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

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ABSTRACT

Rizatriptan benzoate, a potent triptan used for the acute treatment of migraine, faces challenges in achieving optimal bioavailability due to its low oral absorption and first-pass metabolism. The development of an in situ nasal gel could offer a viable alternative for rapid drug delivery, bypassing gastrointestinal degradation and first-pass metabolism. This study focuses on the formulation, development, and in vitro evaluation of an in situ nasal gel containing Rizatriptan benzoate. The gel was formulated using various gelling agents and evaluated for its physicochemical properties, gelation behavior, drug release, and nasal mucosal compatibility.

KEYWORDS: Rizatriptan benzoate, In situ nasal gel, Formulation, Drug delivery, Nasal mucosa, Gelation.

INTRODUCTION

Nasal administration is a logical choice for topical nasal treatments such as antihistamines and corticosteroids. Conventionally, the nasal route has been used for local delivery of drugs for treating nasal allergy, nasal congestion, or nasal infections. The nasal route has been potentially explored as an alternative route for the administration of vaccines and bio molecules such as proteins, peptides and non-peptide drugs that are susceptible to enzymatic or acidic degradation and first-pass hepatic metabolism. The nasal mucosa is one of the most permeable and highly vascularized sites for drug administration ensuring rapid absorption and onset of therapeutic action. Many drugs are not effectively and efficiently delivered to the brain using conventional drug delivery approaches. Transport of drugs from systemic circulation into the central nervous system (CNS) is restricted by the BBB and blood-CSF barrier.[1,2] While the BBB serves to protect the brain spinal cord from a variety of pathogens and toxic substances, it also presents a significant barrier to treating CNS disorders. Mainly charged, hydrophilic, water-soluble substances, and large therapeutic agents are inhibited or prevented from entering the brain by the BBB.[3] Innovation is a key driver of growth that in the recent years there has been a continuous effort in the direction of achieving controlled and sustained drug delivery systems. Considerable attention has been received in the in-situ gelling systems over the past few years. In situ gel formulation is executed for targeted delivery through the vaginal and rectal routes, and the nasal mucosa, circumventing the hepatic first pass metabolism.[4]

MATERIALS AND METHODS

Materials

Rizatriptan Benzoate was obtained as a gift sample from Dr. Reddy's Lab, India. All other reagents of analytical grade (AR) were used in the study.

Methods

Characterization of drugs

Rizatriptan benzoate was characterized by using UV spectroscopy infrared Spectroscopy (IR), Differential Scanning calorimetry (DSC) and melting point determination.

Drug-excipient compatibility study

Drug excipient interaction study was carried out by differential Scanning Calorimetry and IR.

Preparation and Optimization of Rizatriptan Benzoate in-situ Nasal Gel

Accurately weighed quantity of LM pectin (1.8 to 2% w / w) was dispersed in distilled water. The dispersions were stirred using magnetic stirrer for 1 h. Methyl paraben (0.032 gm) and propyl paraben (0.029 gm) was also added simultaneously. Then Rizatriptan benzoate (5 mg) was added in it. The composition for prototype formulation is shown n table 6.5. The pH of all formulations was in the range of 4.5- 6.5. Formulations were filled in amber colored glass vials, capped with

rubber closures and sealed with aluminum caps. Formulations were stored at room temperature until further use.

Table 1: Formulation of Rizatriptan Benzoate in-situ Nasal Gel.

No.	Ingredients	Formulation Batches (%W/W)		
		B1	B2	B3
1	Rizatriptan benzoate	5	5	5
2	LM pectin	1.8	1.9	2.0
3	Methyl paraben	0.032	0.032	0.032
4	propyl paraben	0.029	0.029	0.029
5	Distilled water	100	100	100

Evaluation parameters

In vitro gelation

Beaker containing 2 ml of formulation and a magnetic bead was placed on a magnetic stirrer. The simulated nasal electrolyte solution (SNES aqueous solution containing 8.77 mg/mL NaCl, 2.98 mg/mL KCl and 0.59 mg/ml CaCl2) which had cationic composition of nasal secretions, (0.5 ml) was added slowly while stirring. Gelation was observed by visual examination. The consistency of formed gel was checked and graded as indicated in Table 6.5 (Belgamwar et al., 2009; Cao et al., 2009).

pH measurement

The pH of formulated in situ gels was measured by using PH meter (Chemline, India)

Gel strength

It is expressed in terms of time (in seconds) required by a 35 g piston for penetration of 5 cm distance, through the 50 g gel formulation. This test was performed using 'Gel strength apparatus' modified at the laboratory as mentioned by Yong et al., (2001).

