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Research Article

FORMULATION AND EVALUATION OF IN-SITU NASAL GEL OF RIZATRIPTAN BENZOATE BY USING MUCOADHESIVE POLYMERS

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ABSTRACT

Rizatriptan Benzoate undergo hepatic first pass metabolism. Aim of present research work is to improve bioavailability by formulating *in-situ* nasal gel. Formulation was developed to decrease the mucociliary authorization by using mucoadhesive polymer in gel, thus rising the contact time with nasal mucosa and humanizing the absorption of drug. Gels were primed by cold technique process and evaluate by Appearance, Viscosity, Gelation Temperature, Permeation Studies, Drug Content, Gel strength etc.. The gelation temperature of all studied gel formulations were found in range. Drug release was initiated in between 68.8-94.7% with K-peppas best fit model. pH of gel was in the rang and drug content was found between 92-99.89 %. Gel strength was found in range of 20-55 sec.

Keywords: Rizatriptan Benzoate, Mucociliary, Strength

Article Info

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INTRODUCTION

The bioavailability of drugs from nasal formulations depends on the physicochemical properties of drug and formulation that work together to yield optimal drug delivery across the membrane. There are certain criteria that the drug should satisfy to be distributed optimally from the nasal formulation. These are molecular weight, lipophilicity, solubility, partition coefficient and pKa.

Extent of the absorption of the drug depends on molecular weight particularly for hydrophilic compounds. The absorption of molecules less than 300 Da may not be influenced by their physicochemical properties. Nasal route is suitable for efficient delivery of the drugs up to 1000 Da. Absorption reduces significantly if the molecular weight is greater than 1000 Da except with the use of penetration enhancers. Lipophilic drugs have been found to be relatively more permeable across the nasal epithelium. Drug solubility is a major factor in determining absorption of drug through biological membranes. As nasal secretions are more watery in nature, a drug should have appropriate aqueous solubility for increased dissolution[1, 2, 3].

The conventional drug delivery systems like solutions, suspensions and ointments, emulsions are no longer sufficient to fulfill the present day requirements of providing a constant rate delivery and prolonged time. One of the main reasons for that is poor residence time of drug at the site of action, which results into poor bioavailability. To overcome this problems gel is the dosage form to improve the residence time and increased the bioavailability[4].

Gels are defined as a substantially dilute cross-linked system, which exhibits no flow when in the steady-state. Gel state exists between solid and liquid phase. It has properties ranging from soft and weak to hard and tough.

In situ is a Latin word which means in position. In situ gel formation is a liquid formulation that generates a solid or semisolid depot after administration and shift to a gel phase when exposed to physiological conditions. This new concept of producing a gel in situ was introduced for the first time in the early 1980s. Both natural and synthetic polymers can be used for the production of in situ gels[5, 6].

Carbomer is high molecular weight, cross linked polyacrylic acid derivative with a strong mucoadhesive property. Carbopol being a pH dependant polymer is present in solution form at acidic pH but at alkaline pH forms a low viscosity gel. Carbopol polymers have very good water sorption property[7]. They swell in water upto 1000 times their original volume and 10 times their original diameter to form a gel when exposed to a pH environment above 4.0-6.0 because the pKa of these polymers is 6.0 ± 0.5.

Rizatriptan benzoate is completely absorbed following oral administration. The mean oral absolute bioavailability of the Rizatriptan benzoate tablet is about 45% and means peak plasma concentration (Cmax) reaches in approximately 1-1.5 hours (Tmax). The presence of a migraine headache did not appear to affect the absorption or pharmacokinetics of Rizatriptan benzoate. Food has no significant effect on the bioavailability of Rizatriptan benzoate but delays the time to reach peak concentration by an hour. In clinical trials, Rizatriptan benzoate was administered without regard to food. The plasma half-life of Rizatriptan benzoate in males and females averages 2-3 hours[8-11].

Present study is to achieve brain targeted drug delivery of rizatriptan benzoate for patients suffering from migraine. It is a general study that tries to cover a nose-to-brain pathway for drug rizatriptan benzoate, intranasal delivery, which significantly increases brain accumulation of rizatriptan benzoate and could be an effective alternative to parentral and oral formulations. The nasal ruote will be able to provide longer residence properties and hence better bioavailability of the drug. Formulation in the nasal cavity exhibited prolonged drug release characteristics with almost negligible toxic effects to the nasal mucosa. The ease of administration coupled with its ability to provide sustained release could probably result in less frequent administration, thus enhancing patient compliance.

