**Research Article**

**FORMULATION AND EVALUATION OF NASAL IN SITU GEL OF RIZATRIPTAN BENZOATE**

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**ABSTRACT**

*In situ* gel drug delivery systems are in elucidation form prior to supervision but once administered, endure gelation *in situ*, to form a gel. In the current revise nasal in situ gel of rizatriptan Benzoate was primed for the cure of nasal infections to give sustained release of drug and to attain site specific action. Carbopol was use as a pH triggered polymer. Different formulations were prepared by varying the concentrations of Carbopol with Hydroxylpropyl Methylcellulose (HPMC). These formulations were evaluated for parameters like drug excipient compatibility, pH, drug content, gelation temperature, viscosity, *in vitro* drug release, mucoadhesion, *ex vivo* permeation and stability studies. FTIR study exposed that there was no interface between drug and polymer. pH of all the formulations were initiate to be in the vary of 5.4-6.2 and the drug substance for all the prepared formulations was initiate to be in the assortment of 94%-99%. The results of *in vitro* drug release and mucoadhesive strength indicated that the optimized formulation F5 is the most successful formulations of the study, exhibited a sustained drug release of in 87.7% in 7 hours. mucoadhesive strength of 2024.64 and 3267.76 dyne/cm2. From the results it is fulfilled that rizatriptan Benzoate nasal *in situ* gel produce extended and site specific drug delivery.

**Keywords:** Nasal drug delivery, Rizatriptan Benzoate, *In Situ* nasal gel, Mucoadhesion.

**INTRODUCTION:**

Incomplete absorption of some drugs following oral administration and first-pass metabolism, results in a low absolute bioavailability1. Unfortunately, potential drugs for the treatment of most brain diseases are therefore often not able to cross these barriers2. As a result, various drug delivery and targeting strategies are currently being developed to enhance the transport and distribution of drugs into the brain3.

Carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as hydrogels4, nanoparticles, dendrimers5, liposomes etc. which modulates the release and absorption characteristics of the drug. nasal drug delivery is an emerging technique and even better option to transport the drug directly to brain bypassing the metabolism. The Delivery from nose to central nervous system occurs within minutes along with both the olfactory and trigeminal neural pathways. The olfactory region is located in the top of the nasal cavity and it is the only site of the body where the CNS is in contact with the external environment6. The nose-to-brain drug delivery of drugs is advantageous as it requires low dose of drug, is fast in action and also avoids blood brain barrier which is important factor to be considered in formulation of CNS targeting drugs. This route of administration is also painless and useful in emergency conditions7, 8.

The physiology of the nasal cavity creates a variety of opportunities for drug companies to develop local and systemic drugs. Many drugs have better bioavailability by nasal route than the oral route9. This has been attributed to rich vasculature and a highly permeable structure of the nasal mucosa coupled with avoidance of hepatic first-pass elimination, gut wall metabolism and destruction in the gastrointestinal tract10. The physiology of the nose presents obstacles, but offers a promising route for non-invasive systemic delivery of numerous therapies11.

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Over the past few decades, advances in the in situ gel technologies have spurred development in many medical and biomedical applications including controlled drug delivery\textsuperscript{12}. Many novel in situ gel based delivery matrices have been designed and fabricated to fulfill the ever increasing needs.

The in situ gel systems are liquid at room temperature but undergo gelation when in contact with body fluids or change in pH\textsuperscript{13}. In situ gel based delivery is a type of mucoadhesive drug delivery system. The formation of gel depends on factors like temperature modulation, pH change, presence of ions and ultraviolet irradiation from which the drug gets released in a sustained and controlled manner\textsuperscript{14}. Drug release kinetic can be controlled by gelation strength of the formulation and viscosity of the in situ gel formulation, so in situ gel nasal drug delivery is also called controlled and sustained drug delivery system\textsuperscript{15}.

For many years drugs have been administered nasally for both topical and systemic action. Topical administration includes the treatment of congestion, rhinitis, sinusitis and related allergic or chronic conditions, and has resulted in a variety of different medications including corticoids, antihistamines, anticholinergics and vasoconstrictors\textsuperscript{16}. In recent years, increasing investigations of the nasal route have focused especially on nasal application for systemic drug deliver\textsuperscript{17}.

