International Standard Serial Number (ISSN): 2249-6807

International Journal of Institutional Pharmacy and Life Sciences 5(4): July-August 2015

INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES

Pharmaceutical Sciences

Research Article……!!!

Received: 02-07-2015; Revised: 21-07-2015; Accepted: 22-07-2015

FORMULATION, DEVELOPMENT AND EVALUATION OF *IN-SITU* NASAL GEL OF RIZATRIPTAN BENZOATE

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Keywords:

Nasal gel, Rizatriptan benzoate, Thermoreversible, Poloxamer 407, HPMC K4M, Mucoadhesive strength

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ABSTRACT

Oral administration did not provide full pain relief to more than 50% of patients, was associated with headache recurrence in over 30% of patients who initially responded. Nasal administration of antimigraine agents was another alternative by which effective and direct central nervous system response can be achieved.

Migraine is a common, chronic disabling condition. It is reported that migraine is among four conditions that cause highest level of disability, the other three are acute psychosis, dementia and quadriplegia. Triptans (serotonin [5-HT] 1B and 1D, 5-HT 1B/1D agonist), are comes under effective pharmacological therapy. Triptans constrict cranial blood vessels by a 5-HT 1B receptor-mediated agonist action and inhibit trigeminal nerve firing with reduced release of pro-inflammatory mediators in response to neural stimulation of the trigeminal nerve via 5-HT1D and 5-HT 1F receptor agonist actions. Rizatriptan benzoate undergoes hepatic first pass, it shows poor bioavailability.

The objective of the study was to develop a nasal formulation for the migraine therapy which can provide effective relief from recurring aura and headache. For this purpose a sustained release mucoadhesive approach was chosen in which Poloxamer 407was used as a Thermoreversible polymer and mucoadhesive polymer as HPMC K4M. Formulations developed using factorial design and evaluated for pH, Mucoadhesive strength, Drug Content, Viscosity and % Drug release, In-vitro permeation study, as the concentrations of polymers increases mucoadhesive strength and viscosity decreases but drug release was found to increase.

INTRODUCTION

Historically, nasal drug delivery has received intensive interest since ancient times. Therapy through intranasal administration has been an accepted form of treatment in the Ayurvedic system of Indian medicine, and also called as Nasaya Karma. Psychotropic drugs and hallucinogens have been used in the form of snuff by Indians in South America. In more recent years many drugs have been shown to achieve a better systemic bioavailability by self-medication through the nasal route than by oral administration. The systemic bioavailability by nasal delivery of some peptide and protein drugs with low nasal absorption has been improved by co-administered them with absorption promoters enzyme inhibitor, and/ or microspheres fabricated from bioadhesive and Bioerodible polymers. [1]

Today, nasal drug delivery is receiving much attention from the pharmaceutical industry. About 2% of overall drug delivery is administered via the nasal route. A transmucosal drug delivery route (which includes the nasal route) can target tissue and use active transdermal processes. It also regarded as a major influence of the market.

In addition, the most popular view of nasal drug delivery is the administration of locally acting products. Topical decongestants or anti-inflammatory drug used to treat a rhinitis or allergy related indications are well known drug products. [2]

Nasal delivery is increasingly considered to be an alternative route for drugs that currently require parenteral administration to achieve good efficacy, or where circumstances make oral delivery difficult. As a site for systemic absorption the nasal route provides a means of avoiding first pass metabolism. The administration of systemically acting products via the nasal route began in the 1980's. The peptide oxytocin, which stimulates uterine contraction and lactation, was one of the first nasally administered peptide hormones. The nose, or more precisely the nasal cavity, is the target of the administration of a drug product. The anatomy and the physiology of the nose play a decisive role in effective drug administration. The nasal mucosa is much more sensitive to external influences than the digestive mucosa in the stomach. On the other side, nasal administration often requires a small amount of drug; therefore, fewer side effects are expected. [3]

MATERIALS AND METHODS:

MATERIALS: Rizatriptan benzoate was obtained from Cipla Ltd, Mumbai; Poloxamer 407 was obtained from Balaji Chemicals, Surat. HPMC K4M, Sodium metabisulphite, Benzalkonium chloride was obtained from Research-Lab Fine Chemical Industry – Mumbai.

METHODS:

Determination of λ_{max} of Rizatriptan benzoate in water:

The UV spectrum of Rizatriptan benzoate was obtained using Ultra violet JascoV630. Accurately weighed 10 mg of the drug was dissolved in sufficient quantity of water and volume made up to 10 ml. The stock solution was diluted to obtain a concentration of 100 µg/ml. 1 ml of aliquot was withdrawn and volume was made up to 10 ml using water to obtain the concentration of 10 µg/ml. The resultant solution was scanned from 200 to 400 nm and the spectrum was recorded to obtain the value of maximum wavelength. Which showed peak at 224.4 nm in distilled water.[4, 5]