MATERIALS AND METHOD

Rizatriptan Benzoate was obtained from M/s Torrent Pharmaceuticals Pvt. Ltd., Other chemicals and instruments were used analytical grade.

METHODS

Preparation of gels

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: Formulation of *in-situ* nasal gel of Rizatriptan Benzoate

Composition (%(w/v))	Rizatriptan Benzoate	Pluronic F127	Carbopol 934P
Batch Code			
F1	2.5	18	-
F2	2.5	18	0.1
F3	2.5	18	0.2
F4	2.5	18	0.3
F5	2.5	18	0.4
F6	2.5	18	0.5

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 gritty by bring the electrode of the pH meter in contact with the surface of the formulation and allowing it to equilibrate for 1min[12, 13].

Gelation Studies

The *in situ* gel forming solution and the artificial nasal fluid were mixed and the gelation was observed by visual examination. Gelation studies were carried out according to (Balasubhramanian J. et al 2003)[14] in different pH Buffers (pH5.0, 6.0, 6.6, 7.4) and was assessed by visual examination. Gelation temperature and gel melting was assessed by a modified process[15] as follow 2 ml aliquot of gel was transferred to test tube, sealed with aluminium foil and increased in increment 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[16, 17].

Determination of Mucoadhesive Strength

Mucoadhesive Strengths of gel was determined by using the modified method reported by Choi et al[18]. 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 2min 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

Viscosity Measurement

The viscosity measurements were carried out by using Brookfield DV Pro-II model with spindle No.62.The instrument was equipped with the temperature control unit and the sample were equilibrated for 10 min before the measurement. The viscocity was measured against increasing shear rate. Measurement was taken at 4^0 c and 34^0 c respectively[19].

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 (Double beam UV-visible spectrophotometer) at 280 nm[20].

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[21,22].

Drug content estimation

Each formulation (1 ml) was taken in a 100 ml volumetric flask diluted with distilled water and shaken to dissolve the drug. The solution was filtered through whatmann filter paper and 1ml of filtered solution was further diluted to 100 ml with distilled water. Drug content was estimated spectrophotometrically by measuring the absorbance of the above solution at 280 nm[23, 24].

RESULTS AND DISCUSSION

Mucoadhesive Polymer Formulations

Mucoadhesive dosage forms have gained and still gaining, considerable interest as a means of providing intimate contact and prolonging the residence time of a dosage form intended for nasal and ocular administration

It generally accepted that process involves three steps; wetting and swelling of the polymer to permit intimate contact with biological tissue, interpenetration of bioadhesive polymer chains with mucin molecules leading to entanglement and formation of weak chemical bonds between entangled chains, the mechanisms by which mucoadhesion bonds form are not completely clear. There are five theories of adhesion have been developed to explain the properties of wide range of materials including glues, adhesives and paint.

Evaluations of Gels

Appearance

Table 2: Appearance of gel

S.NO.	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

Clarity of all the formulations was found to be satisfactory.

pH of mucoadhesive nasal gels

The pH of the formulations was found to be satisfactory and was in the range of 4.5-5.5.

Gelation Temperature

It was previously proved that pluronics undergo thermal gelation or sol-gel transition at a temperature of about 25 to 37°C. Below the transition temperature Pluronic solutions allow a comfortable and precise delivery in the nasal cavity where thermogelation occurs. Immediate gelling increases residence time and enhances bioavailability of drug. The gelation temperature of all batches is shown in table 3. In Pluronic gels, gelation studies in 20-24 %(w/w) concentration showed that gelation temperature decreases with increase in gel melting temperature as Pluronic concentration increases. Gelation of PF-127 was found dependent on aqueous solubility of the polymer.