Viscosity

Viscosity of formulations before and after gelation were measured by Brookfield viscometer (RVT model, Brookfield, USA) using a 80 ml of aliquot. Measurements were performed using spindle number 2 at 50 rpm (Belgamwar et al., 2009).

Critical Cation Concentration (CCC)

When in situ gel cation concentration exceeds the CCC phase transition (sol to gel) will occur instantaneously. All the batches with different concentrations of LM pectin (batch B_1 to B3 i.e. 1.8-2.0%) were treated with different amounts of SNES (0.1 ml to 2.0 ml). If stiff gelation occurs after 20 s then it was considered '+' whereas, flowing/sliding formulations are considered as " (Cai et al 2011).

Drug content

The vials containing the formulation were shaken for 2-3 min manually and 500 µl of the preparation was transferred to 10 ml volumetric flasks with a micropipette and the final volume was made up with distilled water. Rizatriptan benzoate concentration was determined at 224.4 nm using UV visible double beam spectrophotometer (V 630, Jasco, Japan) (Belgamwar et al., 2009).

In vitro mucoadhesive strength

Mucoadhesive strength of in situ nasal gel was determined with sheep nasal mucosa using modified physical balance method (Fig. 6.3) with slight modification and phosphate buffer pH 7.4 was used as the moistening fluid. The mucoadhesive force, expressed as the detachment stress in dyne/cm² was determined using following equation:

Detachment stress (dyne/cm²) = mg/A

Where,

m = Weight of water added to the polytene bag (gms)

g = Acceleration due to gravity taken as 980 cm/sec²

A = Area of tissue exposed and is πr²(r is radius of rubber closure)

In vitro drug release

In vitro release of drug from the phase transition system was carried out using a Franz diffusion cell apparatus (EDC-07, Electrolab, India) with dialysis membrane (cut-off 12,000-14,000 kDa) (Cao et al., 2007).

Selection of optimized batch

Based on the required properties of in situ gel, the optimum batch was selected on the basis of immediate gelation for extended period (++), optimum viscosity pH, gel strength and In vitro drug release. The batch B2 containing 1.9% w/w of the LM pectin concentration was selected as the optimized batch.

RESULTS AND DISCUSSION

Preformulation study

Identification and Characterization of drug

Organoleptic characterization

The organoleptic characteristics of drug like appearance, color, and odor were studied and shown in Table 2.

Table 2: Organoleptic characterization of drug.

No.	Test	Observation
1	Appearance	Solid Crystalline Powder
2	Colour	White to off white
3	Odor	Odorless

Melting point determination

The melting point of the drug was found to be in the range 178-180°C. Observed melting point was compared with the reference melting point available in chemical book and found to be accurate (Indian Pharmacopoeia, 2014).

UV spectroscopy

Solution of rizatriptan benzoate (200 ug/ml) in distilled water was scanned. Wavelength (max) was found to be 224.4 nm, which was similar as reported and absorbance was noted (Indian Pharmacopoeia, 2014).

IR spectroscopy

The IR spectrum of rizatriptan benzoate was obtained after scanning in the wavelength region of 400-4000 cm^{1} is shown in Fig. 1. (Indian Pharmacopoeia, 2014).

