric fluid for prolong period before it reaches its site of absorption and thereby ensures optimal bioavailability of drugs having stability and more solubility in gastric fluids (Vyas et al., 2002; Bandari et al., 2010). Among the above methods used for gastric retention, floating systems are most commonly used now-a-days. Floating systems are distinctly different technologies have been utilized to mucosal layer in GI tract. Floating matrix tablets are type of sustained release drug delivery system to release the drug for prolonged period of time. The system is floating over the gastric contents, the drug is slowly released at the desired rate. This results in an increase in the gastric retention time and decrease in fluctuation in plasma drug concentration (Arora et al., 2005).

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in development of FDDS which are: A. Effervescent System, and B. Non- Effervescent System. Effervescent systems include use of gas generating agents, carbonates (ex. Sodium bicarbonate) and other organic acid (e.g. citric acid and tartaric acid) present in the formulation to produce carbon dioxide (CO2) gas, thus reducing the density of the system and making it float on the gastric fluid. The Non-effervescent FDDS based on mechanism of swelling of polymer or bioadhesion to mucosal layer in GI tract. Floating matrix tablets are type of sustained release drug delivery system which floats on gastric fluids for longer period of time by generating CO2 gas or by swelling and release the drug for prolonged period of time (Arora et al., 2005; Abdelbarry et al.; 2010).

Migraine headache are the most common disease described as vascular headache that causes a throbbing and pulsating pain around the head. It involves abnormal sensitivity of arteries within the brain resulting in triggers that often lead to rapid changes in the diameter of artery, resulting from spasm. As a result of this other arteries in the brain and scalp dilate resulting in terrible pain in the head. The pathophysiology of migraine includes a combination of neuronal, vascular, and inflammatory components (Dubey et al., 2014).

Zolmitriptan is a selective serotonin receptor agonist used in the acute treatment of migraine. Zolmitriptan binds with high affinity to human 5-HT1B and 5-HT1D receptors leading to cranial blood vessel constriction. It is having oral bioavailability 40% and plasma half-life 2.5-3 hours. Zolmitriptan is almost white powder slightly soluble in water (1.3 mg/ml at 250°C) but shows greater solubility in 0.1M hydrochloric acid belonging to class III of BCS classification. The recommended starting dose is 1.25 or 2.5 mg. The maximum recommended single dose is 5mg 2 to 3 times in a day (Dubey et al., 2014; Prajapati et al.; 2014).

The objective of the present study was to develop bilayer floating tablets of Zolmitriptan with a fast-release layer using sodium starch glycolate and croscarmellose as superdisintegrant and a sustaining layer using different grades of hydroxyl propyl methylcellulose (HPMC K4M, K15M, and K100M) and Ethyl cellulose as polymeric retardant materials. In these studies sodium bicarbonate was used as an effervescence agent as matrix system along with sustained release layer that was responsible for floating behaviour of bilayer tablets (Kyad et al., 2011; Murphy et al., 2012).

2. Material and Methods

2.1 Materials
Zolmitriptan was procured as a gift sample from Dr Reddy’s laboratories Ltd, Hyderabad. HPMC K4M, HPMC K15M, HPMC K100M, and ethyl cellulose polymers were received as gift sample from Glenmark Pharma, Nasik, India. Primojel, AC-Di-Sol, talc and magnesium Stearate were purchased from S.D. fine chemicals Pvt. Ltd’ Mumbai, India. Microcrystalline cellulose was purchased from Signet Chemicals. All other ingredients used were of analytical grade and purchased from SD fine chemicals Pvt Ltd, Mumbai, India.

2.2 Calculation of dose in a bilayer floating tablets containing single drug
The total dose of Zolmitriptan for a bilayer sustained release tablet formulation containing an immediate release layer and sustained release layer was calculated by the following four equations using available pharmacokinetic data from a design of one compartment model with simultaneous release of loading dose and maintenance dose with a zero-order release as described by Robison and Eriksen (Prajapati et al., 2012).

\[ K_p = D_p K_p \]  
\[ D_M = K_p T \]  
\[ D_L = D_2 - K_p T \]  
\[ D_M = \frac{D_L}{T_{1/2}} \]

\[ D_L = D_2 + D_2 \]

\[ K_p = 0.93/2.75h \]

Elimination rate constant
\[
\text{Ph} \text{ton} 491 = 0.252 \text{ h}^{-1}
\]

Zero-order release constant \( K_0 = D_T \times K_e \)

\[
= 2.5 \text{ mg} \times 0.252 \text{ h}^{-1}
\]

Loading dose \( D_L = D_T - (K_0 \times T_{max}) \)

\[
= 2.5 - (0.63 \times 2.25 \text{ h})
\]

\[
= 2.5 - 1.42
\]

\[
= 1.08 \text{ mg}
\]

So, maintenance dose = Total dose – loading dose

\[
= 10 \text{ mg} - 1.08 \text{ mg}
\]

\[
= 8.92 \text{ mg}
\]

Hence, the bilayer matrix tablet should contain a total dose of 10 mg for 12 h SR dosage form and it should release 2.5 – 1.42 = 1.08 (10.8%) mg in the 1st hour like conventional dosage form and the remaining dose (10 – 1.08) in 12 h, i.e. 8.92mg (89.2%) or 0.74 (8.30%) mg per hour up to 12 h as it is a biphasic dosage form.