Table 3: Gelation Temperature

S.No.	Formulation	Gelation Temp.
1	F1	42^0 c
2	F2	38^0 c
3	F3	32^0 c
4	F4	36^0 c
5	F5	38^0 c
6	F6	40^0 c

Viscosity: Viscosity measurement of the formulations at 4^0 c and 37^0 c temperatures showed that there was increase in viscosity with increase in temperature. This indicated the formation of temperature induced gel structure of poloxamer.in addition to this Carbopol 934 showed viscosity enhancing effect. At constant concentration, abrupt changes in viscosities were observed due to sudden rise in micellar concentration. At low temperature region the liquid shows a very slight decrease in viscosity which was attributed to the dehydration of PPO blocks of the unimers .with rise in temperature. The unimers start to form spherical micelles causing increase in intrinsic viscosity as a result of extremely high salvation in the micellar shell. At 1◦ C temperature increase causes 10% increase in the micellar concentration and 3.3% decrease in the intermicellar distance as well as two-fold increase in viscosity. Viscosity of all formulation at 4^0 c and 37^0 c showed in table

Table 4: shows measurement of viscosity

S.NO	Formulation	Viscosity (CP) at 4^0 C	Viscosity (CP) at 37^0 C
1	F1	23.4	144
2	F2	33	947
3	F3	42.3	2879
4	F4	51.3	164000
5	F5	27.3	287.9
6	F6	36.9	1236

Measurement of gel strength

It is very important that the nasal gel formulation must have suitable gel strength. The gel strength of nasal gel formulation at 37^o C, increased as the concentration of Carbopol and Poloxamers increased The mechanism of the increase gel strength might be related to hydrogen bonding between Pluronic and bioadhesive polymers in the nasal gel.

Table 5: Measurement of Gel Strength

S.N.	Formulation	Gel strength in Sec	Bioadhesive Force (Dynes/cm^2)
1	F1	110	2496.81±10
2	F2	117	4369.42±0.113
3	F3	130	8114.64±0.118
4	F4	115	2746.49±0.11
5	F5	120	3745.22±0.12
6	F6	118	2496.81±0.12

Mucoadhesive strength was determined in term of detachment stress i.e. force required to detach the formulation from mucosal surface. Results indicated that the variation in concentration of Carbopol 934 and Poloxamers 407 showed changes in Mucoadhesive strength. The gradual increase was observed in Mucoadhesive strength as the level of Carbopol 934 increased .Our findings are similar with previously reported work with Carbopol polymer. In this review, bioadhesion was observed due to the availability of carboxyl group. Carbopol has very high percentage of (58%-68%) of carboxyl group that undergoes hydrogen bonding with sugar residues in oligosaccharide chain in mucus membrane, resulting in strengthened network between polymer and mucus membrane. The stronger the Mucoadhesive force is, the more it can prevent the gelled solution coming out of the nose.

Table 6: Gelling Capacity and Drug Content

S.No	pH	Gelling Capacity	Drug Content
F1	4.2	++	98.01±0.83
F2	4.5	+++	97.19±0.92
F3	5.0	+	98.51±0.13
F4	4.2	++	97.26±0.12
F5	5.5	+++	96.54±0.98
F6	4.8	+++	98.04±0.18

Drug content uniformity determination

The percent drug content for formulations F7 to F11. The drug content was found to be in acceptable range for all the formulations. Percent drug content of formulations F7, F8, F9, F10 and F11 was found to be 91.80%, 98.33%, 99.19%, 97.03% and 94.09% respectively. This indicates that process employed to prepare gels in this study was capable of producing gels with uniform drug content and minimal gel variability.

Drug Release

Diffusion studies were carrying out using franz diffusion cell, F5 showed the persistent drug release. F3 showed drug release 79.76% at 8hrs. Concentration of HPMC raise leads to decrease the drug release. Poloxamer concentration distress on drug release.

Table 7: Cumulative Drug Release

Time (min)	% CDR F1	% CDR F2	% CDR F3	% CDR F4	% CDR F5	% CDR F6
0	0	0	0	0	0	0
15	12.13	14.935	15.217	10.456	9.562	10.9934
30	16.85	18.1264	16.6659	13.006	12.0156	13.001
45	22.56	21.6749	21.4845	16.002	14.2212	15.5397
60	28.57	28.123	25.75339	20.5432	17.1237	18.3132
90	30.26	30.9835	30.3671	23.728	24.8414	21.8782
120	36.57	39.2554	35.2461	29.123	29.3833	26.2274
180	38.12	45.07651	41.4426	32.747	37.012	30.5667
240	43.46	54.132	47.3362	38.4563	38.3215	35.2564
300	63.5623	81.8279	67.779	58.8701	54.7415	54.45616
360	69.12	83.125	74.1256	68.4589	64.9871	63.1456
420	44.4562	88.125		77.5045	72.1207	68.459
480		91.456		86.1829	81.002	77.5947