The encouraging results and the desire to overcome some new challenges stimulated the development of new generations of polymers based on pH or thermal responsiveness or modified existing polymers having improved bioadhesive or permeation enhancing properties\textsuperscript{18}. Even though a number of challenges are still to be overcome, especially with respect to toxicity, the potential of nasal drug delivery (NDD), including the ability to target drugs across the blood–brain barrier (BBB), are very high and continues to stimulate academic and industrial research groups so that we will keep witnessing increasing number of advanced nasal drug delivery products\textsuperscript{19}.

**MATERIALS AND METHOD**

Pure drug Rizatriptan Benzoate was obtained from torrent pharmaceuticals. All the chemicals used analytical grade.

**Methods**

**Preformulation Studies**

**Determination of wave length of Rizatriptan Benzoate**

100 mg of Rizatriptan benzoate was weighed accurately and dissolved in 100 ml 0.2 M Phosphate buffer pH 6.4 in a 100 ml of volumetric flask. 10 ml of this solution was diluted to 100 ml with 0.2 M Phosphate buffer pH 6.4 to obtain a stock solution of 100ug/ml.

From this stock solution, aliquots of 1ml, 2ml, 3ml, 4ml......10ml were transferred 10 ml volumetric flasks and volume was made up to 10 ml 0.2 M Phosphate buffer pH 6.6. The absorbances of these solutions were measured at 282 nm against a blank 0.2 M Phosphate buffer pH 6.6. The calibration curve was plotted between concentration and absorbance.

The absorbance of every concentration was calculated at λmax of 280 nm by UV Visible spectrophotometer alongside reagent vacant. Standard curve was plotted with concentration on x-axis and absorbance on y-axis\textsuperscript{20}.

**IR Interpretation**

FT-IR spectroscopy was carrying out to confirm the compatibility with drug and polymer. The FT-IR spectra of drug with polymers were compared with the standard FT -IR spectrum of the chaste medicine and investigate any possible interactions between the drug, polymer and physical mixture. The scanning range was 400-4000 cm\textsuperscript{-1}. The spectra obtained were compared and interpreted for the functional group peaks\textsuperscript{21}.

**Solubility and Dissolution**

It not only limits the drug absorption but it can also limit a formulator’s ability to formulate a product if the drug is not sufficiently soluble in the desired vehicles. As nasal secretions are more watery in nature, a drug should have appropriate aqueous solubility for increased dissolution. Particles deposited in the nostrils need to be dissolved prior to absorption.

**Preparation of In-Situ Nasal Gel of Rizatriptan Benzoate**

**Preparation of the Nasal Gel**
Nasal gels were prepared using bioadhesive polymers at its optimum concentrations as determined by viscometric studies. The materials were dissolved in a measured volume of nasal solution. The insides were sonicated using Pci Ultrasonic cleaner for 10 min and stirred in a magnetic stirrer for 15 min. The whole substance was sealed and stored in the refrigerator overnight to allow complete swelling. An aliquot amount of Rizatriptan Benzoate was added and stirred again for 15 min. The prepared gel was sonicated to ensure the complete removal of air bubbles. Similarly gels were prepared using different enhancers.

Table 1: Showing Formulation of in-situ nasal gel of Rizatriptan Benzoate

<table>
<thead>
<tr>
<th>Composition (%(w/v))</th>
<th>Chitosan</th>
<th>HPMC K15</th>
<th>Rizatriptan Benzoate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Batch Code</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C1</td>
<td>10</td>
<td>-</td>
<td>2.5</td>
</tr>
<tr>
<td>C2</td>
<td>15</td>
<td>-</td>
<td>2.5</td>
</tr>
<tr>
<td>C3</td>
<td>20</td>
<td>-</td>
<td>2.5</td>
</tr>
<tr>
<td>C4</td>
<td>30</td>
<td>20</td>
<td>2.5</td>
</tr>
<tr>
<td>C5</td>
<td>20</td>
<td>20</td>
<td>2.5</td>
</tr>
<tr>
<td>C6</td>
<td>30</td>
<td>20</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Evaluation of Gels

Appearance

The developed formulations were inspected visually for clarity in sol and gel form.

pH of the gels

The pH of the formulations was measured as per Gibert et al.

Gelation Studies

Gelation studies were carried out according to in different pH Buffers (pH 5.0, 6.0, 6.6, 7.4) and was assessed by visual examination. Gelation temperature and gel melting was assessed by a modified process as follow 2 ml aliquot of gel was transferred to test tube, sealed with aluminium foil and increased in increments of 1°C and left to equilibrate for 5 min at each new setting. The samples were then examined for gelation which was said to have occurred when meniscus no longer move upon tilting through 90°C. The gel melting temperature, a critical temperature when the gel starts flowing upon tilting 90°C, was recorded.

