PREPRATION OF RIZATRIPTAN SUBLINGUAL TABLETS PREPARED BY DIRECT COMPRESSION WITH DIFFERENT POLYMERS

IN VITRO EVALUATION

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ABSTRACT: Sublingual tablet of oral formulations of these drugs have been developed to improve their acceptability to patients and thus improve compliance. The focus of present investigation was to improve solubility, bioavailability and to achieved rapid onset action. Sublingual tablets of Nimodipine were prepared by direct compression technique. The aim of the research was to prepare and evaluate the Rizatriptan sublingual tablets by using direct compression technique. Rizatriptan is a headache medicine that narrows the blood vessels around the brain. Eight Formulations were formulated using excipients are the chitosan, povidine, sodium starch glycol. Friability, Disintegration time. In addition, the prepared tablets were also evaluated for weight variation, thickness, diameter, friability, content uniformity, wetting time and drug release studies. The eight formulations are done in this F6 formulation are release the drug up to the 8 hrs. combination sodium starch glycolate and Chitosan showed better results. So it is more effective in combination with Chitosan. All parameters are come within range of limits. The stability studies are done for 90 days. The kinetic profile data is calculated it is follow the zero order and higuchi model.

Key words: Rizatriptan, Dry granulation technique, FTIR studies, Polymers, Drug release studies, stability studies.

I. INTRODUCTION

The word ‘novel’ about the drug delivery system (DDS) is a search for something that will ultimately lead to minimizing the disadvantages associated with the existing dosage form (DF) and optimizing therapy while maximizing patient comfort1. Drug delivery system is a relatively modern term used in place of ‘dosage form’ to describe a system carrying a drug. The ideal form of DDS would be the ‘magic bullet’ envisioned by the 1908 Nobel Laureate Paul Ehrlich. His aim was, as he put it, to find chemicals which have special affinities for pathogenic organisms, to which they would go, and would be, as Ehrlich expressed it, ‘magic bullets’ but should have very little affinity for non-target cells.2 Sublingual Delivery This is systemic delivery of drugs through mucosal membranes lining the floor of the mouth. Sublingual drug delivery system is enteral route of administration, but as far as absorption is concerned, it is oral trans mucosal type of drug absorption.3 Sublingual drug delivery systems have been introduced to overcome the drawback of low bioavailability problems associated with conventional oral dosage forms4. Therapeutically active molecules for the treatment and prevention of new and existing diseases are currently being developed. The aim of the research was to prepare and evaluate the Rizatriptan sublingual tablets by using direct compression technique.5 Rizatriptan is a headache medicine that narrows the blood vessels around the brain. Rizatriptan also reduces substances in the body that can trigger headache pain, nausea, sensitivity to light and sound, and other migraine symptoms. Rizatriptan is used to treat migraine headaches.6

II. MATERIALS AND METHOD

2.1 Materials

Rizatriptan was collected as a gift sample from Hetero labs, Hyd, polymers and other excipients were purchased from Vijaya Chemicals, Hyd.

2.2 Methodology

Drug excipient compatibility

Compatibility studies of Rizatriptan and the disintegrants were carried out by using Fourier Transform Infrared Spectroscopy (FTIR). Fourier transform infrared spectra of the samples were obtained in the range of 4000 to 450
cm-1 using a FTIR by the KBr disc method.

**Preparation of tablets by Direct compression method:**

Different matrix embedded formulations of Rizatriptan were prepared by direct compression method using varying proportion of super disintegrants either alone or in combination. The ingredients were passed through a 60 mesh sieve. Calculated amount of the drug, Various Super disintegrant agent and filler (MCC) was mixed thoroughly. Magnesium stearate was added as lubricant; the appropriate amount of the mixture was weighed and then compressed using a Ten station rotary press at a constant compression force equipped with a 6-mm flat-faced punches at a compression force required to produce tablets of about 5–6 kg/cm² hardness. All the tablets were stored in airtight containers for further study. Prior to compression, granules were evaluated for their flow and compressibility characteristics.