Figure 1: Drug Release Kinetics Zero Order Formulation (F1)

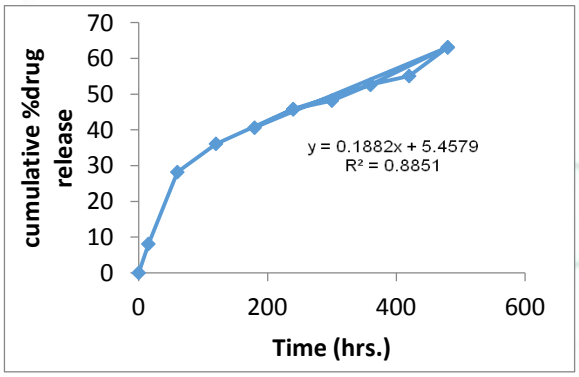


Figure 2: Drug Release Kinetics First Order Formulation (F1)

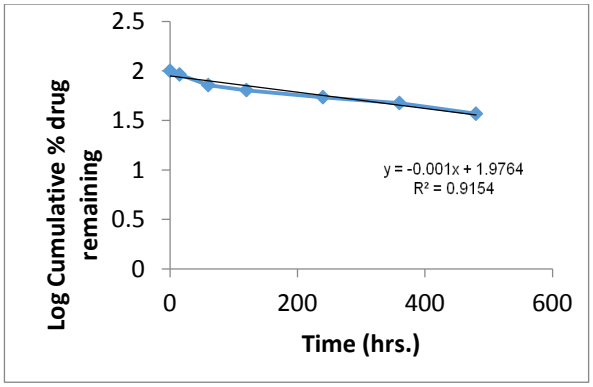


Figure 3: Drug Release Kinetics Higuchi Formulation (F1)

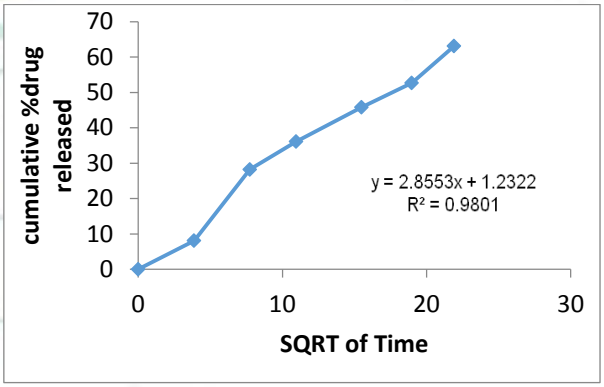


Figure 4: Drug Release Kinetics Kors - Peppas Formulation (F1)

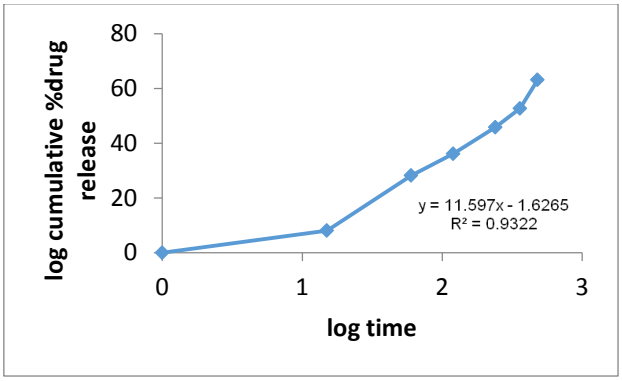


Figure 5: Drug Release Kinetics Zero Order Formulation (F2)

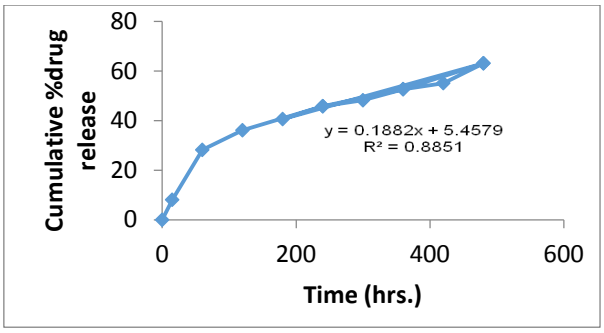


Figure 6: Drug Release Kinetics First Order Formulation (F2)