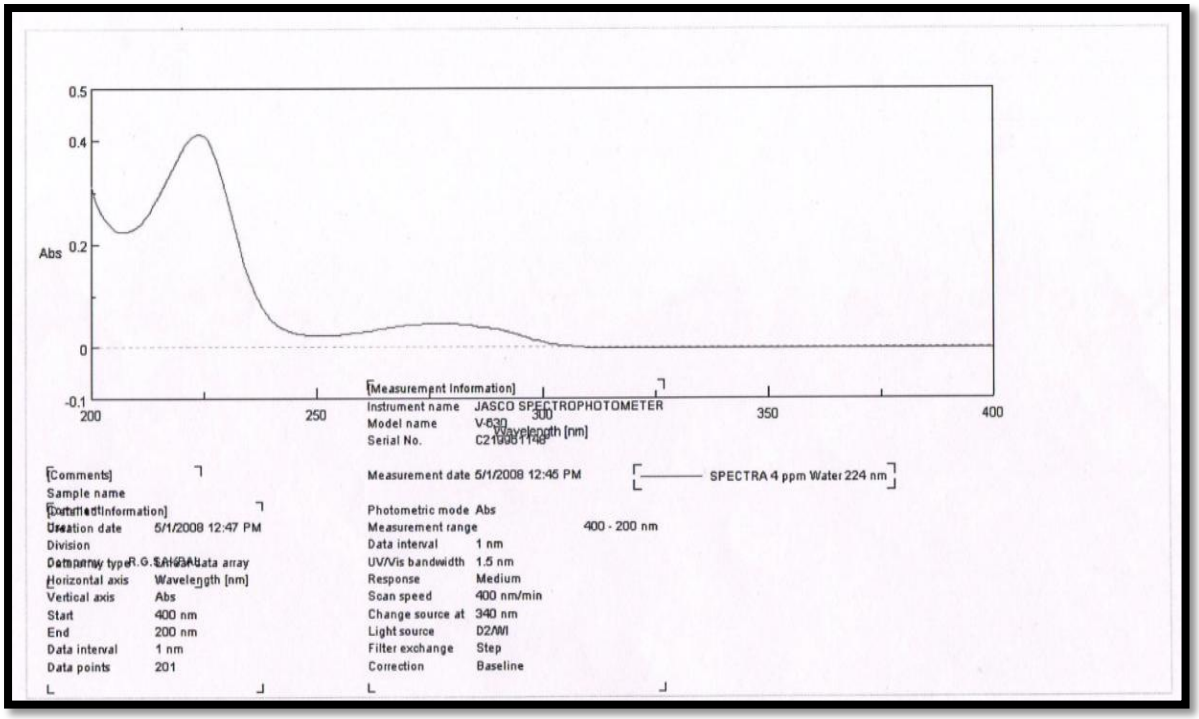

Figure 1:UV-visible spectrum of Rizatriptan benzoatein distilled water

Drug-Excipient Compatibility Study:

Compatibility study was carried out by using Fourier transform infrared spectrophotometer (BRUKER, Model-Eco ATR). FTIR study was carried on pure drug and physical mixture of drug and polymers. Physical mixtures were prepared and samples kept for 1 month at 40^0C. The infrared absorption spectrum of Rizatriptan benzoate and physical mixture of drug and polymers was recorded with a KBr disc over the wave number 4000 to 400 cm^{-1}.[6]

Differential scanning calorimetric studies [Mettlar Toledo]:

Thermal analysis was performed using a differential scanning calorimeter equipped with a computerized data station. The sample of pure drug, physical mixture of drug and polymer

were weighed and heated at a scanning rate of 10°C/min between 40°C - 300°C and 40 ml/min of nitrogen flow. The Differential Scanning Calorimetric analysis gives an idea about the interaction of various materials at different temperatures. It also allows us to study the possible degradation of the material.

Method for Preparation of Rizatriptan benzoate Thermoreversible *In-Situ* Nasal Gel:

The cold method described by Schmolka (1972) was adopted.

Briefly, the Rizatriptan benzoate, HPMC K4M, Benzalkonium chloride, Sodium metabisulphite and thermoreversible polymer Poloxamer 407 were stirred in the calculated amount of distilled water at room temperature. The dispersions were cooled down to 4^{o}C; the Poloxamer 407 was added slowly with continuous stirring (thermostatically controlled magnetic stirrer, Remi). The dispersions were then stored in a refrigerator until clear solutions were obtained. The optimization of batch was carried out by 3^2 full factorial designs. Different formulation codes were assigned to all batches containing ratios of Poloxamer 407 and HPMC K4M.[7, 8]

Formulation optimization:

3^2full factorial designs were applied to the formulation that showed the satisfactory results. Different formulae's of gel were prepared by using ingredients mentioned in table 1. In this formulation concentration of Poloxamer 407 was ranged between 15 to 25 %, concentration of HPMC K4M in between 0.10 to 0.30%. Drug was dissolved in mixture of distilled water and Sodium metabisulphite; both the polymers were hydrated separately. Preservative was added in polymeric solution. Mixing of drug and polymeric solution was done at cold condition. Kept solutions at 4^{o}C until clear gel was obtained.[9]

Table 1: Composition of formulation

Composition → / Formulation Code ↓	Rizatriptan benzoate (w/v)	PF 127 (w/v)	HPMC K4M (w/v)	Sodium metabisulphite (w/v)	Benzalkonium Chloride (v/v)	Distilled water (ml)
F1	2.5	15	0.1	0.1	0.01	q.s.
F2	2.5	15	0.2	0.1	0.01	q.s.
F3	2.5	15	0.3	0.1	0.01	q.s.
F4	2.5	20	0.1	0.1	0.01	q.s.
F5	2.5	20	0.2	0.1	0.01	q.s.
F6	2.5	20	0.3	0.1	0.01	q.s.
F7	2.5	25	0.1	0.1	0.01	q.s.
F8	2.5	25	0.2	0.1	0.01	q.s.
F9	2.5	25	0.3	0.1	0.01	q.s.

EVALUATION OF *IN-SITU* NASAL GEL:

1. Appearance:[10]

The formulation was visually checked for clarity**.**

2. pH:[11, 12]

pH of each formulation was determined by using digital pH meter (Systronics Digital pH meter 335). The pH meter was calibrated using pH 4 and pH 7 bufferby using standard buffer tablet.

3.Viscosity Determination: [7, 8]

The rheological properties of the *in situ*gels were determined by the Brookfield viscometer (Brookfield viscometer; type DV-II PRO using spindle no. SC4-18). Viscosities of the formulation were taken at two different temperatures that is at 25^{o}C and the 37^{o}C with varying shear rate.

4. Determination of Drug content: [13]

Drug content was determined by taking 1ml of formulation in 100ml volumetric flask. It was dissolved in distilled water properly and final volume was made to 100ml with distilled water. 1ml quantity from this solution was transferred into the 10ml volumetric flask and final volume was made to 10ml by using distilled water. Finally the absorbance of prepared solution was measured at 224.4 nm by using UV visible spectrophotometer. By using absorbance value % drug content in the formulation was calculated.

5.*In -Vitro* drug release study: [14]

In-vitro release study of the formulation was carried out by using laboratory designed diffusion cell through egg membrane. 1ml of gel was placed in donor compartment and freshly prepared simulated nasal solution in receptor compartment (100ml). Egg membrane was mounted between donor and receptor compartment. Temperature of receiver compartment was maintained at 37±2^{o}C during experiment and content of the receiver compartment was stirred using magnetic stirrer. The position of donor compartment was adjusted so that egg membrane just touches the diffusion fluid. An aliquot of 1 ml was withdrawn from receiver compartment after 30 min, 1, 2, 3, 4, 5, 6, 7, and 8 hrs. and same volume of fresh medium was replaced. Aliquots so withdrawn were suitably diluted and analyzed using UV visible spectrophotometer at 224.4 nm.