**Formulation table:**

<table>
<thead>
<tr>
<th>INGREDIENTS</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
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<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Cross caramellose</td>
<td>2.5</td>
<td>5</td>
<td>7.5</td>
<td>10</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Sodium starch glycolate</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>2.5</td>
<td>5</td>
<td>7.5</td>
<td>10</td>
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<tr>
<td>chitosan</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>
</tr>
<tr>
<td>Lactose</td>
<td>76.5</td>
<td>74</td>
<td>71.5</td>
<td>69</td>
<td>76.5</td>
<td>74</td>
<td>71.5</td>
<td>69</td>
</tr>
<tr>
<td>Saccharrine sodium</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>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
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<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Talc</td>
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<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
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<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

**Evaluation studies**

**Bulk Density**

Mass thickness is characterized as the mass of powder isolated by mass volume.

It is ascertained utilizing the accompanying condition:

Mass thickness = weight of test taken/volume noted

**Tapped density**

A precisely measured amount of the powder (W) was deliberately filled the graduated barrel and the volume (vo) was estimated.

Tapped thickness = weight of test taken/tapped volume

Where,

Vo = beginning volume

Vf = last volume.

**Compressibility index**

In view of the obvious mass thickness and the tapped thickness, the rate Compressibility of the mass medication was dictated by the accompanying recipe.

Carr’s index = Tapped thickness - Bulk thickness/Tapped thickness X 100

**Hausner's ratio**

It shows the stream properties of the powder. The proportion of tapped thickness to the mass thickness of the powder is called Hausner proportion.

Hausner's proportion = Tapped thickness/Bulk thickness

**Angle of repose**

The stream attributes are estimated by point of rest. Edge of rest is characterized as the most extreme point conceivable between the surface of a heap of the powder and the even plane.

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

Where

h = tallness of heap
Evaluation of tablets\textsuperscript{14,15,16}

Weight variation
Twenty tablets were characterized chosen from each group and exclusively weighed. The normal weight and standard deviation of 20 tablets was ascertained. The cluster finishes the test for weight variety test if not more than two of the individual tablet weight digress from the normal weight by more than the rate.

Thickness
Twenty tablets were evaluated chosen from each group and thickness was estimated by utilizing vernier caliper. Thickness of three tablets from each cluster was estimated and mean was computed.

Hardness
Hardness demonstrates the capacity of a tablet to withstand mechanical stuns while taking care of. The hardness of the tablets was resolved utilizing Monsanto hardness analyzer. It is communicated in kg/cm\textsuperscript{2}. Three tablets were arbitrarily picked and hardness of the tablets were resolved.

Friability
Friability test is performed to survey the impact of erosion and stuns, which may regularly make tablet chip, top or break. Roche friabilator was utilized for the reason. This gadget subjects various tablets to the consolidated impact of scraped spot and stun by using a plastic chamber that spins at 25 rpm dropping the tablets at separation of 6 creeps with every upheaval. Twenty tablets were weighed and set in the Roche friabilator, which was then worked for 25 rpm for 4 min. After unrest Tablets were dedusted and reweighed. Packed tablets ought not free over 1% of their weight.

\[ \% F = \{1-(\text{Wo}/\text{W})\} \times 100 \]

Where,
\[ \% F = \text{friability in rate} \]
\[ \text{Wo} = \text{Initial weight of tablet} \]
\[ \text{W} = \text{weight of tablets after insurgency} \]

Content Uniformity
Twenty tablets from each clump were powdered and weighed precisely identical to 100 mg Rizatriptan. Break down the measured amount of powder into 100 ml of 6.8 phosphate support arrangement by blending it for 15 min. 1 ml of arrangement was pipette out into 10 ml volumetric flask.

In vitro drug release studies
In the USP drug release test for sublingual tablets, the breaking down mechanical assembly for oral tablets is utilized without the covering plastic plates, and 2 min is indicated as the satisfactory time confine for tablet deterioration satisfying the official necessities (<2 min) for the sublingual measurements frame. The test was done utilizing a tablet breaking down contraption. Refined water was utilized as the crumbling medium at 24 ± 0.2°C. The time required to acquire finish breaking down of the considerable number of tablets was noted.