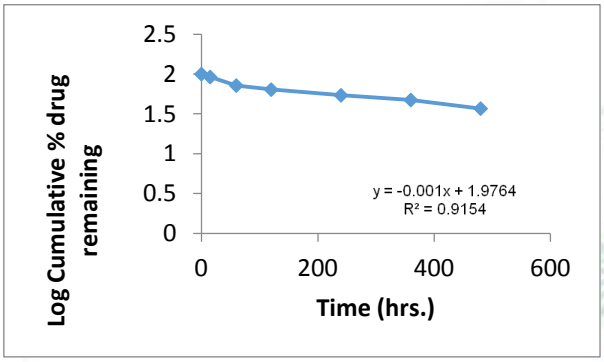


Figure 7: Drug Release Kinetics Higuchi Formulation (F2)

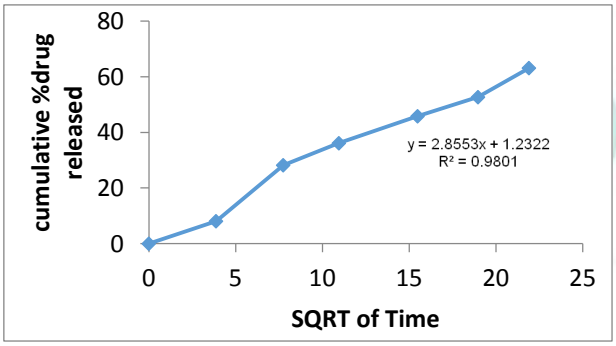


Figure 8: Drug Release Kinetics Kors-Peppas Formulation (F2)

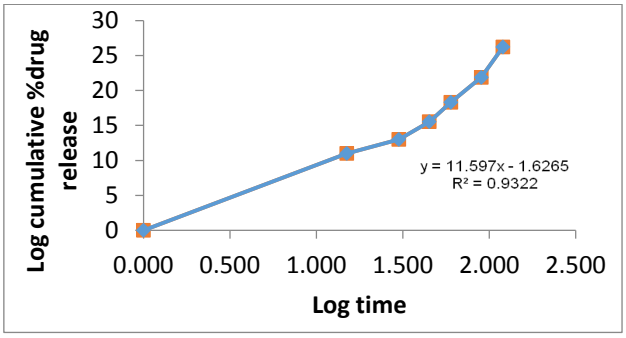


Figure 9: Drug Release Kinetics Zero Order Formulation (F3)

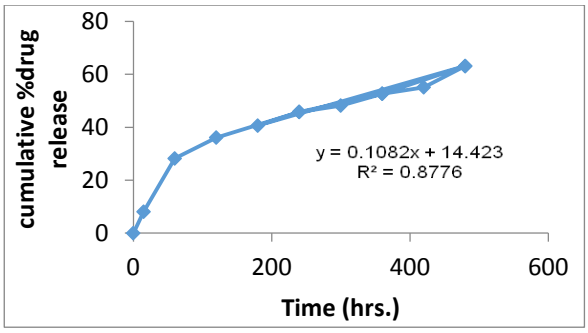


Figure 10: Drug Release Kinetics First Order Formulation (F3)

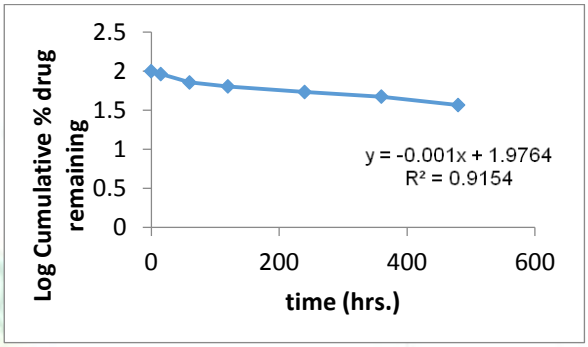


Figure 11: Drug Release Kinetics Higuchi Formulation (F3)

