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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 Carbopo 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 and 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 bioavailability[1]. Unfortunately, potential drugs for the treatment of most brain diseases are therefore often not able to cross these barriers[2]. As a result, various drug delivery and targeting strategies are currently being developed to enhance the transport and distribution of drugs into the brain[3].

Carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as hydrogels[4], nanoparticles, dendrimers[5], 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 environment[6]. 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 conditions[7, 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 route[9]. 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 tract[10]. The physiology of the nose presents obstacles, but offers a promising route for non-invasive systemic delivery of numerous therapies[11].

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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[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[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[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[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[16]. In recent years, increasing investigations of the nasal route have focused especially on nasal application for systemic drug deliver[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[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[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[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-1. The spectra obtained were compared and interpreted for the functional group peaks[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[22].

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

Composition (%(w/v)) Batch Code	Chitosan	HPMC K15	Rizatriptan Benzoate
C1	10	-	2.5
C2	15	-	2.5
C3	20	-	2.5
C4	30	-	2.5
C5	20	20	2.5
C6	30	20	2.5

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[23].

Gelation Studies

Gelation studies were carried out according to in different pH Buffers (pH5.0, 6.0, 6.6, 7.4) and was assessed by visual examination[23]. Gelation temperature and gel melting was assessed by a modified process[24] as follow 2 ml aliquot of gel was transferred to test tube, sealed with aluminium foil and increased in increaments of 1^0C 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 90^0C. The gel melting temperature, a critical temperature when the gel starts flowing upon tilting 90^0C, 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[24].

Determination of Mucoadhesive Strength

Mucoadhesive Strengths of gel was determined by using the modified method reported by Choi et al[25]. 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. 50mg 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/cm^2 was determined from the minimal weight that detached the

mucosal tissue from surface of each formulation[26, 27].

Mucoadhesive Strength (dynes/cm 2) = mg/A---------- (2.1)

Where,

m = weight required for detachment in gram,

g = Acceleration due to gravity (980cm/s^2)

A = Area of mucosa exposed.

Viscosity Measurement

The viscosity measurements were carried out as per Pisal et al. Measurement was taken at 4^{0}c and 34^{0}c respectively[28]

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°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[29].

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 R2-value or n-value, the best-fitted model was selected

Zero - order kinetic model - Cumulative % drug release versus time.

Q= kt + Qo (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.

First - order kinetic model - Log cumulative percent drug remaining versus time.

Q= Qoe 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.

Higuchi's model - Cumulative percent drug released versus square root of time.

Q1/3= kt + Qo 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.

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 (R2).

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^{0}C), room temperature and oven (45±2^{0}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[30, 31].

RESULT AND DISCUSSION

Determination of absorption maxima

The absorption maxima (λ_{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^2 0.9985.

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^{-1} (Aromatic secondary amine N-H stretching), 2974 CM^{-1} (Aromatic C-H Stretching), 1608 CM^{-1} (C = O Five member cyclic stretching) and 1270 CM^{-1} (C-N aliphatic amine stretching). All of these pecks have appeared in both formulation of rizatriptane. At 3291 CM^{-1} (Aromatic secondary amine N-H Stretching), 2948 CM^{-1} (Aromatic C –H Stretching), 1608 CM^{-1} (C=O Five member cyclic

stretching) and 1280 CM^{-1} (C-N aliphatic amine stretching). The IR spectra of all formulations did not show any new peak, indicating no new chemical bond was created due to any interaction.