Wetting time
The tablet was put at the focal point of two layers of permeable paper fitted into a petridish. After the paper was altogether wetted with refined water, overabundance water was totally depleted out of the dish. The time required for the water to diffuse from the wetted spongy paper all through the whole tablet was then recorded utilizing a stopwatch.

In vitro drug release studies
In-Vitro sedate discharge thinks about were done utilizing Tablet dissolution apparatus USP II at 50 rpm. The disintegration medium comprised of 900 ml of Standard support pH 1.2 for the initial 2 hrs, trailed by pH 6.8 for residual timeframe. Temperature kept up at 37 °C. The example of 5ml was pulled back at foreordained time interims and a proportional measure of new disintegration liquid equilibrated at a similar temperature was supplanted. From that 5 ml test, 1 ml test was pulled back and set in a 10 ml volumetric flask. The aliquots were tested.

Swelling study
Swelling of tablet includes the assimilation of a fluid bringing about an expansion in weight and volume. Fluid take-up by the molecule might be because of immersion of slender spaces inside the particles or hydration of macromolecule. The fluid enters the particles through pores and tie to huge atom; breaking the hydrogen bond and bringing about the swelling of molecule. The degree of swelling can be estimated as far as % weight gain by the tablet. one tablet was weighed and set in a Petri plate containing 25 ml of 6.8 pH cushion arrangement. After
every interim the tablet was expelled from recepticle, evacuates overabundance of cushion by utilizing channel paper and weighed again up to 12 hours. The swelling list was ascertained utilizing following equation.

Swelling Index (S.I.) = \{(W_t-W_0)/W_0\} \times 100

Where,
S.I. = Swelling list
W_t = Weight of tablet at time t
W_0 = Weight of tablet before putting in the petri plate.

**Drug release kinetics**

The models utilized were zero request (condition 1) First request (condition 2) and Higuchi show (condition 3) and Koresmeyer Peppas display (condition 4).

**Zero order kinetics**

\[ R = K_0 \cdot t \]  

R=cumulative percent tranquilize discharge  
Ko=zero arrange rate steady

**First order kinetics**

\[ \log C = \log C_0 - K_1 \cdot t / 2.303 \]

where  
C = total percent medicate discharge  
K_1 = first request rate steady

**Higuchi Model**

\[ R = K_H \cdot t^{0.5} \]

where  
R = aggregate percent medicate discharge  
K_H = higuchi display rate consistent

**korsermeyer peppas :**

\[ M_t/M_0 = k \cdot t^n \]

log \( M_t/M_0 \) = log k + n \cdot log t  
where  
k = korsermeyer peppas rate consistent  
'M t/M 0' is the partial medication discharge, n = diffusional type, which describes the instrument of medication discharge (Simon Benita, 2007).

The acquired relapse co-effective (which neared 0.999) was utilized to comprehend the discharge example of the medication from the Sublingual tablets.

**Stability studies**

The sublingual tablets of Rizatriptan were set on plastic tubes containing desiccant and put away at surrounding conditions, for example, at room temperature, 40±2oc and icebox 2-8oc for a time of 3 months.\(^{17}\)

**III. RESULTS AND DISCUSSIONS**

**FT-IR Spectrum of Rizatriptan**

FT-IR Spectra of Rizatriptan and F6 formulation were recorded. All these peaks have appeared in formulation and physical mixture, indicating no chemical interaction between Rizatriptan and polymer. It also confirmed that the stability of drug during microencapsulation process.
Evaluation studies

Pre compression parameters

a) Bulk Density: The bulk density for the formulated blend was carried out for all formulation and found in the range of 0.431-0.471.

b) Tapped density: The tapped density for the formulated blend was carried out for all formulation and found in the range of 0.515-0.563.

c) Angle of repose: The angle of repose for the formulated blend was carried out. It concludes that all the formulations blend was found to be in the range of 29 to 31°.

c) Compressibility index: Compressibility index was carried out, it found between 10% to 14.90 % indicating the powder blend have the required flow property for compression.