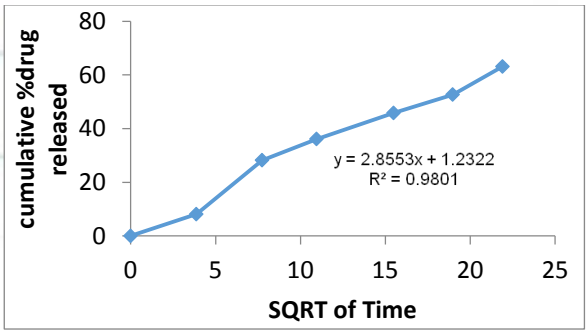


Figure 12: Drug Release Kinetics Kors-Peppas Formulation (F3)

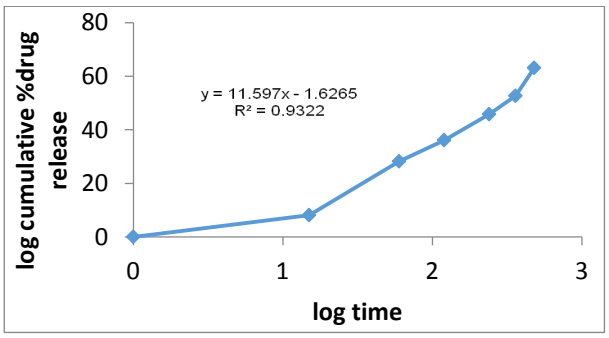


Figure 13: Drug Release Kinetics Zero Order Formulation (F4)

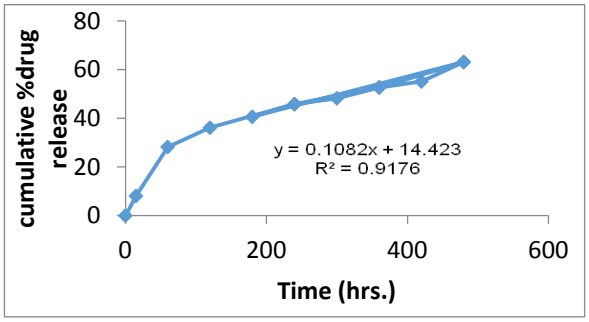


Figure 14: Drug Release Kinetics First Order Formulation (F4)

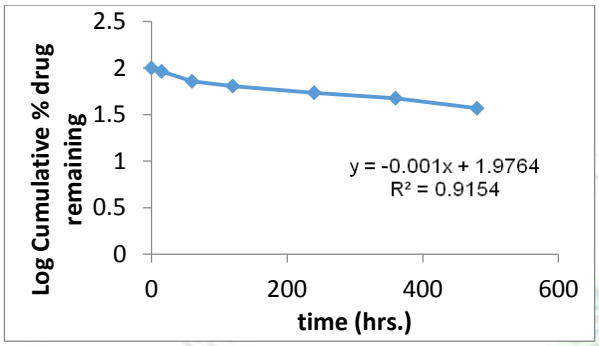


Figure 15: Drug Release Kinetics Higuchi Formulation (F4)

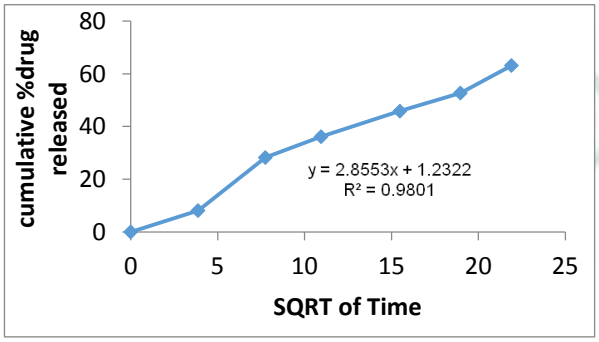


Figure 16: Drug Release Kinetics Kors - Peppas Formulation (F4)

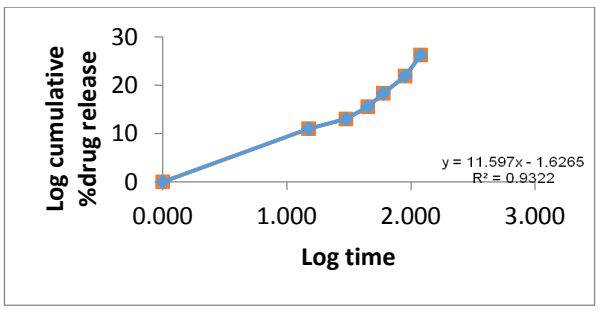


Figure 17: Drug Release Kinetics Zero Order Formulation (F5)