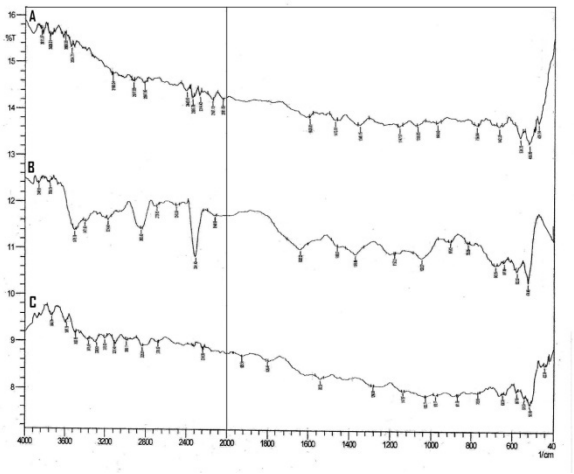


Figure 1: IR Spectra of drug and poylmers

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

Appearance

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

Table 2: physical, chemical properties of the formulations

S.N.	Formulation Code	Appearance
1	C1	Transparent solution
2	C2	Transparent & Viscous solution
3	C3	Transparent solution
4	C4	Transparent solution
5	C5	Transparent solution
6	C6	Transparent &Viscous solution

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.

Gelation studies

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

Gelation and Gelling capacity: The gelation temperature of chitosan and Pectin gels were in the range of 35.0 to 37.4^{0}C and 35.3 to 36.8 ^{0}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.

Table 3: Physical Characteristic of Prepared Gelling System of Rizatriptan Benzoate

Batch Code	Drug Content (%) mean ± S.D.	Viscosity (CPS)	Gelation Temp. (^{o}C) mean ± S.D.	Gel Strength	Mucoadhesion (%) mean ± S.D.
C1	98.20±0.82	1535.0	34.0±0.4	++	85.56±2.36
C2	97.76±0.95	1595.0	35.2±0.2	++	88.00±0.36
C3	98.5±0.44	1745.0	35.8±0.3	++	91.76±2.06
C4	99.11±0.23	1890.0	37.1±0.2	++	93.15±1.77
C5	98.58±0.96	1910.0	37.2±0.3	+++	81.16±1.04
C6	97.20±0.99	2165.0	37.6±0.4	+++	84.12±2.36
P1	99.12±0.22	360.0	37.4±0.3	++	71.50±1.08
P2	98.35±0.12	390.0	35.4±0.3	++	75.85±1.32
P3	98.64±0.28	405.0	35.7±0.3	++	77.33±1.67
P4	99.14±0.08	420.0	36.1±0.3	++	78.86±2.16
P5	99.35±0.78	595.0	36.4±0.2	+++	70.32±1.55
P6	99.64±0.65	656.0	36.6±0.2	+++	73.65±1.36

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 & P1to 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.

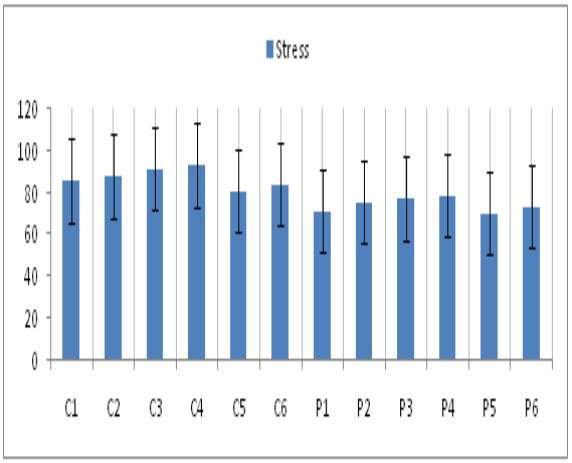


Figure 2: In vitro Stress measured (values are expressed mean ±SD, n = 3)

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 thining 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.

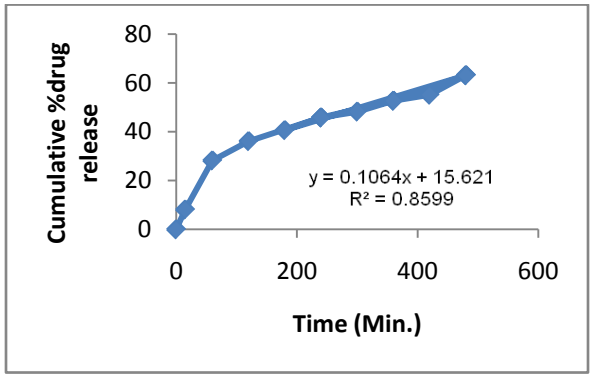
Bioadhesive Polymer (Chitosan)