2.3 Formulation of Zolmitriptan bilayer floating matrix tablets

The bilayer floating matrix tablets of Zolmitriptan were formulated by direct compression method. It has of two types of layers i.e. the first layer consists of the optimized immediate release (IR) layer powder and for second layer, different proportion of polymers were used for sustained release (SR) action to optimise drug release profile according the need. All the powders passed through 40 mesh sieve individually. The required quantity of Zolmitriptan, various ingredients were mixed separately for IR and SR layer by method of trituration. Required quantities of sodium bicarbonate as an effervescent agent were mixed with different ingredients of SR layer and triturated thoroughly to form a matrix system. Magnesium stearate and talc were finally added as a lubricant and glidant respectively and mixed slowly for 2-3 minutes. The dry blends of immediate release layer and sustained release layer were tested for various precompression parameters like bulk density, tapped density, angle of repose, Carr’s index, Hausner’s ratio etc. The evaluated mixture of powder was directly compressed (8 mm diameter, circular flat faced punches) in a 10 station bilayer rotary tablet punching machine (SHAIMAC Technology Pvt. Ltd, Hyderabad, India). Each bilayer floating tablet contained 10 mg of Zolmitriptan (1.08mg in IR layer and 8.92mg SR layer). All the tablets were stored in airtight containers for further study.

Table 1: Compositions of immediate release layer for Zolmitriptan bilayer floating matrix tablets

<table>
<thead>
<tr>
<th>Formulations (mg)</th>
<th>ZIRF₁</th>
<th>ZIRF₂</th>
<th>ZIRF₃</th>
<th>ZIRF₄</th>
<th>ZIRF₅</th>
<th>ZIRF₆</th>
<th>ZIRF₇</th>
<th>ZIRF₈</th>
<th>ZIRF₉</th>
<th>ZIRF₁₀</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zolmitriptan</td>
<td>1.08</td>
<td>1.08</td>
<td>1.08</td>
<td>1.08</td>
<td>1.08</td>
<td>1.08</td>
<td>1.08</td>
<td>1.08</td>
<td>1.08</td>
<td>1.08</td>
</tr>
<tr>
<td>Avicel 101</td>
<td>40.67</td>
<td>39.67</td>
<td>38.67</td>
<td>37.67</td>
<td>40.67</td>
<td>39.67</td>
<td>38.67</td>
<td>37.67</td>
<td>38.67</td>
<td>38.67</td>
</tr>
<tr>
<td>PVP K30</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Primojel</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>AC-Di-Sol</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Mg. stearate</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Talc</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Colour</td>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>Total wt.</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

Table 2: Composition of sustained release layer for Zolmitriptan bilayer floating matrix tablets

<table>
<thead>
<tr>
<th>Formulations (mg)</th>
<th>ZSR₁</th>
<th>ZSR₂</th>
<th>ZSR₃</th>
<th>ZSR₄</th>
<th>ZSR₅</th>
<th>ZSR₆</th>
<th>ZSR₇</th>
<th>ZSR₈</th>
<th>ZSR₉</th>
<th>ZSR₁₀</th>
<th>ZSR₁₁</th>
<th>ZSR₁₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPMC K4M</td>
<td>30</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>35</td>
<td>-</td>
<td>-</td>
<td>40</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HPMC K15M</td>
<td>-</td>
<td>30</td>
<td>-</td>
<td>-</td>
<td>35</td>
<td>-</td>
<td>-</td>
<td>40</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HPMC K100M</td>
<td>-</td>
<td>-</td>
<td>30</td>
<td>-</td>
<td>-</td>
<td>35</td>
<td>-</td>
<td>40</td>
<td>-</td>
<td>35</td>
<td>35</td>
<td>30</td>
</tr>
<tr>
<td>Ethyl cellulose</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>15</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>NaHCO₃</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>MCC</td>
<td>70.08</td>
<td>70.08</td>
<td>70.08</td>
<td>60.08</td>
<td>60.08</td>
<td>50.08</td>
<td>50.08</td>
<td>50.08</td>
<td>50.08</td>
<td>45.08</td>
<td>50.08</td>
<td>50.08</td>
</tr>
<tr>
<td>PVP K30</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Mg. Stearate</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Talc</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Total weight</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>
<td>150</td>
<td>150</td>
<td>150</td>
</tr>
</tbody>
</table>
2.4 Evaluation of pre-compression parameters of dry powder blend of all formulations

The prepared dry blend powder of both the layers of Zolmitriptan bilayer floating matrix tablets were taken in the ratio if 1:3 and evaluated for different precompression parameters like Angle of repose, bulk density, tapped density, Carr’s index, and Hausner’s ratio to ensure good flow properties of the same during tablet compressions. All the precompression parameters are outlined below (He et al., 2014).