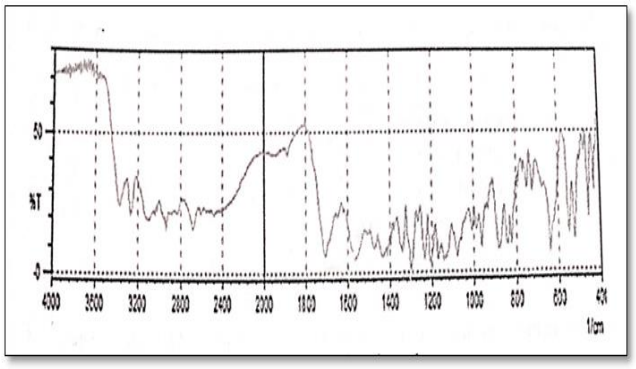

Figure 1: IR Spectrum of rizatriptan benzoate.

Differential Scanning Calorimetry (DSC)

The differential Scanning Calorimetry thermogram of Rizatriptan benzoate and physical mixtures of the drug was recorded by using the DSC equipped with the computerized data station. The DSC thermogram of rizatriptan benzoate is shown in Fig. 2.

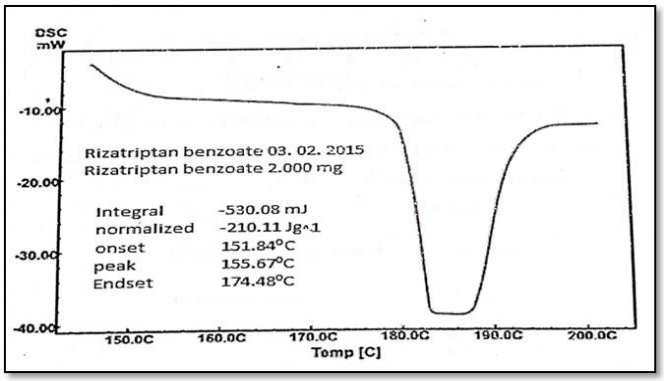

Figure 2: DSC thermogram of rizatriptan benzoate.

Standard calibration curve of Rizatriptan benzoate in distilled water

The standard calibration curve data for Rizatriptan benzoate is shown in Table 3.

Table 3: Calibration curve data of Rizatriptan benzoate in distilled water.

No.	Conc. (µg/ml)	Absorbance*
1	2	0.165±0.001
2	4	0.351±0.002
3	6	0.525±0.002

4	8	0.690±0.002
5	10	0.900±0.002

*Mean ± S.D., n=3

The graph of standard calibration curve of Rizatriptan benzoate in distilled water is shown in Fig. 3.

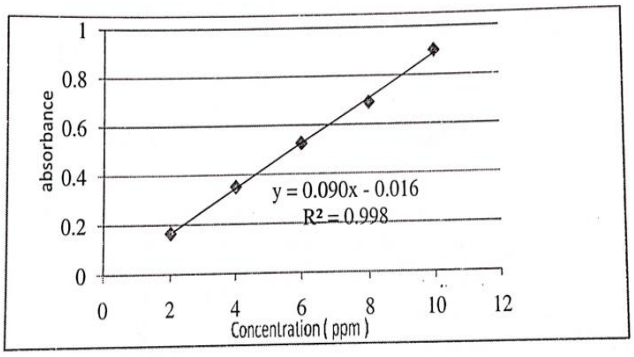

Figure 3: Standard calibration curve of rizatriptan benzoate in distilled water.

Standard calibration curve of rizatriptan benzoate in phosphate buffer pH 7.4

The standard calibration curve data for rizatriptan benzoate is shown in Table 4.

Table 4: Calibration curve data of Rizatriptan benzoate in phosphate buffer pH 7.4.

No.	Conc. (µg/ml)	Absorbance*
1	10	0.168±0.041
2	20	0.214±0.063
3	30	0.448±0.018
4	40	0.500±0.005
5	50	0.650±0.011

*Mean ± S.D., n=3

The graph of the standard calibration curve of Rizatriptan benzoate in phosphate buffer pH 7.4 is shown in Figure 4.