Table 4: Cumulative drug release of various formulations

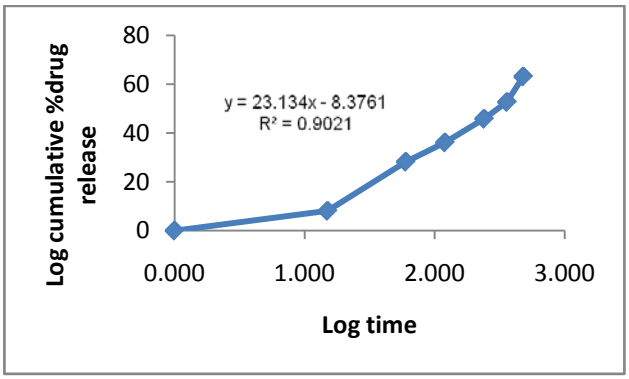
Time (min)	% CDR F1	%CDRF2	%CDRF3	% CDRF4	% CDRF5	%CDRF6
0	0	0	0	0	0	0
15	8.10	14.935	07.8949	5.0156	03.5891	10.9934
30	16.85	16.264	16.6659	13.006	13.0043	11.8331
45	24.67	25.4597	25.75339	20.5432	21.1237	18.3132
60	28.21	30.9835	30.3671	23.728	24.8414	21.8782
90	32.46	37.2234	35.2461	27.5405	29.3833	26.2274

120	36.12	45.07651	41.4426	32.747	33.8412	30.5667
180	40.63	54.5132	47.3362	38.4563	38.3215	35.2564
240	45.81	66.8512	53.3944	44.7782	44.1454	40.5181
300	48.21	79.6744	60.2556	51.7935	48.5523	45.4478
360	52.68	83.4569	67.779	58.8701	54.7415	50.1236
420	55.11	87.9871	74.1256	68.4589	60.2914	56.8814
480	63.1256	92.8279	83.5365	77.5045	65.1289	62.9365

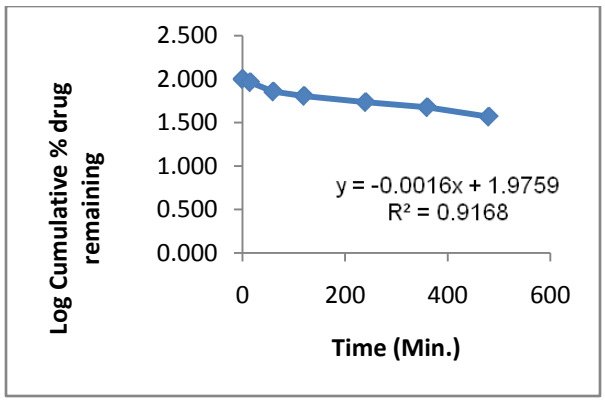
Drug Release Kinetics zero order Formulation (F1)



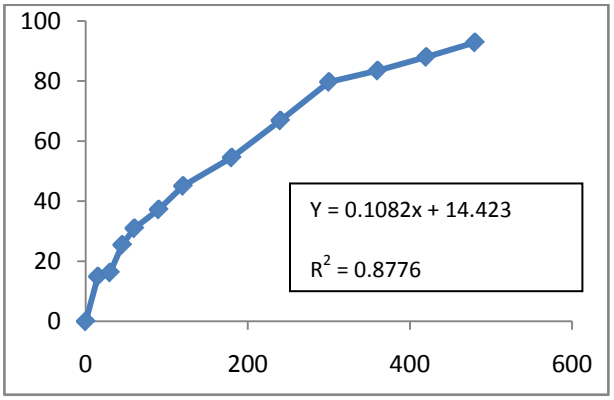
Drug Release Kinetics Kors-Peppas Formulation (F1)