Content uniformity

Formulations were tested for content uniformity. Bottles containing the formulation were properly shaken for 2.3 min. The formulation, 1.0 ml was transferred into a 100-ml volumetric flask and 50 ml of simulated nasal fluid was added. The formed gel was completely crushed with the help of a glass rod, followed by vigorous shaking until the formed gel got completely dispersed to give a clear solution. The volume was adjusted to 100 ml with simulated tear fluid. The solution was filtered through a 0.45-mm filter membrane and the drug concentration was determined with a UV-Visible spectrophotometer at 280 nm.

Determination of Mucoadhesive Strength

Mucoadhesive Strengths of gel was determined by using the modified method reported by Choi et al. Nasal mucosal tissues, obtained from the local slaughterhouse, were carefully removed from the nasal cavity of goat and mounted on glass surface using adhesive tape while another mucosal section was fixed in inverted position to the cylinder. 50 mg of gel was placed on mucosal surface. The glass mounted mucosal surface with gel formulation and mucosal surface attached to cylinder were held in contact with each other for 2 min to ensure intimate contact between them. In second pan, the weights were kept rising until two mucosa get detached from each other. The nasal mucosa was changed for each measurement. The Mucoadhesive force expressed as the detachment stress in dynes/cm² was determined from the minimal weight that detached the
mucosal tissue from surface of each formulation\textsuperscript{26, 27}.

\textbf{Mucoadhesive Strength (dynes/cm}\textsuperscript{2} = mg/A--------
\textsuperscript{-} (2.1)

Where,
m = weight required for detachment in gram,
g = Acceleration due to gravity (980cm/s\textsuperscript{2})
A = Area of mucosa exposed.

\textbf{Viscosity Measurement}

The viscosity measurements were carried out as per Pisal et al. Measurement was taken at 4\textdegree c and 34\textdegree c respectively\textsuperscript{28}

\textbf{In-vitro Release Studies}

The drug release of the Rizatriptan Benzoate in situ gel was measured using Franz diffusion cell. Assembly was set and the temperature was maintained at 37±0.5\textdegree C, then 2 ml of nasal in situ gel of Rizatriptan Benzoate in was applied in the donor compartment, which was separated by the receptor compartment with the cellophane membrane. Three ml aliquots of samples were withdrawn at regular time intervals and replaced with an equal volume of phosphate buffer as fresh receptor medium. The samples were appropriately diluted with Phosphate buffer and analyzed spectrophotometrically (using Shimadzu® 1700, double beam UV-visible spectrophotometer) at 280 nm\textsuperscript{29}.

\textbf{Drug release kinetics and mechanism:}

In order to understand the kinetic and mechanism of drug release, the result of in vitro drug release study of nasal in situ gels were fitted with various mathematical models. Based on the R\textsuperscript{2}-value or n-value, the best-fitted model was selected

\textbf{Zero - order kinetic model} - Cumulative % drug release versus time.
\[Q= kt + Q_o \] (2.2)

Where Q represents the drug released amount in time t, Qo is the start value of Q and k is the rate constant.

\textbf{First - order kinetic model} - Log cumulative percent drug remaining versus time.
\[Q= Q_o e^{kt} \] (2.3)

Where Q represents the drug released amount in time t, Qo is the start value of Q and k is the rate constant.

\textbf{Higuchi’s model} - Cumulative percent drug released versus square root of time.
\[Q(1/3)= kt + Q_o 1/3 \] (2.3)

Where Q represents the drug released amount in time t, Qo is the start value of Q and k is the rate constant.

\textbf{Korsmeyer equation / Peppa’s model} - Log cumulative % drug release versus log time.
\[Q= ktn \] (2.4)

Where Q represents the drug released amount in time t, k is the rate constant and n is the diffusional exponent, indicative of drug release mechanism. The accuracy and prediction ability of these models were compared by calculation of squared correlation coefficient (R\textsuperscript{2}).

\textbf{Stability studies}

Stability studies were conducted for the best formulation of Rizatriptan Benzoate in situ gel. The stability of the formulation was assessed by keeping the formulation at three different temperature conditions, i.e., refrigeration temperature (4-8\textdegree C), room temperature and oven (45±2\textdegree C). Throughout the study, nasal in situ gel formulation was stored in aluminium foil sealed glass bottles. The stored formulations were evaluated periodically for drug content, pH, viscosity and in vitro drug release at predetermined time interval\textsuperscript{30, 31}.