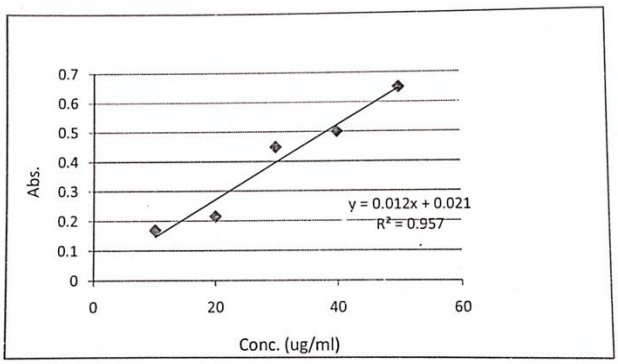

Figure 4: Calibration curve of Rizatriptan benzoate in phosphate buffer pH 7.4

Drug-excipient compatibility study

Solid compatibility

Rizatriptan benzoate, physical mixtures of drug and LM pectin (1:1) with their physical observation are shown in Table 5.

Table 5: Physical observations of compatibility study of Rizatriptan benzoate and excipients without moisture.

No.	Composition	Period (Days)	Physical observations			
			Caking	Liquification	Discoloration	Odor/gas
1	Drug	Initial	Free flow	Solid	White	No
		14 days	No change	No change	No change	No
2	Drug+ LM Pectin (1:1)	Initial	Free flow	Solid	White	No
		14 days	No change	No change	No change	No

Infrared spectroscopy

The IR spectrum of rizatriptan benzoate was obtained after scanning in the wavelength region of 400-4000 cm¹ is shown in Fig. 5.

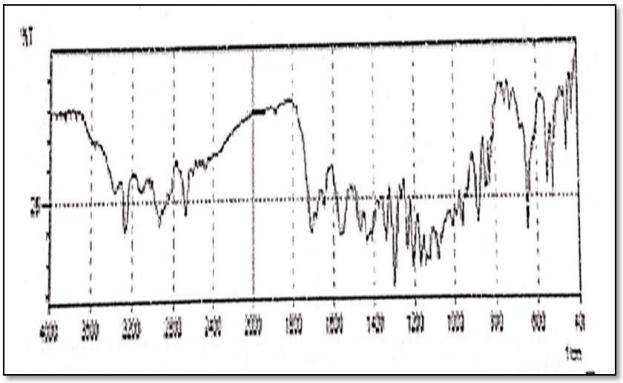

Figure 5: IR spectrum of LM pectin.

The IR spectrum of rizatriptan benzoate and LM pectin was obtained after scanning in the wavelength region of 400-4000 cm is shown in Fig. 6.

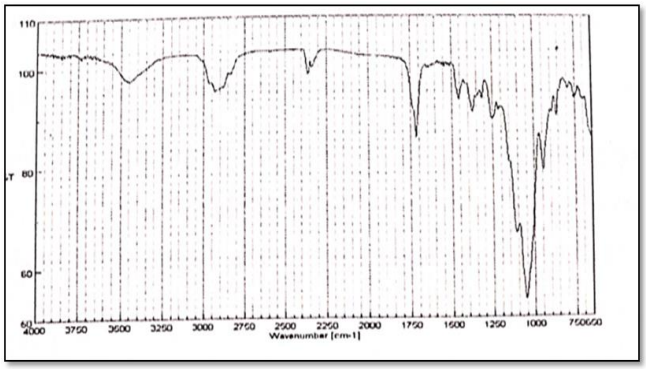

Figure 6: IR spectrum of Rizatriptan benzoate and LM pectin.

Differential Scanning Calorimetry (DSC)

The DSC thermogram of LM pectin and DSC thermogram of physical mixture of Rizatriptan benzoate and LM pectin are as shown in fig. 7 and 8 respectively.

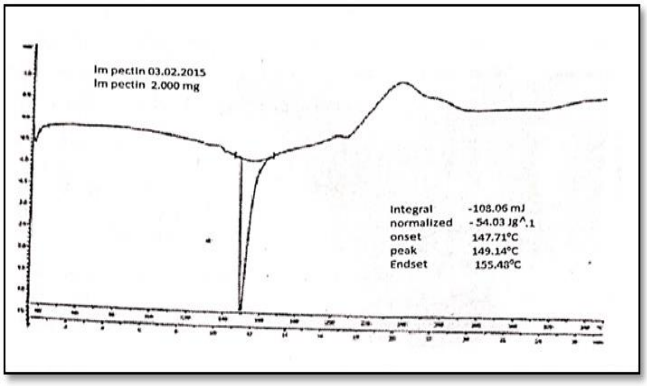

Figure 7: DSC thermogram of LM pectin.