2.4.1 Angle of Repose (θ)

Angle of repose is indicated as maximum angle possible between the surface of a pile of granules and the horizontal plane. The granules were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

\[
\theta = \tan^{-1} \frac{h}{r}
\]

Where θ was called as angle of repose, h and r were height and radius of the granule heap respectively. According to the specifications the angle of repose of dry powder should be less than 25° as it indicates excellent flow (Prajapati et al., 2012; Panda et al., 2015).

2.4.2 Bulk density and tapped density

The flow ability of powder can be evaluated by comparing the loose bulk density (LBD) and tapped bulk density (TBD) of powder and the rate at which it packed down. Both loose bulk density (LBD) and tapped bulk density (TBD) were determined for the calculation of Carr’s index and Hausner’s ratio. LBD and TBD of dry powder blends of both the layer of Zolmitriptan bilayer floating tablets were calculated using the following formulas (Gaikwad et al., 2014).

\[
LBD = \frac{\text{weight of the powder}}{\text{volume of the packing}}
\]

\[
TBD = \frac{\text{tapped volume of the powder}}{\text{weight of the powder}}
\]

2.4.3 Compressibility Index (Carr’s index)

Compressibility index (Carr’s index) of dry power blends of both the layer of Zolmitriptan bilayer floating tablets were calculated by following formula

\[
\text{Carr’s index} (%) = \frac{TBD-LBD}{TBD} \times 100
\]

According to the specification the Carr’s index values “between” 5-15 indicates excellent flow where as between 12-16 indicates good flow. Values “between” 18-21 indicate just-passable where as between 23-25 indicates poor. Between 33-38 indicates very poor and greater than 40 indicates extremely poor (Lakshmi et al., 2013).

2.4.4 Hausner’s ratio

The Hausner’s ratio of dry power blends of both the layer of Zolmitriptan bilayer floating tablets were determined by following formula.

\[
\text{Hausner’s ratio} = \frac{TBD}{LBD}
\]

According to specifications values less than 1.25 indicate good flow (=20% of Carr’s index), whereas greater than 1.25 indicates poor flow (=33% of Carr’s index). Between 1.25 and 1.5, normally glidant need to be added to improves flow (Lakshmi et al., 2013).

2.5 Evaluation of Zolmitriptan bilayer floating matrix tablets

2.5.1 Thickness

From each batch of Zolmitriptan bilayer floating matrix tablets; ten tablets were randomly selected and used for thickness determination. Thickness of each tablet was measured by using digital Vernier Calliper (Mitutoyo dial Thickness Gauge, Mitutoyo, Japan) and the results were expressed as mean values of ten readings, with standard deviations (Chen et al., 2013).

2.5.2 Tablet Hardness

The hardness of prepared Zolmitriptan bilayer floating tablets from each formulation was measured by using Monsanto hardness tester (Cad Mach). From each batch; ten bilayer floating tablets with known weights were recorded for crushing strength in kg/cm² and average was calculated and presented with standard deviation. According to specifications of USP hardness values of 5-7 Kg for bilayer matrix tablet is considered as acceptable limit (Prajapati et al., 2012).

2.5.3 Friability

Previously weighed 10 tablets from each batch were taken in Roche friabilator (Roche friabilator, Pharma labs, Ahmedabad, India). After 100 revolutions of friabilator tablets were recovered. The tablets were then made free from dust and the total remaining weight was recorded. Friability was calculated from the following formula.

\[
\%F = \left(\frac{W_{f} - W_{f}}{W_{f}}\right) \times 100
\]

Where \(W_{f}\) and \(W_{f}\) were the initial and final weight of the tablets before and after friability test. For compressed tablet that lose between 0.1 to 0.5 % and maximum upto 1% of the tablet weight are consider acceptable (Prajapati et al., 2012).

2.5.4 Weight variation test

According to USP monograph, the weight variation tolerance limit for the uncoated tablet having average weight between 130-324 mg is 7.5%. For the tablet to be accepted, the weight of not more than two tablets deviate from the average weight by not more than 7.5% and no tablet deviates by more
than 15%. All formulated Zolmitriptan bilayer floating matrix tablets were evaluated for weight variation as per USP monograph. Twenty tablets were weighed collectively and individually using an electronic balance (Citizen CTG-302). The average weight and percent variation of each tablet was calculated (Lakshmi et al., 2013).

2.5.5 Content uniformity
Twenty tablets from each batch of Zolmitriptan bilayer floating tablets were taken and powdered; powder equivalent to one tablet was taken and dissolved in 100 ml of pH 1.2 HCl buffer. The solution was filtered, suitably diluted and the Zolmitriptan content was measured by using UV Spectrophotometer (Analytical Technologies Ltd. Spectro 2080) at 283 nm. Each measurement was carried out in triplicate and the average drug content in the floating tablet was calculated (Lifang et al., 2014; Lakshmi et al., 2013).