\textbf{RESULT AND DISCUSSION}

\textbf{Determination of absorption maxima}

The absorption maxima (λ\textsubscript{max}) of Rizatriptan (10 ug/ml) in phosphate buffer pH 6.4 was found to be 225 nm and 280 nm and obeyed Beer-Lambert’s law in the concentration range of 0-10μg/ml with R\textsuperscript{2} 0.9985.

\textbf{IR Interpretation:}

Rizatriptan benzoate exhibits characteristic pecks, it was confirmed that there is no interaction between drug and polymer because the IR spectra of all formulations retains the principal drug peaks at 3120 CM\textsuperscript{-1} (Aromatic secondary amine N-H stretching), 2974 CM\textsuperscript{-1} (Aromatic C-H stretching), 1608 CM\textsuperscript{-1} (C = O Five member cyclic stretching) and 1270 CM\textsuperscript{-1} (C-N aliphatic amine stretching). All of these peaks have appeared in both formulation of rizatriptane. At 3291 CM\textsuperscript{-1} (Aromatic secondary amine N-H Stretching), 2948 CM\textsuperscript{-1} (Aromatic C – H Stretching), 1608 CM\textsuperscript{-1} (C=O Five member cyclic
stretching) and 1280 \text{ CM}^{-1} \text{ (C-N aliphatic amine stretching).} \text{ The IR spectra of all formulations did not show any new peak, indicating no new chemical bond was created due to any interaction.}

\textbf{Figure 1: IR Spectra of drug and polymers}

(A) Pure Drug (B) Excipients (Chitosan) + Drug (C) Excipients (Pectin) + Pure Drug

\textbf{Appearance}

All the formulations were found to clear. Terminal sterilization with autoclaving had no effect on physical, chemical properties of the formulations.

\textbf{Table 2: physical, chemical properties of the formulations}

<table>
<thead>
<tr>
<th>S.N.</th>
<th>Formulation</th>
<th>Appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C1</td>
<td>Transparent solution</td>
</tr>
<tr>
<td>2</td>
<td>C2</td>
<td>Transparent &amp; Viscous solution</td>
</tr>
</tbody>
</table>

\textbf{pH of gels}

The normal physiological pH of the nasal mucosa ranges from 5.5-6. pH of All formulations were found to have pH value in between range 5-6. i.e. within the range of nasal mucosa. The results are presented in table.

\textbf{Gelation studies}

All the prepared formulations were in pH ranges within ranges of nasal mucosa.

\textit{Gelation and Gelling capacity:} The gelation temperature of chitosan and Pectin gels were in the range of 35.0 to 37.4°C and 35.3 to 36.8 °C, respectively. All the prepared formulations gelled immediately and remained as gels for longer time. Addition of HPMC in both chitosan and pectin based gelling system increased the viscosity and gel strength. The higher gelation rate of the formulation with HPMC might have resulted from the stronger association of HPMC with other components via hydrogen – bonding leading to a prolonged retention of rizatriptan benzoate in the nasal cavity. It was also observed that an increase in gelation temperature. This might be caused by the increased viscosity due to the additional bioadhesive polymer.

\textbf{Table 3: Physical Characteristic of Prepared Gelling System of Rizatriptan Benzoate}