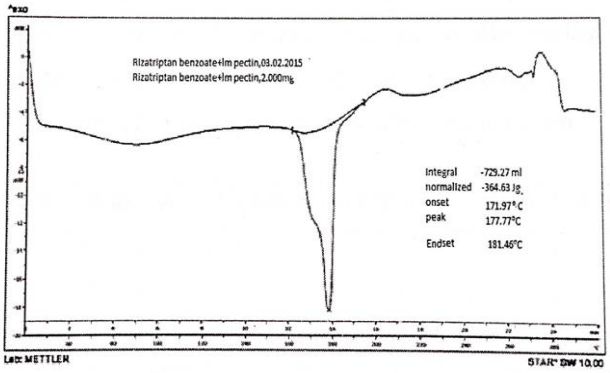

Figure 8: DSC thermogram of physical mixture Rizatriptan benzoate and LM pectin.

Formulation and Development

Preliminary trials for formulation development

Trials for gelation by taking various concentration of LM pectin

Various pectin concentrations (1 to 2%) were evaluated for gelation studies by taking 1:1 ratios of pectin to that of SNES. The 2.0% pectin (batch B3) solution showed very stiff gelation. The in vitro gelation behaviors of various preliminary batches (B_1 to B3) are shown in table 6.

Table 6: In vitro gelation behavior of preliminary batches B1-B3.

No.	Batch code	Conc. of pectin (%)	Degree of gelation
1	B1	1.8	+
2	B2	1.9	++
3	B3	2.0	+++

The results were noted according to following:

- No gelation.
+ Weak gelation (drip).
++ Immediate gelation but shows dripping.
+++ Immediate gelation with "no drip" property.

Evaluation of preliminary batches (Placebo formulation)

A. In vitro gelation

All formulations (1.8-2.0%) were showing gelation depending upon the gelling polymer concentration (Table 7). Formulation B1 showed weak gelation (+), Formulation B2 showed immediate gelation which remained for extended period (stiff gel, ++) and B3 showed very stiff gelation (+++).

Table 7: In vitro gelation behavior of preliminary batches B1-B3.

No.	Batch code	Conc. of pectin (%)	Degree of gelation
1	B1	1.8	+
2	B2	1.9	++
3	B3	2.0	+++

B. pH

The pH of all formulations B1 to B3 were as shown in Table 8.

Table 8: pH of formulations B1 to B3.

No.	Batch code	pH
1	B1	4.6
2	B2	4.56
3	B3	5.1

C. Gel Strength of formulation

In the development of nasal in situ gels, gel strength is an important parameter which allows easy administration as droplets and B1 delays the post nasal drip or anterior leakage. Gel strength of all formulations is shown in Table 9.

Table 9: Gel strength of formulations B1 to B3.

No.	Batch code	Gel Strength (s)
1	B1	10.67±0.054
2	B2	11.26±0.068
3	B3	13.46±0.046

D. Viscosity

Apparent viscosity values were measured for both sol and gel using Brookfield viscometer (RVT model) as shown in Table 10.

Table 10: Viscosity of sol-gel state of formulation B1 to B3.

No.	State	Viscosity (cp)		
		B1	B2	B3
1	Sol	34	36	40
2	Gel	328.5	330	338

E. Critical cation concentration (CCC)

All the batches with different concentrations of LM pectin were treated with different concentrations of SNES (0.1 ml to 2.0 ml). Batch B2 shows CCC of 0.5 ml.

Evaluation of prototype formulations

A. In vitro gelation

All formulations were showing gelation depending upon the gelling polymer concentration (Table 11). Formulations B1, B2 and B3 showed weak gelation (+), Formulation B2 showed immediate gelation which remained for extended period (stiff gel, ++) and B3 showed very stiff gelation (+++).

Table 11: In vitro gelation behavior of preliminary batches B1 to B3.