Characterization of Formulation

Table-2 Pre compression parameters of Rizatriptan sublingual tablets

<table>
<thead>
<tr>
<th>S.</th>
<th>Bulk density</th>
<th>Tapped density</th>
<th>Compressibility index</th>
<th>Hausner ratio</th>
<th>Angle of repose(°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.431</td>
<td>0.522</td>
<td>17.43</td>
<td>1.21</td>
<td>29°c</td>
</tr>
</tbody>
</table>

Fig. 1. FTIR Studies of Rizatriptan

Fig. 2. FTIR Studies of optimized formulation
Post compression parameters

Weight variation:
All the formulated (F1 to F8) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Thickness:
Tablets mean thickness (n=3) were uniform in F1 to F8 formulations and were found to be in the range of 2.3 mm to 2.6 mm.

Hardness:
The measured hardness of tablets of each batch ranged between 3.24 to 3.46 kg/cm². This ensures good handling characteristics of all batches.

Friability:
The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Content Uniformity:
The percentage of drug content for F1 to F8 was found to be between 95.20% and 98.55% of Rizatriptan, it complies with official specifications.

Disintegration Time:
In the presented studies, three different types of in vitro methods of tablet disintegration were used: those where the only factor leading to the disintegration was water wicking into the matrix of the tablet, the tests with water agitation or stirring, and the methods where direct destructive forces were put on the tested tablet, such as grinding or pressing with additional weight. Therefore, disintegration tests showed great variability in the data measured with different methods. The shortest registered disintegration time was 2.25 s, while the longest greatly exceeded 2.81 sec.

Wetting Time:
The weight of the tablet before keeping in Petri dish was noted (W₀) using Shimadzu digital balance. The wetted tablet from the Petri dish was taken and re weighed (Wₚ) using the same. The shortest registered wetting time was 1.25 s, while the longest greatly exceeded 1.52 sec.

<table>
<thead>
<tr>
<th>F. No.</th>
<th>Weight variation (mg)</th>
<th>Thickness (mm)</th>
<th>Hardness (kg/cm²)</th>
<th>Friability (%)</th>
<th>Drug Content (%)</th>
<th>Disintegration time (sec)</th>
<th>Wetting time (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>99</td>
<td>2.3</td>
<td>3.24</td>
<td>0.52</td>
<td>96.10</td>
<td>54</td>
<td>125</td>
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<tr>
<td>F2</td>
<td>98</td>
<td>2.4</td>
<td>3.26</td>
<td>0.45</td>
<td>95.20</td>
<td>53</td>
<td>134</td>
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<td>F3</td>
<td>100</td>
<td>2.6</td>
<td>3.28</td>
<td>0.54</td>
<td>98.55</td>
<td>51</td>
<td>155</td>
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<tr>
<td>F4</td>
<td>97</td>
<td>2.4</td>
<td>3.46</td>
<td>0.51</td>
<td>97.50</td>
<td>49</td>
<td>152</td>
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<tr>
<td>F5</td>
<td>100</td>
<td>2.5</td>
<td>3.40</td>
<td>0.53</td>
<td>96.58</td>
<td>45</td>
<td>128</td>
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</tbody>
</table>

Table-3: Evaluation parameters of Rizatriptan sublingual tablets
Dissolution studies
All the eight formulation of Rizatriptan sublingual tablets were subjected to in vitro release studies these studies were carried out using dissolution apparatus. The dissolution medium consisted of 900 ml of Standard buffer pH 6.8 for period of time.