<table>
<thead>
<tr>
<th>Batch Code</th>
<th>Drug Content (mean ± S.D.)</th>
<th>Viscosity (CPS)</th>
<th>Gelation Temp. (°C) mean ± S.D.</th>
<th>Gel Strength</th>
<th>Mucoadhesion (°) mean ± S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td>98.20±0.82</td>
<td>1535.0</td>
<td>34.0±0.4</td>
<td>++</td>
<td>85.56±2.36</td>
</tr>
<tr>
<td>C2</td>
<td>97.76±0.95</td>
<td>1595.0</td>
<td>35.2±0.2</td>
<td>++</td>
<td>88.00±0.36</td>
</tr>
<tr>
<td>C3</td>
<td>98.5±0.44</td>
<td>1745.0</td>
<td>35.8±0.3</td>
<td>++</td>
<td>91.76±2.06</td>
</tr>
<tr>
<td>C4</td>
<td>99.11±0.23</td>
<td>1890.0</td>
<td>37.1±0.2</td>
<td>++</td>
<td>93.15±1.77</td>
</tr>
<tr>
<td>C5</td>
<td>98.58±0.96</td>
<td>1910.0</td>
<td>37.2±0.3</td>
<td>+++</td>
<td>81.16±1.04</td>
</tr>
<tr>
<td>C6</td>
<td>97.20±0.99</td>
<td>2165.0</td>
<td>37.6±0.4</td>
<td>+++</td>
<td>84.12±2.36</td>
</tr>
<tr>
<td>P1</td>
<td>99.12±0.22</td>
<td>360.0</td>
<td>37.4±0.3</td>
<td>++</td>
<td>71.50±1.08</td>
</tr>
<tr>
<td>P2</td>
<td>98.35±0.12</td>
<td>390.0</td>
<td>35.4±0.3</td>
<td>++</td>
<td>75.85±1.32</td>
</tr>
<tr>
<td>P3</td>
<td>98.64±0.28</td>
<td>405.0</td>
<td>35.7±0.3</td>
<td>++</td>
<td>77.33±1.67</td>
</tr>
<tr>
<td>P4</td>
<td>99.14±0.08</td>
<td>420.0</td>
<td>36.1±0.3</td>
<td>++</td>
<td>78.86±2.16</td>
</tr>
<tr>
<td>P5</td>
<td>99.35±0.78</td>
<td>595.0</td>
<td>36.4±0.2</td>
<td>+++</td>
<td>70.32±1.55</td>
</tr>
<tr>
<td>P6</td>
<td>99.64±0.65</td>
<td>656.0</td>
<td>36.6±0.2</td>
<td>+++</td>
<td>73.65±1.36</td>
</tr>
</tbody>
</table>
n= 3 for each parameter, ++ gelation immediate remains for few hrs, +++ gelation immediate, remains for extended period (≥12 H)

**Drug Content**

Drug content of the developed formulations C1 to C6 & P1 to P6 varied from 97.20±0.99% to 99.64±0.65 % which was within the required limits.

**Mucoadhesive Strength**

Two minutes of contact time was found to give optimum mucoadhesive strength. Further increase in contact time did not affect the mucoadhesive strength, whereas decreased contact time resulted in less mucoadhesive strength resulting from insufficient time for enlargement of polymer chains with mucin. Assessment of the mucoadhesive strength in terms of detachment of stress showed that the chitosan based preparation possessed adhesive properties that increased with addition of diluents. Mucoadhesive strength changes with concentrations, resulting in formulation of a strengthened network between polymer and mucus membrane.

Thus Chitosan having high density of available hydrogen bonding groups would be able to interact more strongly with mucin glycoproteins. It is specified that the broader mucoadhesive strength of the delivery system may lead to the prolonged retention and increased absorption across mucosal tissue.

**Rheological Studies**

The formulation exhibited pseudoplastic rheology as evidenced by shear thinning and an increase in the shear stress with increased angular velocity. The viscosity was directly dependent on the polymeric content of the formulations. Addition of HPMC led to increase in the viscosity of formulations and exhibited more pseudoplasticity (batch C5, C6, P5, P6) as compared to batches prepared without HPMC.

**In Vivo Drug Release**

The In-vitro drug release studies were carried out for all formulated of nasal in situ gel containing in phosphate Rizatriptan Benzoate buffer pH 6.4. All batches showed prolong sustained release of Rizatriptan Benzoate over 8 h. The cumulative drug release from this nasal in situ gel containing Rizatriptan Benzoate was within the range of 47.81+0.71 to 83.88+0.25 a sustained drug release from nasal in situ gel. Diffusion studies were carried out using the Franz diffusion cell, it was obvious that the release of Rizatriptan Benzoate was not only affected by concentration but also by the type of bioadhesive used. The bioadhesive polymer retarded the drug release from nasal gel, the retarding effect of the bioadhesive polymers could be attributed to their ability to increase the overall product viscosity as well their ability to distort or squeeze the extramicellar aqueous channels of micelles through which the drug diffuses thereby delaying the release process.

**Bioadhesive Polymer (Chitosan)**

Thus Chitosan having high density of available hydrogen bonding groups would be able to interact more strongly with mucin glycoproteins. It is specified that the broader mucoadhesive strength of the delivery system may lead to the prolonged retention and increased absorption across mucosal tissue.