No.	Batch code	Conc. of pectin (%)	Degree of gelation
1	B1	1.8	+
2	B2	1.9	++
3	B3	2.0	+++

B. pH

The pH of all formulations B1 to B3 was as shown in Table 12.

Table 12: pH of formulations B1 to B3.

No.	Batch code	pH
1	B1	4.7±0.023
2	B2	5.3±0.030
3	B3	5.2±0.022

C. Viscosity

Apparent viscosity values were measured for both sol and gel using Brookfield viscometer (RVT model) as shown in Table 13.

Table 13: Viscosity of sol-gel state of formulation B1 to B3.

No.	State	Viscosity (cp)		
		B1	B2	B3
1	Sol	30	34	38
2	Gel	324	326.5	336

D. Gel strength of formulation

Gel strength of all formulations is shown in Table 14.

Table 14: Gel strength of formulations B1 to B3.

No.	Batch code	Gel Strength (s)
1	B1	10.67±0.054
2	B2	11.26±0.068
3	B3	13.46±0.046

E. Critical cation concentration (CCC)

All the batches with different concentrations of LM pectin were treated with different concentrations of SNES (0.1 ml to 2.0 ml). Batch B2 shows CCC of 0.4 ml.

F. Drug content

Drug content of all formulations are as shown in Table 15.

Table 15: Drug content of formulations B1 to B3.

No.	Batch code	Gel Strength (s)
1	B1	99.11±0.002
2	B2	99.84±0.010
3	B3	99.44±0.023

G. In vitro mucoadhesive strength

Table 16 displays the muco-adhesion force of formulation B1 to B3.

Table 16: Mucoadhesive force of formulation B1 to B3.

No.	Batch code	Mucoadhesive force (dyne/cm^2)
1	B1	2875.58±8.01
2	B2	3082.03±8.58
3	B3	3565.73±7.592

H. In vitro drug release

In vitro drug release data of formulations B1 to B3 are shown in Table 17.

Table 17: In vitro drug release data of formulations B1 to B3.

Time (h)	% CDR		
	B1	B2	B3
0	0.43	0.88	2.07
0.5	9.48	13.93	10.67
1	13.04	16.00	15.87
2	21.93	24.88	22.81
3	31.11	33.19	30.22
4	41.18	50.66	45.34
5	47.18	64.88	57.48
6	58.96	81.18	72.29
7	77.04	98.67	75.55

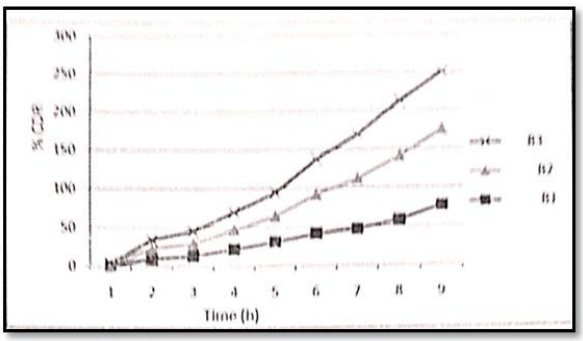

Figure 9: Release profiles of all formulations B1 to B3 (1.8 to 2.0%).

Selection of optimized batch

The batch B, containing 1.9% w/w of the LM pectin concentration was selected as the optimized batch.

Evaluation of optimized batch

A. In vitro gelation

The in vitro gelation study of the optimized batch was performed which showed immediate gelation with desired gel property.

B. pH

The pH of the optimized batch was found to be 5.3 ± 0.030 which was in the pH range of nasal cavity.

C. Gel strength

The gel strength of the optimized formulation was found to be 11.26 ± 0.068 s, performed by gel strength measuring apparatus.

D. Viscosity

The viscosity of optimized formulation before gelation was found to be 34 cps and after gelation was found to be 326.5 cp, performed by brookfield viscometer.

E. Critical cation concentration

The critical cation concentration of the optimized batch (B2) was found to have addition of 0.4 ml of SNES which mimics the available natural nasal fluid quantity in nasal cavity.

F. Drug content

The drug content of the optimized formulation was found to be (99.84± 0.01%).