6. Measurement of the Gel Strength:[15] A sample of 50gm of the nasal gel was put in a 50 ml graduated cylinder. A weight of 5 gm was placed onto the gel surface. The gel strength,

which is an indication for the viscosity of the nasal gel at physiological temperature, was determined by the time in seconds required by the weight to penetrate 5 cm deep into the gel.

7. Mucoadhesive Strength (detachment stress):[16]

The following procedure was used for all the test formulations using the above equipment. The nasal mucosa was removed from refrigerator and allowed to attain equilibrium with ambient conditions in the laboratory. The goat nasal mucosa was carefully excised, without removing connective and adipose tissue and washed with simulated nasal solution. The tissue was stored in fresh simulated nasal solution. Immediately afterwards the membrane was placed over the surface of lower polypropylene cylinder (B) and secured. This assembly was placed into beaker containing simulated nasal solution pH 6.4 at 37 ± 2°C.

From each batch, some quantity of gel was taken and applied on the lower surface of the upper polypropylene cylinder. The beaker containing mucosal tissue secured upon lower cylinder (B), was manipulated over the base of the balance so that, the mucosal tissue is exactly below the upper cylinder (A). The exposed part of the gel was wetted with a drop of simulated nasal solution, and then a weight of 10 gm was placed above the expanded cap, left for 10 minutes. After which the gel binds with mucin. The weight was removed. Then slowly and gradually weights were added on the right side pan till the gel separates from the mucosal surface/ membrane.

The weight required for complete detachment is noted (W1) (W1-5.20G) gives force required for detachment expressed in weight in grams. Procedure was repeated for two more times. Average was computed and recorded.

i. Calibration of test equipment:

Initially, a gel from the same batch was taken ten times and individual force required for complete detachment was noted and S. D. was calculated.

ii. Force of adhesion(N) = (Bioadhesive strength/1000) × 9.81

Bond strength (N/m^2) = force of adhesion (N)/surface area of disk (m^2)

The Apparatus for Bioadhesive study is shown in Figure 2.

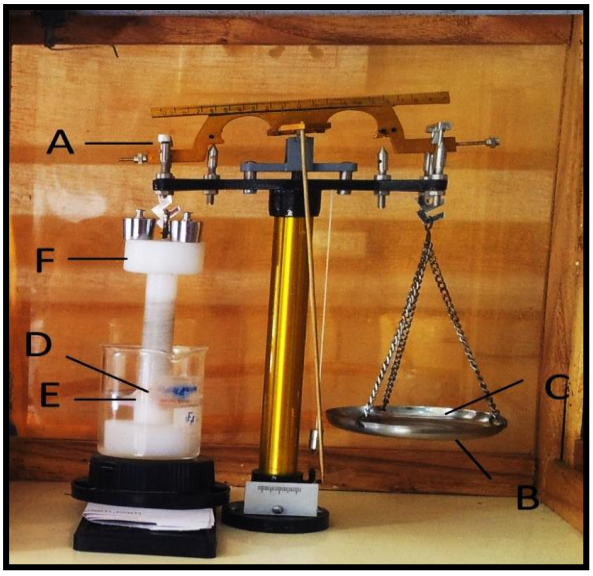

Figure 2: Modified balance for Bioadhesive study.

A: Modified balance, B: Weighing pan, C: Weight, D: Gel, E: Nasal mucosa F: Polypropylene cylinder.

8. Drug release kinetics:[17, 18]

To examine the drug release kinetics, the release data were fitted to models representing zero order, first order, Higuchi's square root of time kinetics and KorsemeyerPeppas kinetics. The coefficient of determination (r^2) values were calculated from the plots of CDR vs. t for zero order, log %CDR remaining vs. t for first order, %CDR vs. $t^{1/2}$ for Higuchi model and log %CDR vs. log t for Korsemeyer Peppas model, where %CDR is the amount of drug released at time t. The data obtained from study of diffusion kinetics of the optimized formulation was studied to obtain the best fit model. The best fitted model is the one which gives the highest R^2 value and least slope value.

9. Stability studies:[19, 20] Test conditions for stability studies are shown in Table 2

Table 2: Test conditions for stability studies

Test Conditions	
Duration of study	**3 months**
Temperature conditions	40°C± 2°C
Relative humidity conditions	75%RH ± 5%RH
Frequency of testing	1 month, 2 month, 3 months

The formulations were evaluated mainly for their physical characteristics at 1, 2 and 3 months.Physical appearance in terms of clarity, appearance, pH, drug content were evaluated.

RESULT AND DISCUSSION

Compatibility study:

FTIR:

The IR spectra of Rizatriptan benzoate, polymer and physical mixture were generated. The IR absorption bands observed in the IR spectrum of drug and polymers resembles with that of found in the physical mixture proves compatibility of drug with polymers.

Differential scanning calorimetry:

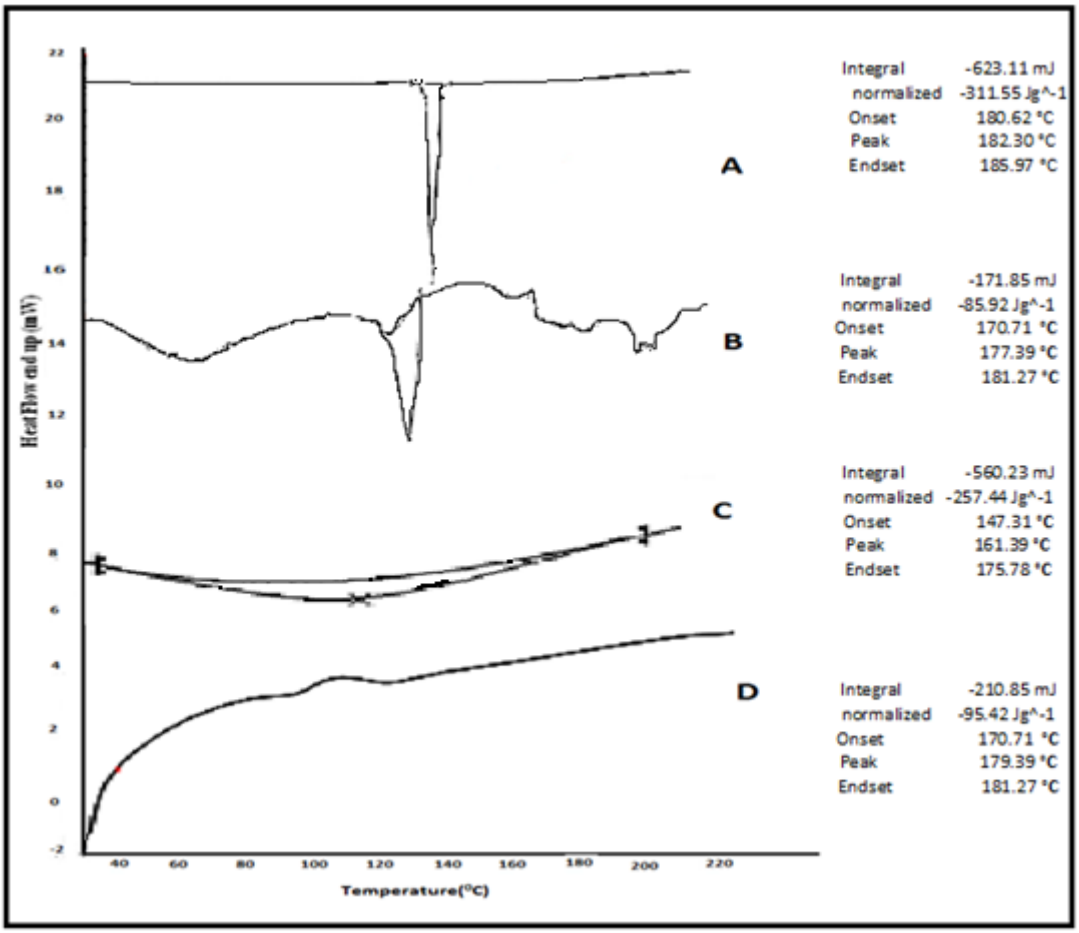

Figure 3: DSC thermogram of drug and polymers

The thermal behaviour of drug and physical mixture of drug with polymers (Rizatriptan benzoate + Poloxamer 407 + HPMC K4M) was studied by using DSC thermogram. DSC thermogram of drug exhibited characteristic peak at 182.30^{o}C and physical mixture exhibited characteristic peak at 177.39^{o}C. From the results it can be concluded that there is no interaction between drug and polymers because there is no shifting of thermogram.

Appearance:

On careful visual inspection against dark and white background, all the prepared nasal gel formulations were found to be free from any suspended particulate matter. All the formulations were found to be clear.

pH:

The pH of all the formulations from F1 to F9 was found to be in the range of 6.00 to 6.9 pH values of formulations shown in Table 3

Table 3: pH values of formulations (n=3)

Sr. No.	Formulation code	Observed pH (±S.D.)
1.	F1	6.00±0.1044
2.	F2	6.13±0.4933
3.	F3	6.86±0.1529
4.	F4	6.15±0.1394
5.	F5	6.26±0.4509
6.	F6	6.80±0.1034
7.	F7	6.46±0.2517
8.	F8	6.40±0.3605
9.	F9	6.83±0.1455

Ideally, the nasal solutions should possess pH in the range of 4-7, so as to minimize discomfort or irritation due to acidic pH and microbial growth due to basic pH.

Viscosity Determination:

The viscosity of formulations at 25^{o}C and 37^{o}C are shown in Table 4 and 5 respectively.

Table 4: Viscosity of formulations at 25^{o}C temperature

Rpm	Viscosity (cp) at 25^{o}C temperature								
	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	537.2	639.1	689.4	788.2	807.4	835.1	935.1	950.2	896.2
10	339.2	703.2	753.2	650.9	845.2	788.2	888.4	991.1	777.3
15	297.1	597.3	650.6	575.2	782	774.4	774.2	876.4	646.1
20	196.2	437.1	487.3	662.4	694.2	632.1	696.3	725.6	592.3
25	55.5	56.3	59.8	64.2	104.3	120.2	129.7	136.8	149.8

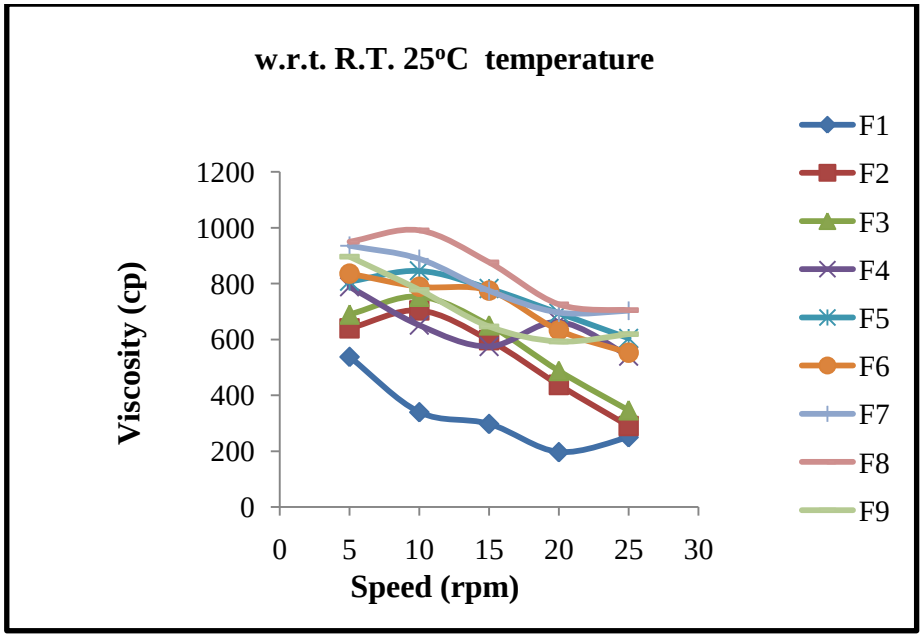

Figure 4: Viscosity profile of formulations at 25°C temperature

Table 5: Viscosity of formulations at 37°C temperature

Rpm	Viscosity (cp) at 37°C temperature								
	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	603.2	834.5	749.2	858.4	997.5	1025.6	1068.4	1295.8	1012.4
10	495.9	903.7	693.1	720.1	945.4	966.8	953.1	1187.4	943.6
15	387.8	707.9	590.3	645.8	882	918.6	912.6	1126.4	887.3
20	379.7	697.3	427.6	732.8	756.8	846.8	843.5	938.8	739.6
25	377.8	442.7	434.1	610.6	798.4	789.9	815.1	874.2	697.8