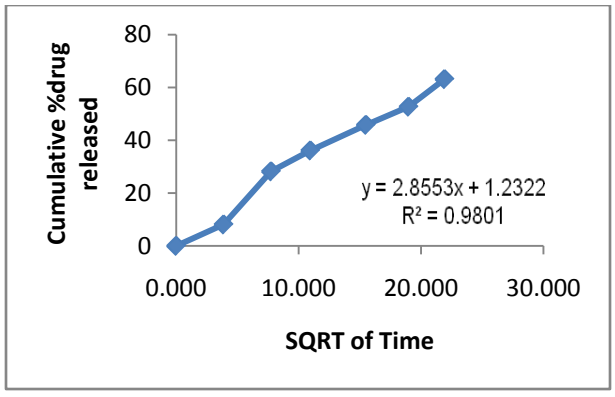
Drug Release Kinetics first order Formulation (F1)



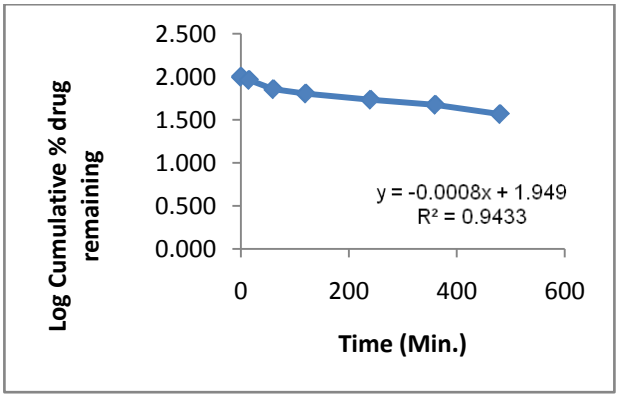
Drug Release Kinetics Zero Order Formulation (F2)



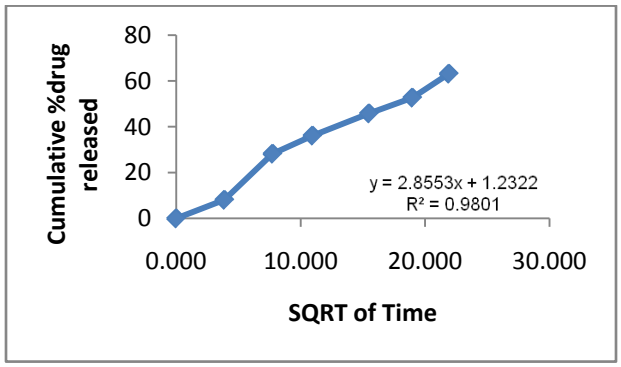
Drug Release Kinetics Higuchi Formulation (F1)



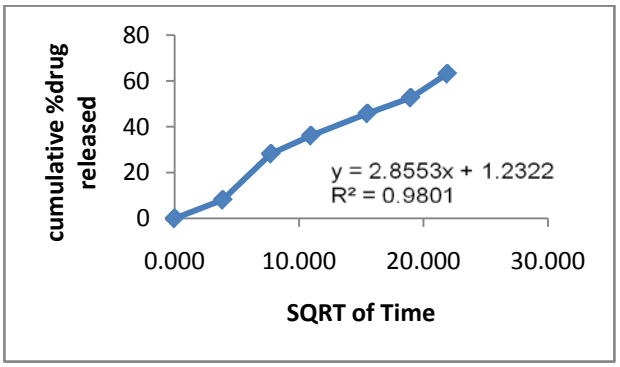
Drug Release Kinetics First Order Formulation (F2)



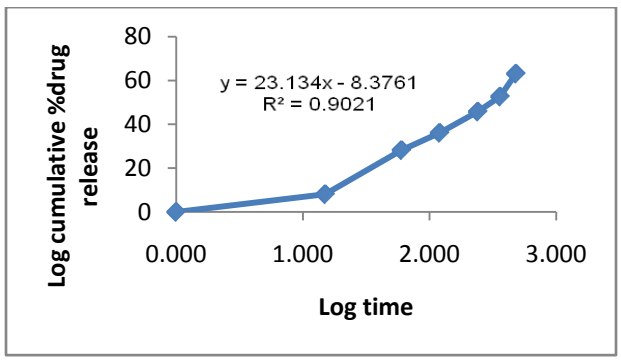
Drug Release Kinetics Higuchi Formulation (F2)