G. In vitro drug release and release rate kinetics

In vitro drug release profile of the optimized formulation is as shown in table 18.

Table 18: In vitro drug release profile of the optimized formulation.

No.	Time (Hr)	% CDR
1	0	0.84±0.213
2	0.5	13.90±0.396
3	1	15.91±2.253
4	2	24.75±2.547
5	3	32.97±1.069
6	4	50.45±0.417
7	5	64.46±1.264
8	6	79.53±0.579
9	7	88.78±0.604
10	8	98.67±0.233

The release profiles of optimized formulation B2 (1.9%) are shown in Fig. 10.

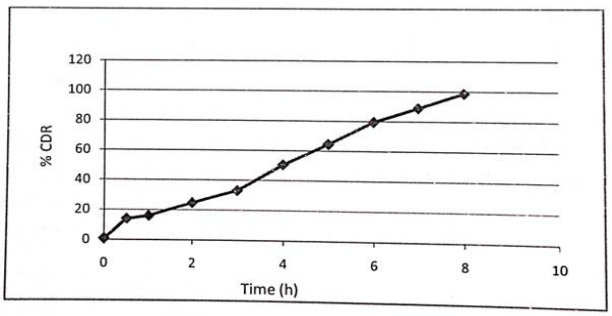

Figure 10: Release profiles of optimized formulation.

H. Water holding capacity

As shown in Table 19, the optimized formulation can hold 92.46% of water even at higher stress conditions.

Table 19: Water holding capacity of the formulation.

No.	Weight before centrifugation Wo (gm)	Weight after centrifugation W (gm)	Water holding capacity So= W/Wo.100	Average water holding capacity (%)
1	1.067	0.982	92.03	92.46±0.428
2	1.067	0.988	92.59	
3	1.067	0.990	92.78	

I. Expansion coefficient

As shown in Table 20, the optimized formulation has only 10.75% expansion coefficient. (Cai et al., 2011).

Table 20: Expansion coefficient of the optimized formulation.

No.	Initial volume V_m (ml)	Volume of gel + additional 2ml ANF, V_1	Volume of gel $V_{G=} V_{1-} 2$	S %	Average S (%)
1	2	4.15	2.15	10.75	10.83±0.428
2	2	4.15	2.15	10.75	
3	2	4.2	2.2	11	

J. No drip property

In situ gels should possess the "No drip property" for its tolerability by the patient. The optimized batch B2 (1.9 % LM Pectin) was analysed for "No drip" property which confirms- Reduced potential for no drip property and improved consistency and tolerability of the formulation.

K. Stability

The stability study of optimized formulation (B2) revealed that no significant changes in the physical parameters when stored at temperature and humidity conditions at 40±2°C and 75±5% RH. The stability data of optimized formulation is shown in Table 21.

Table 21: Stability study of optimized formulation at 40±2°C and 75±5% RH.

No.	Period	Evaluation Parameters								
		Physical Properties	In Vitro gelation	Viscosity		pH	Drug Content (%)	% CDR (After 8Hr.)	Gel strength (S)	In Vitro mucoadhesive strength
				Sol	Gel					
1	0 Month	No gelation	++	36	326.5	4.56±0.01	99.84±0.524	98.67±0.233	11.26±0.068	3082.03±8.58
2	1 Month	No change	No change	36	326.2	4.56±0.02	99.84±0.069	98.64±0.06	11.06±1.87	3082.03±7.58
3	2 Month	No change	No change	36	326	4.56±0.05	99.8±0.375	98.63±0.173	11.26±1.58	3182.03±8.58
4	3 Month	No change	No change	36	326	4.56±0.05	99.64±0.259	98.67±0.157	11.30±0.564	3082.03±8.58

CONCLUSION

This study successfully formulated and developed an in-situ nasal gel of rizatriptan benzoate, aiming to enhance the drug's nasal delivery and therapeutic efficacy. The developed gel demonstrated favourable in vitro characteristics, including optimal gelation properties, suitable drug release kinetics, and stability under physiological conditions. The in-situ gel system showed promise for improved bioavailability and patient compliance compared to conventional dosage forms.

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