2.5.6 In Vitro Buoyancy studies
The prepared bilayer floating tablets were subjected to in vitro buoyancy test by placing them in 250 ml beaker containing 200ml of HCl buffer pH 1.2 maintaining temperature at 37±0.5°C. The time required for the tablet to rise to the surface for floating was determined as the floating lag time and floating duration of all tablets was determined by visual observation (Bomma et al., 2009; Lifang et al., 2014).

2.5.7 Swelling studies
The swelling behaviour of all formulations of Zolmitriptan bilayer floating tablet was measured by studying its weight gain in the dissolution medium under study. The swelling index of selected bilayer matrix tablets were determined by placing the tablets in the basket of dissolution apparatus maintaining dissolution medium (HCl buffer pH 1.2) at 37 ± 0.5°C. After every one hour interval and up to 12 hour, each dissolution basket containing tablet was withdrawn and blotted with tissue paper to remove the excess water and weighed on the analytical balance (Shimadzu, Ax 120). The experiment was performed in triplicate for each time point. Swelling index was calculated by using the following formula.

\[
Swelling\ Index\ (SI) = \frac{W_t - W_i}{W_i} \times 100
\]

Where \( W_t \) and \( W_i \) is called as wet and dry weight of the tablet respectively (Bomma et al., 2009; Tadros et al., 2010).

2.5.8 In vitro drug release studies
In vitro drug release studies were carried out using USP XXII dissolution apparatus type II (Lab India DS 8000, Mumbai, India) at 37 ± 0.5°C. The studies were performed with rotation speed of 50 rpm using 900ml of HCl buffer pH 1.2 as dissolution medium. 5ml of the samples were withdrawn at one hour intervals and replaced with an equal volume of buffer. The Zolmitriptan release at different time intervals was measured using an UV visible spectrophotometer (Analytical Technology Ltd, Spectro 2080) at 283 nm after suitable dilution. The study was performed in triplicate (He et al., 2014; Panda et al., 2015).

2.5.9 Calculation of similarity and difference factors for Zolmitriptan immediate release layer
The optimized formulation for immediate release layer was chosen according to a comparative dissolution study with a reference marketed product of ZOMIG TAB (AstraZeneca) containing Zolmitriptan 2.5mg, employing the similarity factor (f2) and difference factor (f1) equation introduced by Moore and Flanner.

The similarity factor (f2) adopted by the U.S. Food and Drug Administration (FDA) was used to evaluate the similarity in release profiles between the two pharmaceutical preparations. The similarity factor, which is a logarithmic transformation of the sum squared error of differences between the test preparation and reference preparation, was calculated by the following equation:

\[
f_2 = 50 \times \log \left( \frac{L + \frac{1}{n} \sum (R_t - T_t)^2}{\sum \sum (R_t - T_t)^2} \right) \times 10^6
\]

Where \( R \) and \( T \), are the accumulated release rates of the reference preparation and test preparation at the predetermined time points, respectively, and \( n \) represents the number of the time points. The value of the similarity factor is between 0 and 100. The value 100 indicates that the test and reference profiles are identical; the more it approaches 0, the more dissimilarity of the two preparations occurs. Generally, if \( f_2 > 50 \), the release profiles are considered to be similar, and the larger the \( f_2 \) value, the higher the similarity.

Difference factor (f1) measures the percent error between two drug release curves over all time points.

\[
f_1 = \frac{\sqrt{\sum \sum (R_t - T_t)^2}}{\sum \sum (R_t + T_t)} \times 100
\]

Dissolution profile was considered satisfactory if \( f1 \) values lies below 15 (nearing zero, more it approaches towards zero more similarity is the product (Gaikwad et al., 2014; Narendra et al., 2006).

2.5.10 Characterization of in vitro drug release profile through kinetics studies
The rate and mechanism of release of Zolmitriptan from the optimised bilayer floating matrix tablets were analyzed by fitting the dissolution data into following exponential equations.
Zero order kinetic equation is expressed as

\[ Q = Q_0 t \]

Where \( Q \) is the amount of drug released at time \( t \) and \( K_0 \) is the zero order release rate constant.

The first order kinetic equation is expressed as

\[ \log(100 - Q) = \log 100 - \frac{K_1 t}{2.303} \]

Where, \( K_1 \) is the first order release rate constant.

The dissolution data was fitted to the Higuchi's equation:

\[ Q = K_2 t^{1/2} \]

Where, \( K_2 \) is the diffusion rate constant.

The dissolution data was also fitted to the Korsmeyer-Peppas equation, which is often used to describe the drug release behaviour from polymeric systems:

\[ \log\left(\frac{M_t}{M_\infty}\right) = \log K + n \log t \]

Where \( M_t \) is the amount of drug released at time \( t \), \( M_\infty \) is the amount of drug release after infinite time, \( K \) is a release rate constant and \( n \) is the diffusion exponent indicative of the mechanism of drug release.

For matrix tablets, if the exponent \( n < 0.5 \), then the drug release mechanism is quasi-fickian diffusion (If \( n = 0.5 \) then fickian diffusion and if the value is \( 0.5 < n < 1 \), then it is anomalous diffusion coupled with erosion. An exponent value of 1 is indicative of Case-II Transport or typical zero-order and \( n > 1 \) non-fickian super Case II). The diffusion exponent was based on Korsmeyer-Peppas equation.