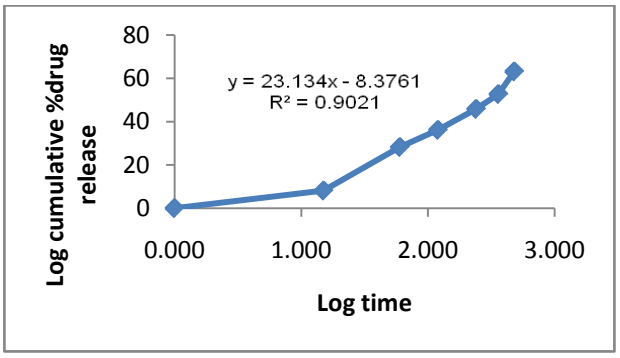
Drug Release Kinetics Higuchi Formulation (F3)



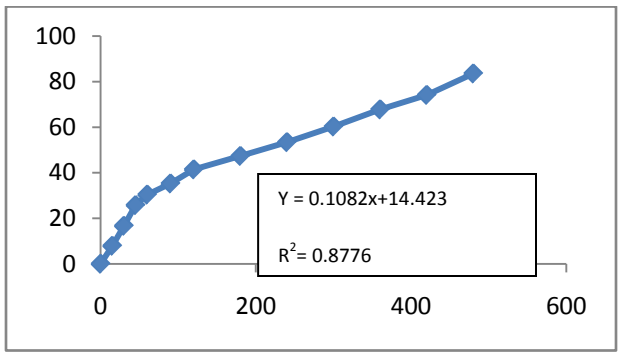
Drug Release Kinetics Kors - Peppas Formulation (F2)



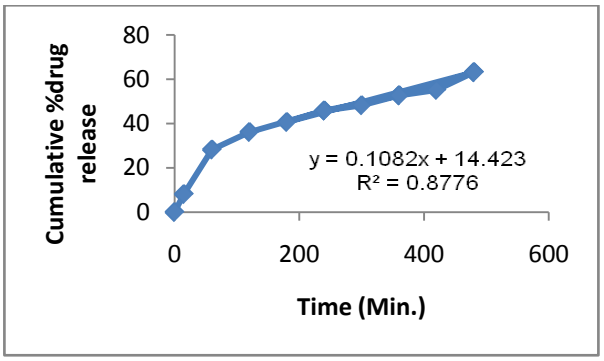
Drug Release Kinetics Kors - Peppas Formulation (F3)



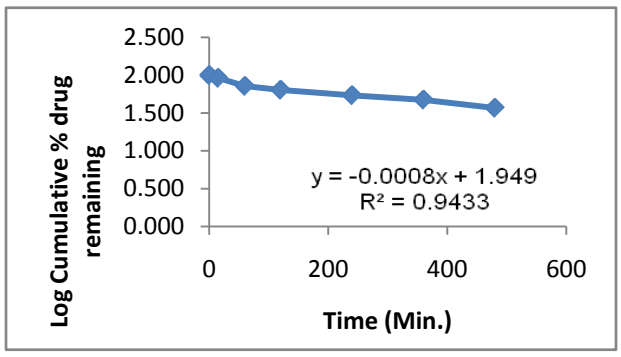
Drug Release Kinetics Zero Order Formulation (F3)



Drug Release Kinetics Zero Order Formulation (F4)



Drug Release Kinetics First Order Formulation (F2)



Drug Release Kinetics First Order Formulation (F4)