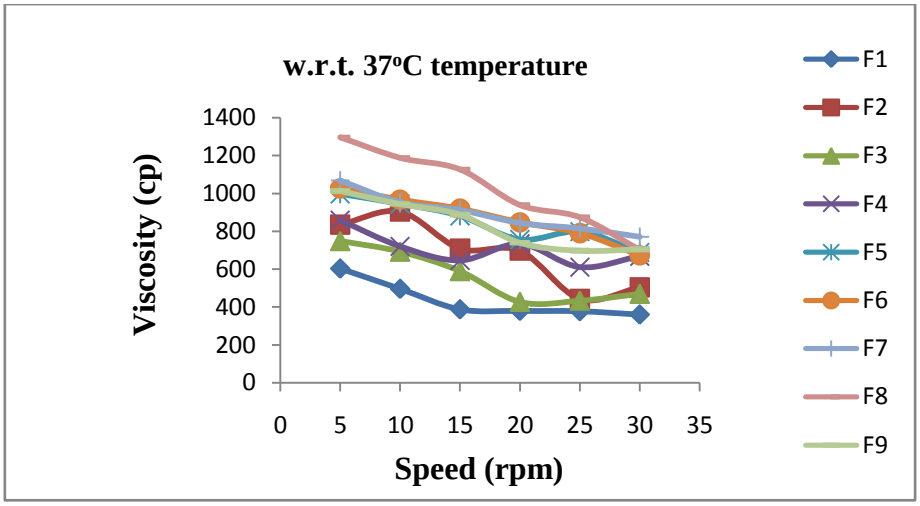

Figure 5: Viscosity profile of formulations at 37°C temperature

Viscosity v/s rpm plots for all formulations shows decrease in viscosity as shear rate (rpm) was increased. Concentration of HPMC K4M and Poloxamer 407 was a major factor affecting viscosity of formulations. As pH was increased, the increase in viscosity was observed which indicate that gel has the pseudo plastic flow. In combination with Poloxamer 407, HPMC K4M has shown considerable increases in viscosity when concentration of Poloxamer 407 is 15% w/v to 25% w/v.

Drug content:

The drug content of formulations is shown in Table 6

Table 6: Percent drug content of all formulations (n=3)

Formulation Code	Drug content (%) (±S.D.)
F1	99.13 ±0.00042
F2	98.69±0.00067
F3	99.29±0.01
F4	97.26±0.00049
F5	99.04±0.01
F6	99.53±0.001
F7	99.72±0.00085
F8	100.02±0.00071
F9	99.83±0.00065

The percentage drug content of all prepared nasal gel formulations was found to be in the range of 99-101%. Therefore uniformity of content was maintained in all formulations.

***In-vitro* Drug Release Study:**

Table 7: Cumulative Drug release of formulations

Cumulative Drug Release (%) (±S.D.)									
ne [hrs.]	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
0.5	15.97± 0.007	20.74± 0.0004	4.25± 0.0009	2.59± 0.0010	19.57± 0.0014	16.87± 0.0023	5.49± 0.0015	16.72± 0.0008	15.90± 0.0006
1	19.96± 0.0032	26.15± 0.0010	11.48± 0.0014	7.95± 0.0015	27.59± 0.0006	23.17± 0.0008	14.11± 0.0015	22.92± 0.0031	24.38± 0.0031
2	23.96± 0.0002	33.22± 0.0010	18.75± 0.0010	13.61± 0.0014	34.74± 0.0009	30.57± 0.0008	21.96± 0.0008	32.50± 0.0008	33.04± 0.0007
3	30.27± 0.00012	38.53± 0.0015	25.83± 0.0010	22.02± 0.0003	41.53± 0.0006	38.37± 0.0008	30.88± 0.00007	41.08± 0.001	41.03± 0.0003
4	36.49± 0.0009	46.97± 0.0007	35.87± 0.00081	29.81± 0.0015	51.54± 0.0013	46..23± 0.0008	38.62± 0.0007	51.15± 0.0003	52.99± 0.001
5	41.02± 0.0010	54.85± 0.0007	43.98± 0.0008	38.62± 0.009	57.77± 0.0001	55.52± 0.0008	48.37± 0.0001	59.55± 0.0003	65.65± 0.0001
6	45.92± 0.0010	59.02± 0.0010	50.96± 0.0023	43.85± 0.0007	62.60± 0.0003	61.85± 0.0008	53.97± 0.0003	62.47± 0.0009	69.64± 0
7	56.87± 0.0008	71.98± 0.0009	63.62± 0.0003	56.85± 0.0014	76.73± 0.0001	75.81± 0.0003	67.19± 0.0008	79.24± 0.0005	86.14± 0.0008
8	66.58± 0.0022	84.21± 0.0031	71.65± 0.0023	64.86± 0.0006	88.17± 0.0008	88.19± 0.0002	77.14± 0.0001	97.92± 0.0003	95.24± 0.0008

Amongst all formulations F8 showed maximum drug release of 97.92% after 8 hr. of study and also showed better contact with biological membrane.