Hixson-Crowell recognized that area of the particle is proportional to the cube root of its volume, and derived an equation as follows

\[ W_0^{1/3} - W_t^{1/3} = K_0 t \]

Where \( W_0 \) is the initial amount of drug, \( W_t \) is the remaining amount of drug in dosage form at time \( t \), and \( K_0 \) is a constant incorporating the surface volume relation. The graphs are plotted as cube root of percent drug remaining versus time (Higuchi et al., 1963; He et al., 2014).

2.5.12 Compatibility studies through DSC analysis

The DSC analysis of Zolmitriptan, HPMC K100M, ethyl cellulose, optimised formulation (ZBFTF10) were carried out using a Shimadzu DSC 60, (Japan) to evaluate any possible polymer drug thermal interaction. Exactly weighed 5 to 6 mg samples were hermetically sealed in aluminium crucible and heated at constant rate of 10°C/min over a temperature range of 40 to 300°C. Inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50 ml/min (Sunghongjeen et al., 2008; Panda et al., 2015).

2.5.13 Stability studies of optimised formulation

The stability studies of optimised formulation (ZBFTF10) were carried out according to ICH guidelines. The optimized formulation was subjected to stressed condition at 40°C ± 2°C/75% ± 5% RH using humidity control oven NEC 210R10 (Newtronic Instruments, India) for 90 days. The product was taken out from humidity control oven at interval of 30 days, 60 days and 90 days to evaluate for physicochemical characteristics i.e friability, hardness, weight variation, thickness, drug content and in vitro release study (Katiyar et al., 2013).

3. Results and Discussion

3.1 Precompression parameters

The bulk densities of dry powder blends (Mixture of IR and SR layer) of all formulations were found in the range of 0.235±0.06 to 0.294±0.05 g/cm³ and the tapped densities were found in between 0.298±0.06 to 0.364±0.08 g/cm³. This indicates good packing capacity of dry blended powders and density of a powder depends on particle packing those changes as the powder consolidates. Values of Carr’s index below 16% usually show good flow characteristics, but readings above 25% indicate poor flowability. Carr’s index was found “between” 11.32 to 24.73 that indicate good to average flow properties. All the formulations except ZBFTF6, ZBFTF10 and ZBFTF12 showed Carr’s index value more than 20% that indicates average flow properties and presents of more fines with lack of uniformity in particles. Hausner’s ratio is simple method to evaluate stability of powder column and to estimate flow properties. Low range was observed of Hausner’s ratio that indicates good flow ability. In all formulations the Hausner’s ratios were found “between” 1.13 to 1.30 that indicates good flow and the formulation having more than 1.25 required to add more glidant to improve flow properties. Angle of repose is suited for particle > 150μm. Values of angle of repose ≤ 25 generally indicates the free flowing
material and angle of ≥ 40 suggest a poor flowing material. The angle of repose is indicative of the flowability of the material. The angle of repose of all formulations fell within the range of 21.15±0.17 to 24.72±0.19 i.e. dry powder blends were of good flow properties. The results of precompression parameters of each formulation were given in table 2.

<table>
<thead>
<tr>
<th>Table 2: Evaluation parameters of dry blends of Zolmitriptan bilayer floating matrix tablet powders formulations (ZBFTF&lt;sub&gt;1&lt;/sub&gt;-ZBFTF&lt;sub&gt;12&lt;/sub&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Formulation code</strong></td>
</tr>
<tr>
<td>ZBFTF&lt;sub&gt;1&lt;/sub&gt;</td>
</tr>
<tr>
<td>ZBFTF&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>ZBFTF&lt;sub&gt;3&lt;/sub&gt;</td>
</tr>
<tr>
<td>ZBFTF&lt;sub&gt;4&lt;/sub&gt;</td>
</tr>
<tr>
<td>ZBFTF&lt;sub&gt;5&lt;/sub&gt;</td>
</tr>
<tr>
<td>ZBFTF&lt;sub&gt;6&lt;/sub&gt;</td>
</tr>
<tr>
<td>ZBFTF&lt;sub&gt;7&lt;/sub&gt;</td>
</tr>
<tr>
<td>ZBFTF&lt;sub&gt;8&lt;/sub&gt;</td>
</tr>
<tr>
<td>ZBFTF&lt;sub&gt;9&lt;/sub&gt;</td>
</tr>
<tr>
<td>ZBFTF&lt;sub&gt;10&lt;/sub&gt;</td>
</tr>
<tr>
<td>ZBFTF&lt;sub&gt;11&lt;/sub&gt;</td>
</tr>
<tr>
<td>ZBFTF&lt;sub&gt;12&lt;/sub&gt;</td>
</tr>
</tbody>
</table>

All values are expressed as average± SD; (n=3)

3.2 Postcompression parameters

The postcompression parameters of the all the formulations of Zolmitriptan bilayer floating matrix tablets were found satisfactory. Typical tablet defects, such as capping, chipping and picking were not observed. The average thicknesses of the tablets were ranged between 3.58±0.10 to 3.78±0.08 mm. All the batches showed uniform thickness. Weight variations for different formulations were found to be 198±2.31 to 202±2.06 mg. The average percentage deviations of all tablet formulations were found to be in between 98.25±1.63 to 102.63±1.42 % w/w. The hardness usually decreased that noticed in case of concentration of sodium bicarbonate. In the present study, the percentage friability for all formulations was within the prescribed limits. The percentages of drug content for ZBFTF<sub>1</sub> to ZBFTF<sub>12</sub> were found to be in between 98.25±1.63 to 102.63±1.42 which were within the acceptable limits. The results of postcompression parameters of each formulation of Zolmitriptan bilayer floating matrix tablets were given in table 3.