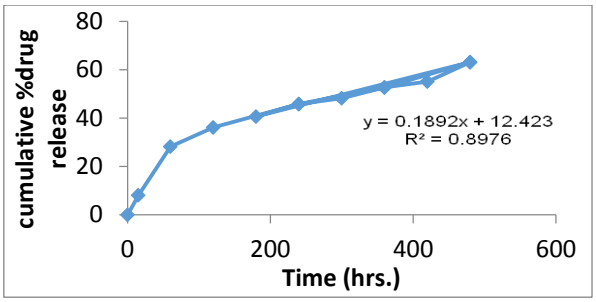


Figure 18: Drug Release Kinetics First Order Formulation (F5)

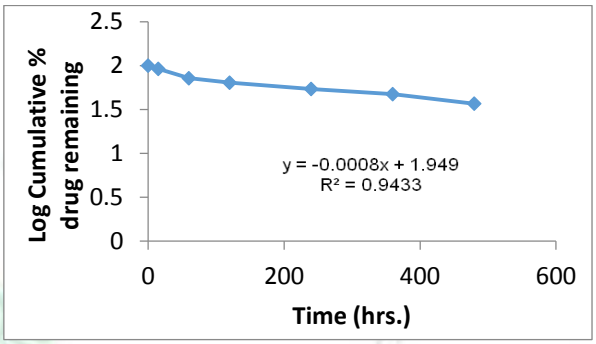


Figure 19: Drug Release Kinetics Higuchi Formulation (F5)

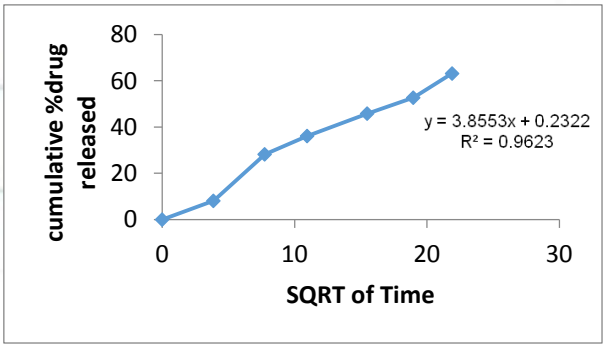


Figure 20: Drug Release Kinetics Kors- Peppas Formulation (F5)

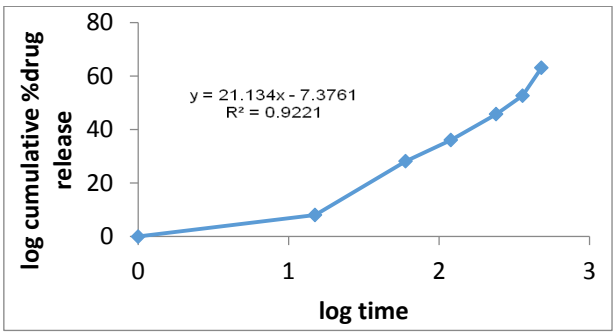


Figure 21: Drug Release Kinetics Zero Order Formulation (F6)

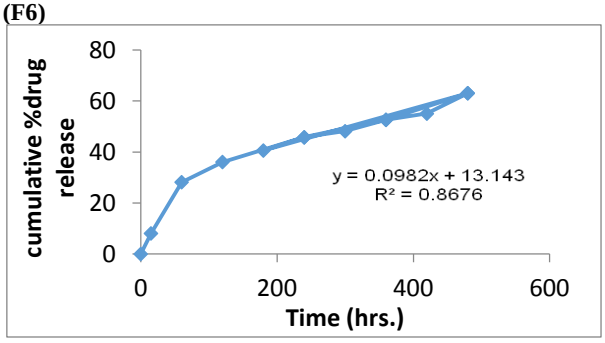


Figure 22: Drug Release Kinetics First Order Formulation (F6)

