

# Formulation and Evaluation of Nasal *in situ* Gel of Eletriptan Hydrobromide

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## Abstract

**Aims:** The nasal route has been found to be useful in targeting drugs to the central nervous system. As a target tissue for medication delivery, nasal mucosa has many advantages. Drug administration through the nose is related with systemic features a number of advantageous characteristics, including avoiding first-pass effects and having a sizable amount of surface area accessible for absorption. **Materials and Methods:** A new dosage form for nasal drug delivery, environment-sensitive gel has recently been used. In contrast to liquid nasal formulations, nasal *in situ* gels are injected into the nasal cavity as low-viscosity solutions. When the polymer comes into contact with the nasal mucosa, it changes conformation and forms a gel, which not only extends the time the drug is in contact with the absorptive sites in the nasal cavity but also allows the drug to be released gradually and continuously. **Results and Discussion:** This study set out to create and perfect a cold method-based nasal *in situ* gel formulation for Eletriptan Hydro bromide. Thermosensitive polymer was used to prepare nasal *in situ* gels. Study of Sol-gel transition temperature (Tsol-gel), rheological properties, *in vitro* release, and *in vivo* study was performed. **Conclusion:** Cumulative drug release from the nasal *in situ* gel containing Eletriptan Hydro bromide was within the range of 42.92–86.12%. The cumulative drug release using nasal mucosa of goat was 70.44%. The enhanced nasal residence time, improved bioavailability, increased brain uptake of parent drug and decreased exposure of metabolites suggested that the *in situ* gel could be an effective intranasal formulation of Eletriptan Hydro bromide.

**Key words:** Eletriptan hydro bromide, *in situ* gel, nasal route, thermo sensitive polymer

## INTRODUCTION

*In situ* gelation is a process of gel formation at the site of action after the formulation has been applied at the site. *In situ* gel phenomenon based upon liquid solution of drug formulation and converted into semi-solid mucoadhesive key depot. It permits the drug must be delivered in a liquid form or solution form. *In situ* gelling systems are the aqueous polymeric solutions that are transformed into gels due to changes in environmental conditions, like temperature and pH.<sup>[1,2]</sup> The *in situ* gels are fluids that can be introduced into the body in a minimally invasive manner before solidifying or gelling within the desired tissue, organ, or body cavity. These systems are currently of interest to the formulation scientist due to their structural and functional benefits.<sup>[3,4]</sup> Variety of therapeutic agents has been formulated as *in situ* gelling systems for their enhanced transport across the mucosal membranes. When the gel

is formed under physiological conditions and maintains integrity for a desired period of time, the process may provide various advantages. In the past few years, there are increasing number of *in situ* forming systems have been reported and the literature for various biomedical applications, including drug delivery, cell encapsulation, and tissue repair.<sup>[5-7]</sup> Intranasal route is considered for the drugs that are ineffective orally and are used chronically where rapid entry into the Circulation is desired and they require small doses.<sup>[8]</sup> The absorption of drugs from the nasal mucosa most probably takes place via the aqueous channels of the membrane. Therefore, as long as the drug is in the form of solution and the molecular size is

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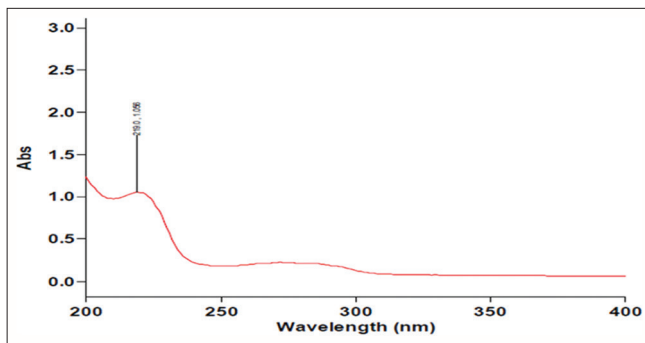