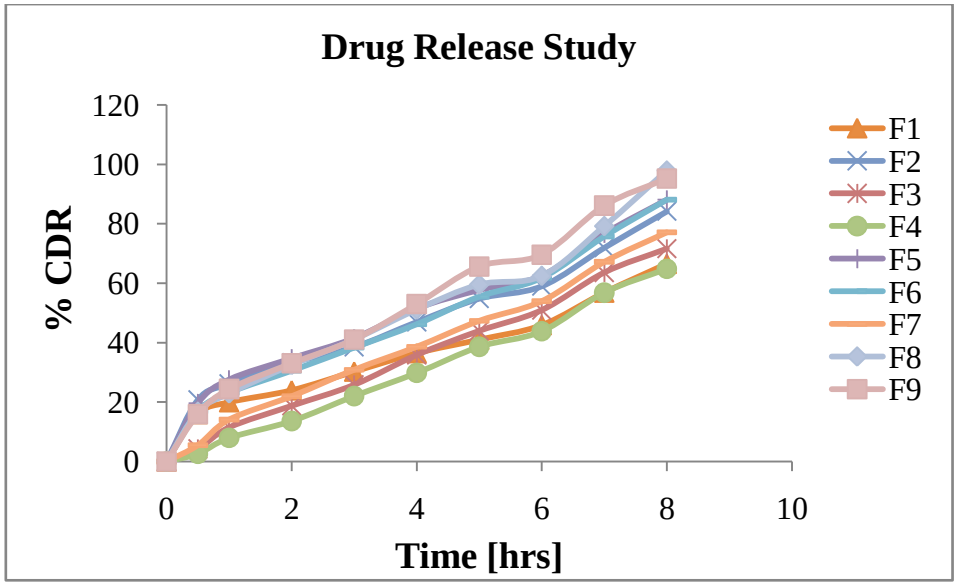

Figure 6: *In-vitro* drug release profile of all formulations.

Measurement of the gel strength:

The gel strength of formulations is shown in Table 8

The gel strength was found to be affected by concentrations of gelling and mucoadhesive polymers. Optimal mucoadhesive gel must have suitable gel strength so as to be administered easily and can be retained at nasal mucosal region without leakage after administration. Gel strength of all formulations showed comparable results as that of viscosity results.

Table 8: Gel strength of formulations (n=3)

Sr. No.	Formulation code	Gel strength (sec)(±S.D.)	Gel strength (sec) (±S.D.)
		At room temperature 25°C	At temperature 37°C
1.	F1	0.87±0.03	1.13 ±0.1155
2.	F2	0.77±0.0141	2.64 ±0.04
3.	F3	0.82±0.0264	0.93 ±0.0244
4.	F4	1.43±0.0578	2.3 ±0.3464
5.	F5	2.2±0.2645	2.76 ±0.3056
6.	F6	1.6±0.4358	2.43 ±0.3055
7.	F7	0.74±0.0070	0.93 ±0.0291
8.	F8	0.97±0.02	1.67 ±0.1609
9.	F9	2.1±0.1	2.4 ±0.1732

Mucoadhesive Strength:

The mucoadhesive strength of formulations is shown in Table 9

Table 9: Mucoadhesive strength of formulations (n=3)

Formulation Code	Detachment stress (gm.)(±S.D.)
F1	0.0719 ±0.5773
F2	0.0421±4.0414
F3	0.0814±2.0816
F4	0.0745±2.3094
F5	0.0843±0.5774
F6	0.0618±2.3093
F7	0.0716±1.5275
F8	0.0716±0.5773
F9	0.0745±1.5275

Mucoadhesive force means the force with which gels bind to nasal mucosa. Greater mucoadhesion is indicative of prolonged residence time of a gel and thus prevents its drainage from nasal cavity. The mucoadhesion force increased significantly as the concentration of mucoadhesive polymers increased. The mucoadhesive strength was determined for nasal gels. Results of this test indicate that the variable Poloxamer 407 and HPMC K4M both are having effect on mucoadhesive strength. It shows that mucoadhesive force was increased with the increasing concentration of the Poloxamer 407 or HPMC K4M.

Drug release kinetics:

The classical zero order release curve was found to be linear. The curves plotted according to first order and Higuchi release model were also found to be linear. For the Korsemeyer-Peppas release curves r^2 was found to be ≥ 0.75 for all 9 formulations and n value was found to be ≥ 0.5 which indicates that all the formulations show anomalous (non-Fickian release).The drug release occurs probably by diffusion and erosion.

Optimization:

A 3^2 full factorial design was selected and the 2 factors were evaluated at 3 levels, respectively. The percentage of Poloxamer 407 (X_1) and HPMC K4M (X_2) were selected as independent variables and the dependent variable was % drug release, mucoadhesive

strengthand viscosity.The data obtained were treated using Design expert version 8.0.7.1 software and analyzed statistically using analysis of variance (ANOVA). The data were also subjected to 3-D response surface methodology to study the interaction of Poloxamer 407 (X_1) and HPMC K4M (X_2) on dependent variable. The values of X_1 and X_2 were found to be significant at **p <0.05**, hence confirmed the significant effect of both the variables on the selected responses. From this data optimum concentration of Poloxamer 407 25%w/v and HPMC K4M 0.20% w/v was found.

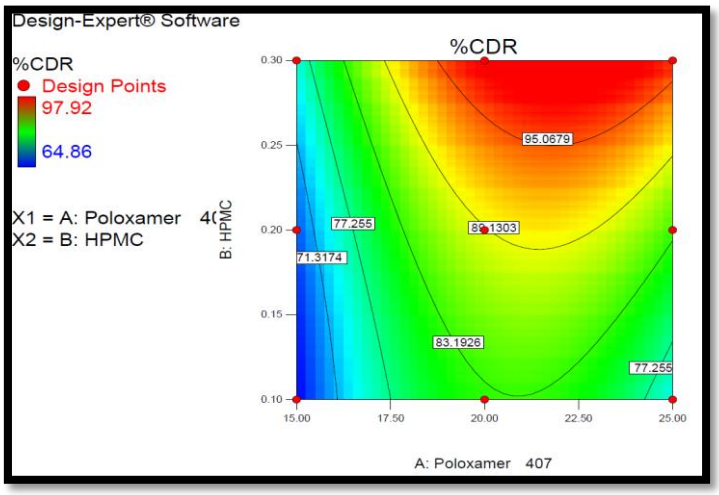

Figure 7: Contour plot showing effect of Poloxamer 407 and HPMC K4M on drug release.

In the above Figure 7 the contour plot shows that as the concentration of Poloxamer 407 increases % CDR increases. Hence it can be concluded that the two factors Poloxamer 407and HPMC K4M have a combined effect on % CDR.