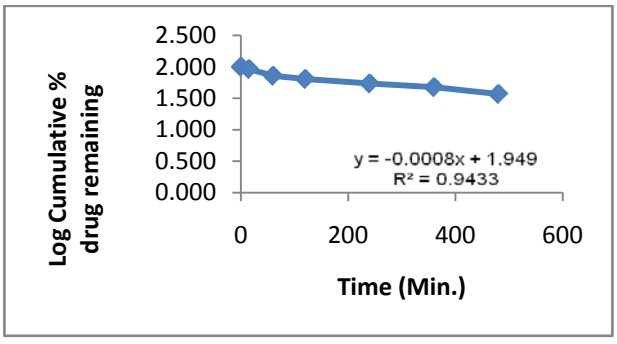
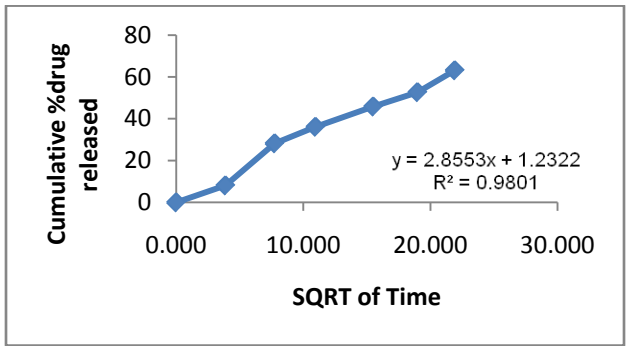
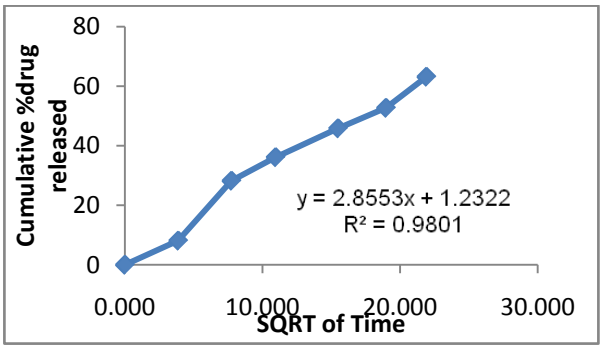


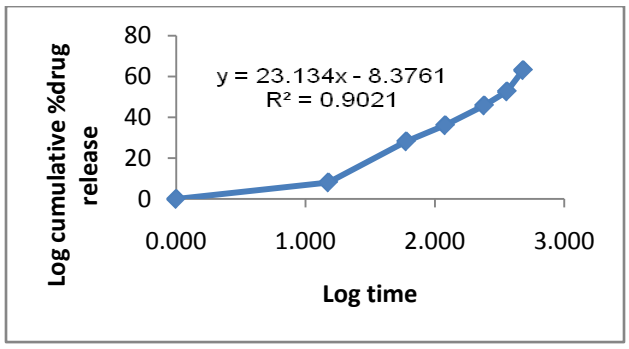
Figure 3.23 Drug Release Kinetics Higuchi Formulations (F4)



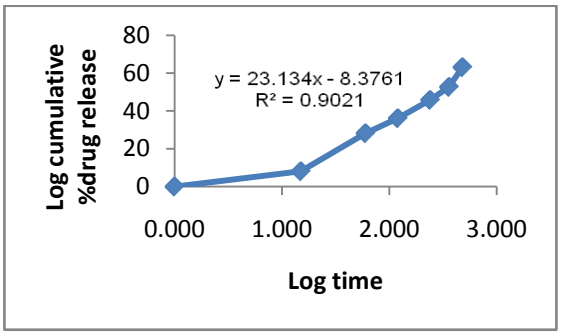
Drug Release Kinetics Higuchi Formulation (F5)



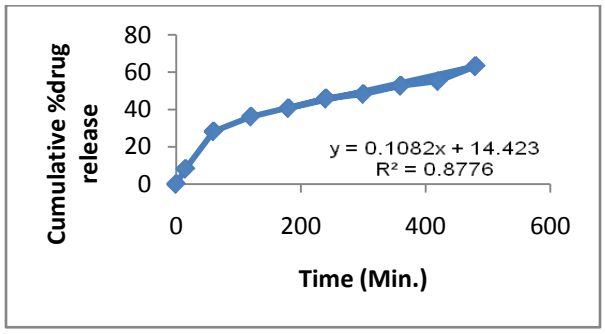
Drug Release Kinetics Kors – Peppas Formulation (F4)