<table>
<thead>
<tr>
<th>Table 3: Evaluation of post-compression parameters of Zolmitriptan bilayer floating matrix tablets formulation (ZBFTF&lt;sub&gt;1&lt;/sub&gt;-ZBFTF&lt;sub&gt;12&lt;/sub&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Formulation code</strong></td>
</tr>
<tr>
<td>ZBFTF&lt;sub&gt;1&lt;/sub&gt;</td>
</tr>
<tr>
<td>ZBFTF&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>ZBFTF&lt;sub&gt;3&lt;/sub&gt;</td>
</tr>
<tr>
<td>ZBFTF&lt;sub&gt;4&lt;/sub&gt;</td>
</tr>
<tr>
<td>ZBFTF&lt;sub&gt;5&lt;/sub&gt;</td>
</tr>
<tr>
<td>ZBFTF&lt;sub&gt;6&lt;/sub&gt;</td>
</tr>
<tr>
<td>ZBFTF&lt;sub&gt;7&lt;/sub&gt;</td>
</tr>
<tr>
<td>ZBFTF&lt;sub&gt;8&lt;/sub&gt;</td>
</tr>
<tr>
<td>ZBFTF&lt;sub&gt;9&lt;/sub&gt;</td>
</tr>
<tr>
<td>ZBFTF&lt;sub&gt;10&lt;/sub&gt;</td>
</tr>
<tr>
<td>ZBFTF&lt;sub&gt;11&lt;/sub&gt;</td>
</tr>
<tr>
<td>ZBFTF&lt;sub&gt;12&lt;/sub&gt;</td>
</tr>
</tbody>
</table>

All values are expressed as average± SD; (n=3)

3.3 In vitro buoyancy studies

All the batches of floating tablets were found to exhibit short floating lag times due to presence of gas generating agent, sodium bicarbonate. The buoyancy properties of various Zolmitriptan floating matrix tablets were given in table 3. The floating lag time of all formulations was less than 60 seconds and the floating lag time decreased due
to increased concentration of sodium bicarbonate. Floating durations were varied from 8 hours to more than 12 hours. From formulations ZBFTF7 to ZBFTF12, which contained 13% of sodium bicarbonate showed an optimum floating duration of more than 12 hours.

3.4 In vitro swelling studies
Swelling study was performed on all the formulations (ZBFTF1 to ZBFTF12) for 12 hours. Formulations that contains HPMC K100M polymer showed higher swelling indices as compared with other formulations containing HPMC K4M and HPMC K15M. The direct relationship was observed between swelling index and polymer concentration and type. As the concentration of hydrophilic polymer (HPMC) increases in floating matrix tablets, swelling index was found to increase but swelling index were found to decrease by increasing the concentration of ethyl cellulose as it is hydrophobic in nature. The swelling indexes of all the formulations were plotted with respect to time (hour) in the form of histogram and shown in figure 1.

![Swelling studies of ZBFTF1-ZBFTF9](image1)

![Swelling studies of ZBFTF4-ZBFTF6](image2)

![Swelling studies of ZBFTF7-ZBFTF9](image3)

![Swelling studies of ZBFTF10-ZBFTF12](image4)

Figure 1: Comparative Swelling studies of Zolmitriptan IR layer floating matrix tablet formulations (ZBFTF1-ZBFTF10)

3.5 Similarity (f2) and difference (f1) factors of Zolmitriptan IR layer
To optimise the immediate release layer that to use in bilayer floating matrix tablet, the similarity and difference factors were calculated by comparing the dissolution data of available marketed formulation. Thus, the dissolution profiles of all the batches of immediate release layer formulations calculated in the present investigation were presented in table 6. Among all the formulations, ZIRF10 showed highest f2 value (57.84) and lowest fi value (10.72) was considered as best formulation. All other formulations showed dissimilarity in dissolution profile with marketed formulation under study.