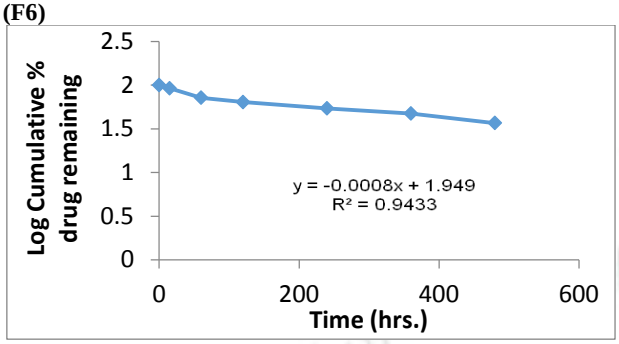


Figure 23: Drug Release Kinetics Higuchi Formulation (F6)

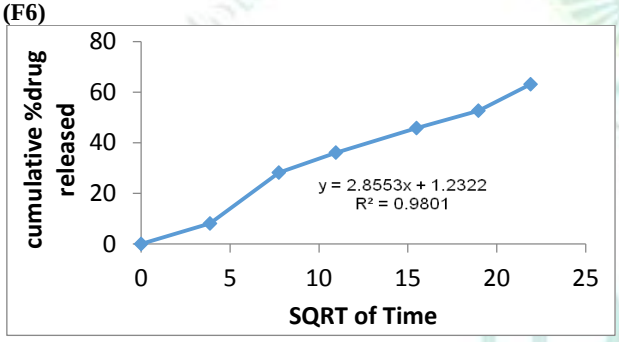
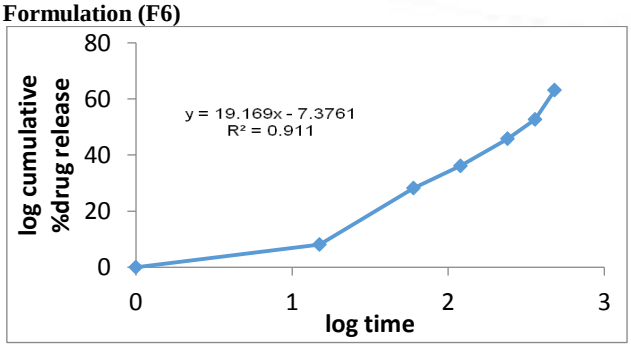
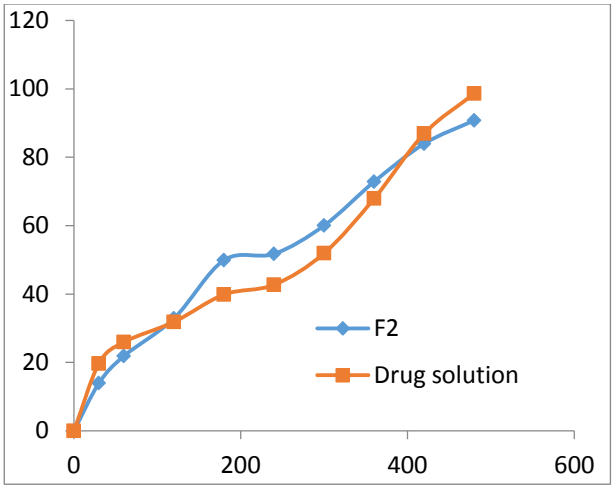


Figure 24: Drug Release Kinetics Kors-Peppas Formulation (F6)



Permeation study

In vitro permeation study



Permeation of selected batch (F2) compare to drug solution.

Ex vivo permeation carried out by using nasal mucosa of goat and permeation profile shown in the above figure.

Stability studies

All the formulation showed good stability at 27 °C/ 60 % RH. There were no significant changes in visual appearance and clarity; pH remained constant for entire stability period; drug content did not deviate by than 2% indicating that the drug is stable in the *in situ* gel formulations and also there was no significant variation in the *in vitro* release studies at the end of 30 day period. A formulation intended for a nasal administration, if prepared as a solution should not show precipitation of the drug present in it for long periods of storage. This is achieved when formulations were stored at normal room temperatures not exceeding 32 °C. The formulation when stored under refrigerated conditions showed settling of the polymer and also the viscosity of the formulation increased. The formulations when stored at 45 °C/ 75 % RH, the formulations remained as a gel for long duration.

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