Table: 4 Dissolution Profile of formulation F1 to F8

<table>
<thead>
<tr>
<th>% Drug Release</th>
<th>Time(mins)</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>
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<tr>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>20</td>
<td>35.26</td>
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<td>39.65</td>
<td>34.56</td>
<td>32.71</td>
<td>33.10</td>
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<td>30</td>
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<td>50.26</td>
<td>49.99</td>
<td>48.26</td>
<td>48.56</td>
<td>46.29</td>
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<tr>
<td>40</td>
<td>62.35</td>
<td>59.66</td>
<td>61.29</td>
<td>64.26</td>
<td>63.54</td>
<td>65.30</td>
<td>59.80</td>
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<td>60</td>
<td>70.26</td>
<td>70.98</td>
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<td>89.56</td>
<td>89.25</td>
<td>90.64</td>
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<tr>
<td>120</td>
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<td>95.35</td>
<td>94.68</td>
<td>93.48</td>
<td>94.56</td>
<td>98.48</td>
<td>95.51</td>
<td>90.58</td>
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</tr>
</tbody>
</table>

![Fig.3. Percentage drug release of all formulations](image)

Release order kinetics

Table: 5 Drug release kinetics of optimized formulation

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>% CDR</th>
<th>SQARE T</th>
<th>LOG T</th>
<th>LOG% CDR</th>
<th>ARA</th>
<th>LOG% ARA</th>
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<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
</tr>
<tr>
<td>Time (min)</td>
<td>Zero order</td>
<td>First order</td>
<td>Higuchi model</td>
<td></td>
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<td>-----------</td>
<td>-------------</td>
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<td>1.47712</td>
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<td>40</td>
<td>65.3</td>
<td>6.32456</td>
<td>1.60206</td>
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<td>60</td>
<td>72.28</td>
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<td>1.77815</td>
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<td>120</td>
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<td>10.9545</td>
<td>2.07918</td>
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</table>

**Zero order kinetics**

![Zero order kinetics plot](image)

*Fig. 4. Zero order plot for optimized formula*

**First order kinetics**

![First order kinetics plot](image)

*Fig. 5. First order for optimized formula*

**Higuchi model**

![Higuchi model plot](image)

*Fig. 6. Higuchi plot for optimized formula*
The drug release from the tablets was found to follow Zero order release based on the “r” value obtained for Zero order (0.801) and first order (0.476) for F6 formulation. Also, the drug release mechanism was found to be “Diffusion” based on the “r” value of 0.975 obtained for Higuchi’s plot. Similarly, the drug release mechanism was found to be of Anomalous diffusion mechanism based on the “n” value of 0.552 obtained for Peppa’s equation.

**Stability Study**
There was no significant change in physical and chemical properties of the tablets of formulation F-6 after 6 months. Parameters quantified at various time intervals were shown.

<table>
<thead>
<tr>
<th>F. Code</th>
<th>Parameters</th>
<th>Initial</th>
<th>1st Month</th>
<th>2nd Month</th>
<th>3rd Month</th>
<th>Limits as per Specifications</th>
</tr>
</thead>
<tbody>
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<td>F-6</td>
<td>25°C/60%RH % Release</td>
<td>98.48</td>
<td>98.46</td>
<td>98.42</td>
<td>98.41</td>
<td>Not less than 85 %</td>
</tr>
<tr>
<td>F-6</td>
<td>30°C/75% RH % Release</td>
<td>98.48</td>
<td>98.45</td>
<td>98.45</td>
<td>98.40</td>
<td>Not less than 85 %</td>
</tr>
<tr>
<td>F-6</td>
<td>40°C/75% RH % Release</td>
<td>98.48</td>
<td>98.46</td>
<td>98.44</td>
<td>98.42</td>
<td>Not less than 85 %</td>
</tr>
</tbody>
</table>

**IV. SUMMARY**
The design, prepare and characterization of the sublingual tablets of the rizatriptan by using direct compression technique. In this formulation development first undergo for the pre formulation studies such as the color, odour, taste and solubility studies are done. The API and polymers compatibility studies are done by the FTIR studies. For formulation studies the used excipients are the chitosan, povidine, sodium starch glycolate and mannitol and talc were used. The eight formulations are done in this F6 formulation are release the drug up to the 8 hrs. combination sodium starch glycolate and Chitosan showed better results. So it is more effective in combination with Chitosan. It is compared to innovator it releases the drug. The post compression parameters are also done. Such as the weight variation, friability, thickness, disintegration are done. All parameters are come within range of limits. The stability studies are done for 90days. The kinetic profile data is calculated it is fallow the zero order and higuchi model

**REFERENCES**