**Figure 2: In vitro Stress measured (values are expressed mean ±SD, n = 3)**

**Table 4: Cumulative drug release of various formulations**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>% CDR F1</th>
<th>%CDRF2</th>
<th>%CDRF3</th>
<th>% CDRF4</th>
<th>% CDRF5</th>
<th>%CDRF6</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>8.10</td>
<td>14.935</td>
<td>07.8949</td>
<td>5.0156</td>
<td>03.5891</td>
<td>10.9934</td>
</tr>
<tr>
<td>60</td>
<td>28.21</td>
<td>30.9835</td>
<td>30.3671</td>
<td>23.728</td>
<td>24.8414</td>
<td>21.8782</td>
</tr>
<tr>
<td>90</td>
<td>32.46</td>
<td>37.2234</td>
<td>35.2461</td>
<td>27.5405</td>
<td>29.3833</td>
<td>26.2274</td>
</tr>
</tbody>
</table>
### Drug Release Kinetics zero order Formulation (F1)

![Drug Release Kinetics zero order Formulation (F1)](image)

**Equation:**
\[ y = 0.1064x + 15.621 \]
\[ R^2 = 0.8599 \]

### Drug Release Kinetics Kors-Peppas Formulation (F1)

![Drug Release Kinetics Kors-Peppas Formulation (F1)](image)

**Equation:**
\[ y = 23.134x - 8.3761 \]
\[ R^2 = 0.9021 \]

### Drug Release Kinetics first order Formulation (F1)

![Drug Release Kinetics first order Formulation (F1)](image)

**Equation:**
\[ y = -0.0016x + 1.9759 \]
\[ R^2 = 0.9168 \]

### Drug Release Kinetics Zero Order Formulation (F2)

![Drug Release Kinetics Zero Order Formulation (F2)](image)

**Equation:**
\[ Y = 0.1082x + 14.423 \]
\[ R^2 = 0.8776 \]

### Drug Release Kinetics Higuchi Formulation (F1)

![Drug Release Kinetics Higuchi Formulation (F1)](image)

**Equation:**
\[ y = 2.855x + 1.2322 \]
\[ R^2 = 0.9801 \]

### Drug Release Kinetics First Order Formulation (F2)

![Drug Release Kinetics First Order Formulation (F2)](image)

**Equation:**
\[ y = -0.0008x + 1.949 \]
\[ R^2 = 0.9433 \]
Drug Release Kinetics Higuchi Formulation (F2)

\[ y = 2.8553x + 1.2322 \]
\[ R^2 = 0.9801 \]

Drug Release Kinetics Kors - Peppas Formulation (F2)

\[ y = 23.134x - 8.3761 \]
\[ R^2 = 0.9021 \]

Drug Release Kinetics Zero Order Formulation (F3)

\[ Y = 0.1082x + 14.423 \]
\[ R^2 = 0.8776 \]

Drug Release Kinetics First Order Formulation (F2)

\[ y = -0.0008x + 1.949 \]
\[ R^2 = 0.9433 \]
Figure 3.23 Drug Release Kinetics Higuchi Formulations (F4)

Drug Release Kinetics Kors – Peppas Formulation (F4)

Drug Release Kinetics Zero order Formulation (F5)

Drug Release Kinetics First Order Formulation (F5)
The correlation coefficient ($r^2$) values for various release models viz., zero-order, first-order, and Higuchi models, Kors- Peppas were found. The $r^2$ values suggest that the drug release from the bioadhesive system predominately followed Higuchi's square root of time kinetics, as the values for $r^2 Q$ vs. $t^{1/2}$ were found. First order rate kinetic coefficient was varied from 0.838 to 0.998 and zero order kineti coefficients were found to be 0.910 to 0.999. Whereas Release exponent mechanism was followed an anomalous or non-Fickian release and suggesting a coupled erosion diffusion mechanism for the tested Rizatriptan Benzoate bioadhesive system.

**Stability Studies**

Stability study indicates that there was no significant change in the Rizatriptan benzoate after 45 days when compared with the initial value. The results indicated that the formulation did not show any change in % drug contain, pH during the stability testing period.

**CONCLUSION**

Results of the study show optimistic sign towards victorious development of preferred formulation. *In-vitro* dissolution studies study showed adequate consequences, it can be auxiliary subjected to clinical trials in standard and contaminated volunteers to get exposed the adverse effects, by Pharmacodynamic and Pharmacokinetic parameter to verify the nasal in situ gel therapeutic efficacy.

**Conflict of Interest:** Authors declared that that is no conflict of interest.

**REFERENCES**

7. Behl CR, Pimplaskar HK, Sileno AP, deMeireles J, Romeo VD. Effects of physicochemical properties and other factors on systemic nasal drug