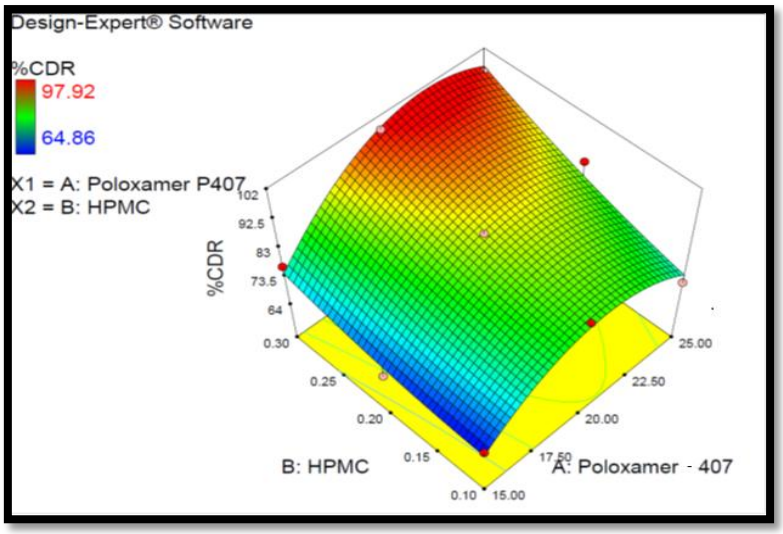

Figure 8: Surface response plot showing effect of Poloxamer 407 and HPMC K4M on drug release.

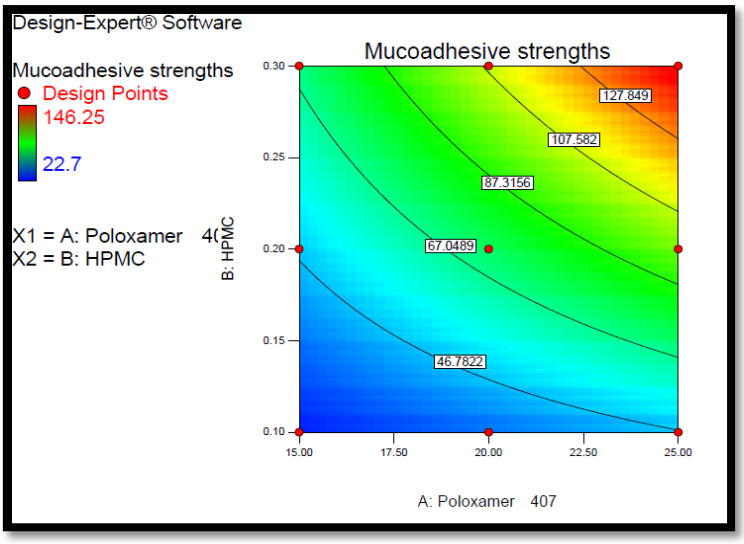

Figure 9: Contour plot showing effect of Poloxamer 407 and HPMC K4M on mucoadhesive strength.

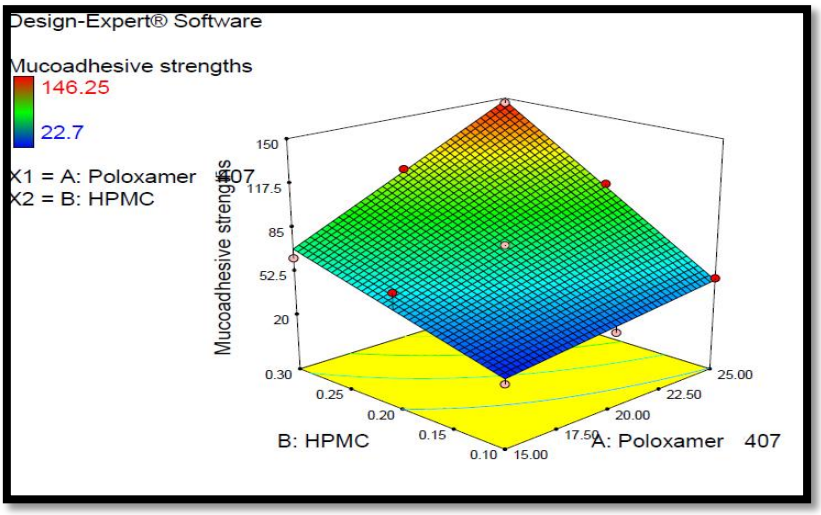

Figure 10: Surface response plot showing effect of Poloxamer 407 and HPMC K4M on Mucoadhesive strength.

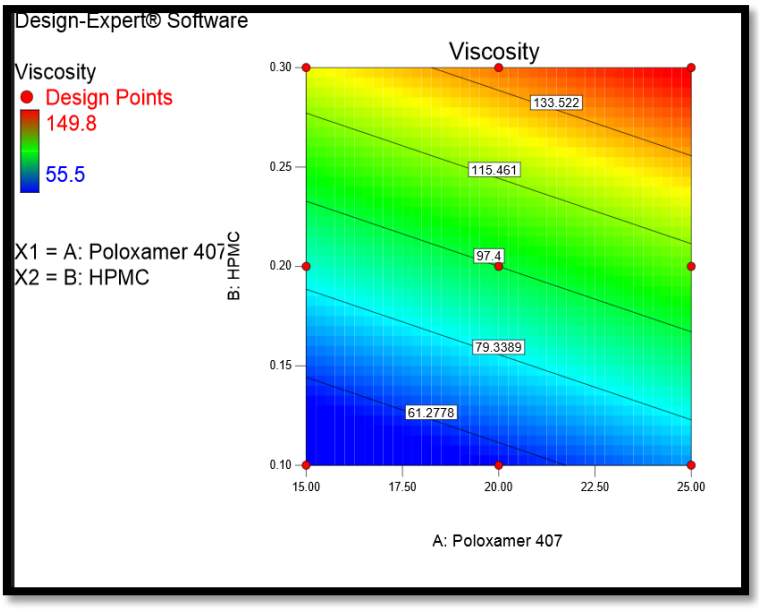

Figure 11: Contour plot showing effect of Poloxamer 407 and HPMC K4M on Viscosity at 25°C temperature.