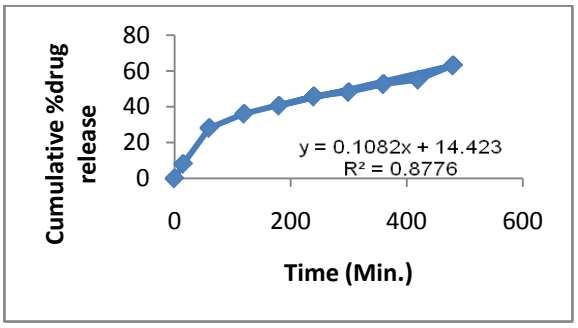
Drug Release Kinetics Kors – Peppas Formulation (F5)



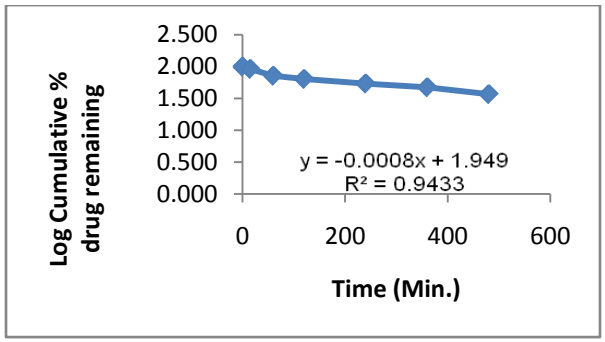
Drug Release Kinetics Zero order Formulation (F5)



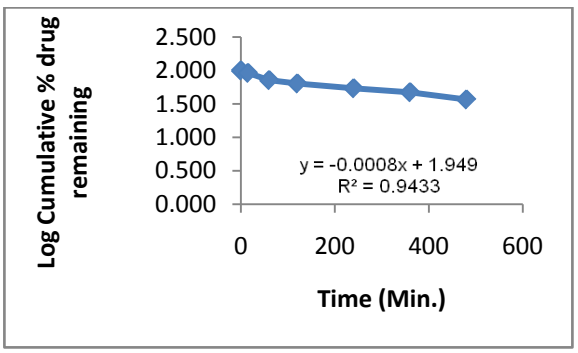
Drug Release Kinetics Zero Order Formulation (F6)



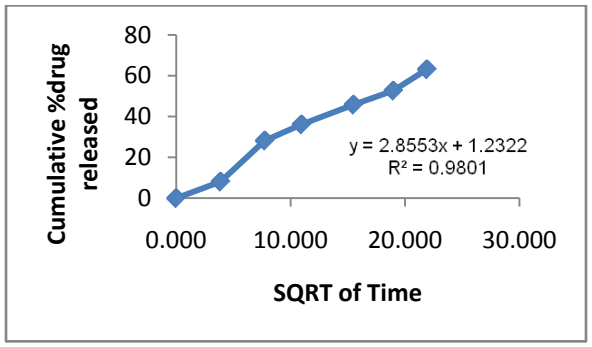
Drug Release Kinetics First Order Formulation (F5)



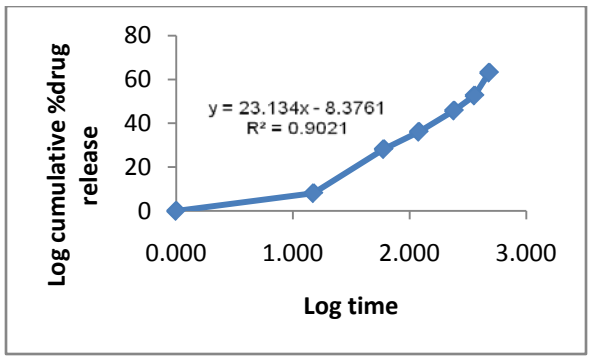
Drug Release Kinetics First Order Formulation (F6)



Drug Release Kinetics Higuchi Formulation (F6)



Drug Release Kinetics Kors - Peppas Formulation (F6)



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 r2 *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.

Table 5: Stability Studies

S.N.	**Days**	% Drug	Ph
		F	**F**
1	0	100	4.66
2	15	99.93	4.61
3	30	99.93	4.6
4	45	99.77	5.5

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.

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