Table 6: Similarity (fi) and difference factor (f2) with dissolution profile of all formulations

<table>
<thead>
<tr>
<th>F. No.</th>
<th>fi</th>
<th>f2</th>
<th>Dissolution profiles</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZIRF1</td>
<td>53.02</td>
<td>23.34</td>
<td>Dissimilar</td>
</tr>
<tr>
<td>ZIRF2</td>
<td>39.73</td>
<td>29.50</td>
<td>Dissimilar</td>
</tr>
<tr>
<td>ZIRF3</td>
<td>26.29</td>
<td>38.54</td>
<td>Dissimilar</td>
</tr>
<tr>
<td>ZIRF4</td>
<td>28.33</td>
<td>36.94</td>
<td>Dissimilar</td>
</tr>
<tr>
<td>ZIRF5</td>
<td>48.18</td>
<td>25.33</td>
<td>Dissimilar</td>
</tr>
<tr>
<td>ZIRF6</td>
<td>34.69</td>
<td>32.37</td>
<td>Dissimilar</td>
</tr>
<tr>
<td>ZIRF7</td>
<td>23.09</td>
<td>41.08</td>
<td>Dissimilar</td>
</tr>
<tr>
<td>ZIRF8</td>
<td>20.58</td>
<td>43.72</td>
<td>Dissimilar</td>
</tr>
<tr>
<td>ZIRF9</td>
<td>23.69</td>
<td>40.55</td>
<td>Dissimilar</td>
</tr>
<tr>
<td>ZIRF10</td>
<td>10.72</td>
<td>57.84</td>
<td>Similar</td>
</tr>
</tbody>
</table>

3.6 In vitro drug release studies
Based on the highest similarity factor (f2) and
lowest difference factor \((f_1)\) value between different formulations of immediate release layer, the formulation ZIRF\(_{10}\) was considered as optimised formulation and was used as IR layer for all the formulations of Zolmitriptan bilayer floating matrix tablet. In order to optimise the \textit{in vitro} drug release of Zolmitriptan bilayer floating matrix tablets different hydrophilic matrix polymers viz., HPMC K4M, HPMC K15M, HPMC K100M and hydrophobic matrix polymer viz., ethyl cellulose were used and 12 different formulations were prepared. Between the three grades of HPMC used, HPMC K100M having better controlled release profile than other two grades of HPMC. By increasing the concentration of HPMC the prolong release effect increases and it was found optimum at HPMC polymer concentration of 23\%. It was observed that using HPMC polymer alone causes initial burst release because drug is hydrophilic in nature and maximum release occurred upto 10 hours. So one more hydrophobic polymer \textit{i.e} ethyl cellulose was added to reduce the initial burst release. Formulation ZBFTF\(_{10}\) that contained 23\% of HPMC K100M and 10\% of ethyl cellulose was considered as optimised formulation as the initial release was 18\% within one hour followed by maximum release as sustained manner upto 12 hours. Further increased in the concentration of ethyl cellulose caused slow initial release rate that was not desirable. So 10\% of ethyl cellulose was considered as optimum. The plots of cumulative percentage drug release with respect to time for all the formulations were shown in \textbf{figure 2}.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Comparative dissolution profile of Zolmitriptan bilayer floating matrix tablet formulations (ZBFTF\(_1\)-ZBFTF\(_{12}\))}
\end{figure}

### 3.7 \textit{In vitro} drug release kinetic studies

The in vitro dissolution data were fitted for optimized formulation (ZBFTF\(_{10}\)) in different kinetic models viz. zero order, first order, Higuchi, Korse Meyer- Pappas and Hixon-Crowell and the graphs were plotted. The Pappas model plots were found to be fairly linear as indicated by their highest regression (0.995) values for ZBFTF\(_{10}\) formulation. The release exponent ‘\(n\)’ for optimized formulation ZBFTF\(_{10}\) was found to be 0.706 (0.5 < \(n\) < 1), which appears to indicate a coupling of the diffusion and erosion mechanism so-called anomalous diffusion. So in present study in vitro drug release kinetic of optimized formulation of Zolmitriptan bilayer floating matrix tablet followed Pappas kinetic models and drug release mechanism is anomalous diffusion coupled with erosion. The comparative regression values of all the kinetic models were shown in table 4 and plotted graphs were shown in figure 3.