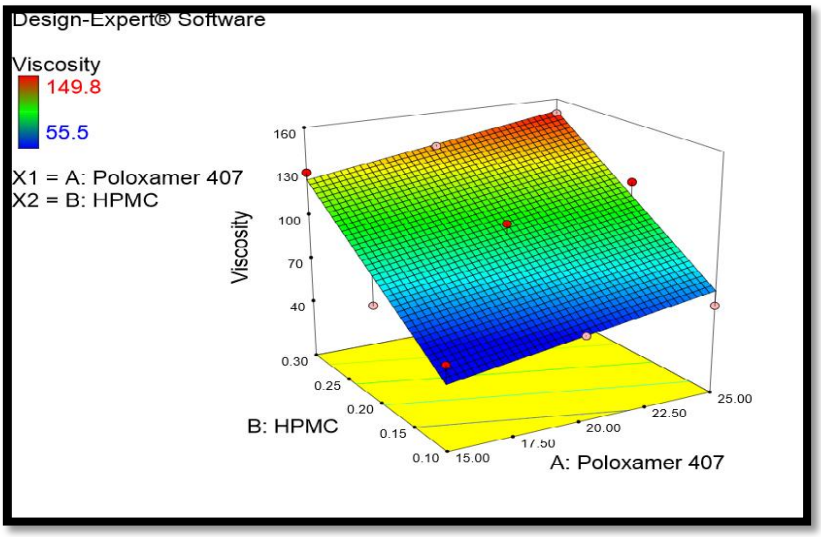

Figure 12: Surface response plot showing effect of Poloxamer 407 and HPMC K4M on Viscosity at 25°C temperature.

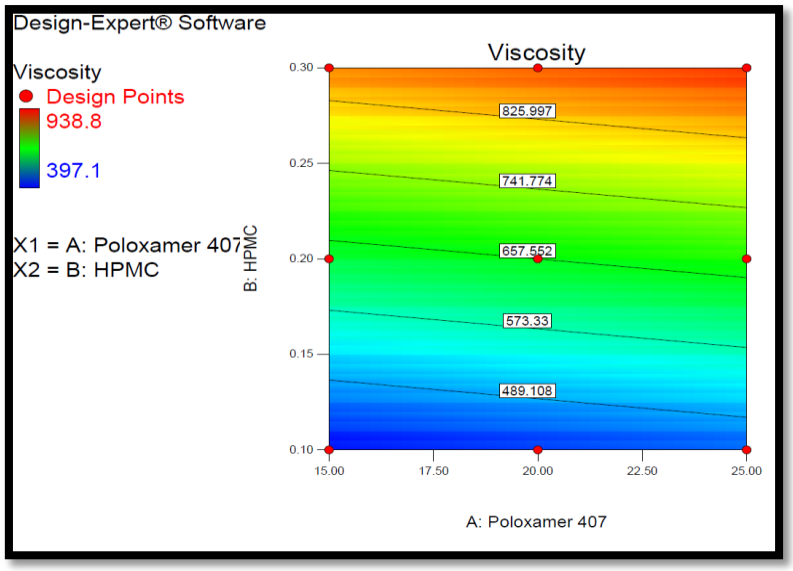

Figure 13: Contour plot showing effect of Poloxamer 407 and HPMC K4M on Viscosity at 37°C temperature.

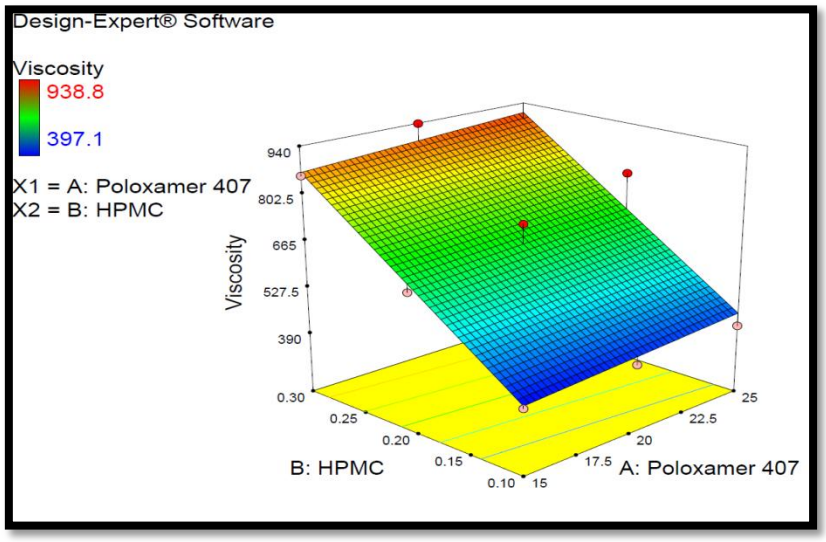

Figure 14: Surface response plot showing effect of Poloxamer 407 and HPMC K4M on Viscosity at 37°C temperature.

Optimized formula:

After generating model, equations relating main effects and responses, various gel formulations containing Rizatriptan benzoate were optimized based on in vitro drug release (Y1), mucoadhesive strength (Y2), viscosity (Y3). The optimal values for responses were obtained by numerical analysis based on the criteria of desirability and optimal batch was selected. Optimized batch (F8) having highest drug release, mucoadhesive strength and optimal viscosity. This revealed that mathematical model obtained by factorial design to produce optimized responses was well fitted.

Accelerated stability study:

Table 10: Results of stability study (n=3)

Sr. No.	Test	Before stability testing	After stability testing		
			1months	2 months	3 months
1.	Clarity	Clear	Clear	Clear	Clear
2.	Visual appearance	Transparent	Transparent	Transparent	Transparent
3.	pH	6.40	6.42	6.38	6.29
4.	Drug content	100.02±0.0007	100.06±0.0007	100.09±0.0006	99.96±0.0003

Results of the stability studies showed that there is no change in the physical parameters of the formulation. Drug content of the formulation was found to be same as that of before stability testing.

CONCLUSION

By preparing the in situ gel of Rizatriptan benzoate the effect of different variables on gel was studied.pH of all the formulations were found to be in between the range (6.0-6.83).The viscosities of all the formulations were determined and it was observed that viscosity was increased due to increasing concentrations of Poloxamer 407.The prepared gel was also evaluated for % drug content, %CDR (In vitro drug release),viscosity.

ACKNOWLEDGEMENT

The authors are grateful to R. G. Sapkal College of Pharmacy, Anjaneri, Nashik; for providing essential laboratory conditions for present research work. Also an author acknowledges to Cipla Ltd; Mumbai for providing gift sample of Rizatriptan benzoate.

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