\begin{table}[h]
\centering
\caption{Regression values of \textit{In-vitro} release kinetic study optimized Zolmitriptan bilayer floating matrix Tablet (ZBFTF\(_{10}\))}
\begin{tabular}{|c|c|c|c|c|}
\hline
Formulation & \textit{R}^2 value of Zero order & \textit{R}^2 value of 1st order & \textit{R}^2 value of Higuchi model & \textit{R}^2 value of Peppa’s model & Hixon-Crowell Kinetic model \\
\hline
ZBFTF\(_{10}\) & 0.988 & 0.876 & 0.966 & 0.995 & 0.699 & 0.706 \\
\hline
\end{tabular}
\end{table}
3.8 FTIR analysis
From the FTIR studies it was found that the spectra of Zolmitriptan exhibits peak due to N-H stretching at 3342.41 cm\(^{-1}\), C = O stretching at 1730.03 cm\(^{-1}\), and C = C stretching at 1650.0 cm\(^{-1}\). These values were complying with the reported values. The FTIR spectra of optimised formulation ZBFTF\(_{10}\) (Zolmitriptan with all the Excipients) exhibit peak due to N-H stretching at 3332.76 cm\(^{-1}\), C = O stretching at 1735.00 cm\(^{-1}\), and C = C stretching at 1647.10 cm\(^{-1}\). Thus it is evident that all the characteristic peaks that were present in the spectra of pure drugs replicated almost in the same region in the spectra of optimised formulations of Zolmitriptan bilayer floating matrix tablet indicating that there is no significant interaction between the drugs and the polymers. The FTIR spectra of pure drug Zolmitriptan and optimised formulations were shown in figures 4.
3.9 DSC analysis
DSC study was conducted for pure drug Zolmitriptan and optimised formulation (ZBFTF\textsubscript{10}). DSC thermogram of pure Zolmitriptan shows sharp endothermic peak at 141.5 °C and similar endothermic peaks were obtained at 201.1°C for the optimized Zolmitriptan bilayer floating matrix tablet formulations. The peaks appeared at higher temperature may be due to presence of other ingredients. The endothermic peak that also appeared at 94.6 °C in optimised formulation ZBFTF\textsubscript{10} may be due to presence of other ingredients like HPMC K100M and ethyl cellulose. The shifting of endothermic peaks to exothermic peaks was not observed in the thermogram of optimised formulation under study. Presence of similar kind of peaks indicated that all ingredients were compatible with Zolmitriptan potassium and there is no incompatibility between the drug and selected ingredients. DSC thermogram of pure drug and optimised formulation are shown in figure 5.

![DSC thermogram of Zolmitriptan pure drug](image)

![DSC thermogram of optimised formulation](image)

Figure 5: Compatibility studies through DSC Analysis

3.10 Stability studies
The optimised formulation ZBFTF\textsubscript{10} was selected for the accelerated stability studies. The Zolmitriptan bilayer floating matrix tablets did not show any significant change in physicochemical parameters as well as \textit{in vitro} drug release characteristics throughout the study period. More than 90% of the drug had been retained from \textit{in vitro} release studies after 90 days of storage under accelerated condition. Thus, it was found that the floating tablets of Zolmitriptan (ZBFTF\textsubscript{10}) were stable under accelerated storage conditions for at least 3 months. Graph was plotted between cumulative percent drug releases with respect to time (hour) after the end of 30 days, 60 days and 90 days that is shown in figure 6.

![In vitro release studies of ZBFTF\textsubscript{10} at Accelerated conditions](image)

Figure 6: In vitro release profiles of optimised formulation under Accelerated storage conditions
Conclusion

In the present investigations bilayer floating matrix tablets of Zolmitriptan were successfully developed by direct compression methods. The major challenge in this work was to design a bilayer floating matrix tablet having an initial loading dose followed by maintenance dose up to 12 hours with prolongation of gastric residence time of drug as drug is having better solubility and stability in gastric environment. FTIR and DSC studies of Zolmitriptan and their physical mixture (optimised formulation) revealed that, Zolmitriptan is compatible with all the material used in the formulation.

On the basis of highest similarity factor and lowest difference factors, the IR layer formulation ZIRF₁₀ was considered as optimised formulation and used in all bilayer tablet formulations with the sustained release layer. The main objective of using hydrophobic polymer ethyl cellulose with HPMC was to prevent initial burst release of the hydrophilic drug under study with hydrophilic polymer like HPMC which was successfully developed.

The Sodium bicarbonate was added in varying concentrations as a gas generating agent to improve the floating capacity of tablet and the formulations containing more than 10% of sodium bicarbonate had floating lag time less than 30 seconds and floating duration more than 12h. From the swelling studies it was revealed that, as the concentration of hydrophilic polymer (HPMC) increased in floating matrix tablets, swelling index was found to increase but swelling index were found to decrease by increased the concentration of ethyl cellulose as it is hydrophobic in nature.

From in vitro release studies, formulation ZBFTF₁₀ containing 23% of HPMC K100M and 10% of ethyl cellulose showed initial release of 18% with controlled drug release for 12h (99%) emerging as optimized formulation. By increase in polymer concentration of both the polymer the drug release profile were much slower. Kinetic of in vitro drug release of optimized formulation ZBFTF₁₀ found to follow Pappas kinetic model having drug release mechanism as anomalous diffusion coupled with erosion.

From the stability studies it was confirmed that optimised formulations ZBFTF₁₀ of Zolmitriptan remained stable at stressed condition (40°C ± 2°C/75% ± 5% RH), no significant difference in physicochemical characteristics as well as in vitro drug release profile.

Thus from the results of the current study clearly indicated a promising potential of the Zolmitriptan bilayer floating system as an alternative to the conventional dosage form as it released an initial loading dose that can be useful for acute migraine followed by maintenance dose as sustained release manner for better therapeutic benefits. However, further clinical studies are needed to assess the utility of this system for patients suffering from migraine.

Acknowledgment

The authors are thankful to Dr Reddy’s laboratories Ltd., Hyderabad and Glenmark Pharma, Nasik, India for providing gift samples of pure drug and polymers. Authors are also thankful to the chairman & principal Anwarul Uloom college of Pharmacy, Hyderabad, Telengana, for permitting to carry out research work.

References