Figure 1: Ultraviolet- Spectra of pure Eletriptan hydrobromide in water

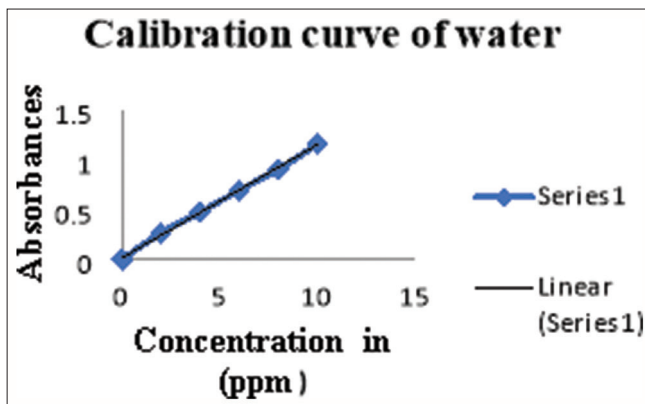


Figure 2: Calibration curve of eletriptan hydrobromide water

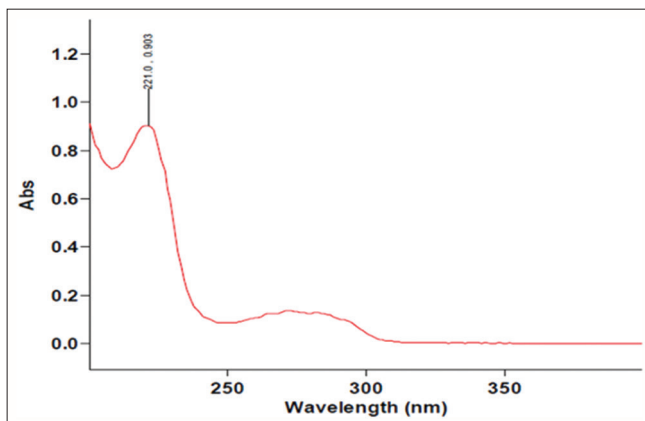


Figure 3: Ultraviolet- spectra of pure eletriptan hydrobromide in Phosphate buffer pH-5

small, the drug will be absorbed rapidly through the aqueous path of the membrane.<sup>[9,10]</sup>

In general, a migraine is a very bad headache that tends to come back. It may occur as often as several times a week or only once every few years. A migraine headache is thought to be caused by widened blood vessel exerting pressure on the brain. In migraine, patients experience one or more short-lived attacks of intense headache, usually at the same time every day and often at night, and are usually of sufficient severity to disturb or prevent daily activities. It can last anywhere

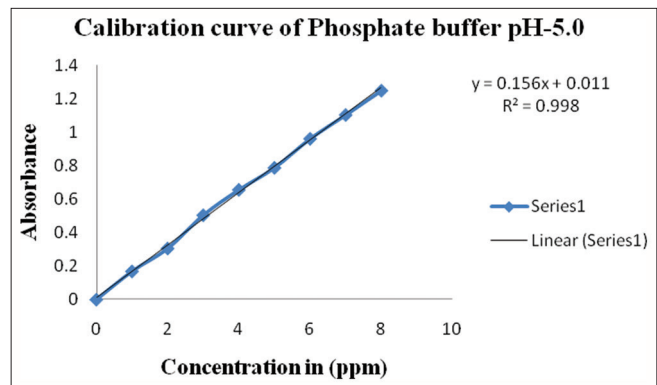


Figure 4: Calibration curve of phosphate buffer pH 5.0

from a few hours to 3 days.<sup>[11-13]</sup> The pain usually begins in the morning, on one side of the head. Less frequently, the entire head is swallowed up by pain Migraine headache afflicts 10–20% of the population, producing a morbidity estimated at 64 million missed workdays per year in the US. Although migraine is a specific neurological syndrome, the manifestations vary widely. The frequency of migraine attacks is extremely variable but usually ranges from 1 to 2 a year to 1–4 per month The therapy of migraine headaches IS complicated by the variable responses among and within individual patients and by the lack of a firm understanding of the pathophysiology of the syndrome.<sup>[14-17]</sup> The goal of current work was to formulate Eletriptan Hydrobromide used for the treatment of migraine in *in situ* gel form by a nasal route.

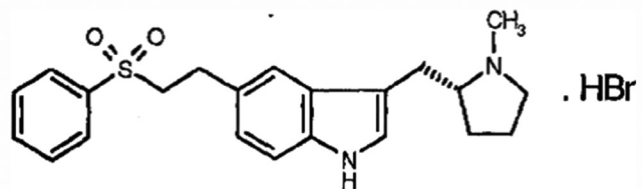
## MATERIALS AND METHODS

### Materials

Eletriptan hydrobromide was obtained as a sample from Mylan Pharmaceuticals, Nashik, India Poloxamer 188, poloxamer 407 where purchase from BASF, Mumbai, India. Polyethylene glycol (PEG) was purchased from Research Laboratory, Mumbai, India.

### Method of preparation

The thermosensitive *in situ* gel systems were prepared by cold method described by (Schmolka, 1972). Briefly, Eletriptan hydrobromide, Poloxamer-188, and PEG 6000 were stirred in distilled water at room temperature until all of them completely dissolved. The mixture, together with the container, was then put into ice bath followed by addition of Poloxamer-407 into the mixture. The final transparent solution was stored at 4°C for further Evaluations.<sup>[18-20]</sup>



**Table 1:** Absorbance's of eletriptan hydrobromide in water

Sr. No.	Concentration ( $\mu\text{g/mL}$ )	Absorbance
1	2	0.2722
2	4	0.4782
3	6	0.6970
4	8	0.9045
5	10	1.1613

**Table 2:** Absorbance of eletriptan hydrobromide in phosphate buffer pH-

Sr. No.	Concentration ( $\mu\text{g/mL}$ )	Absorbance
1	1	0.1686
2	2	0.3053
3	3	0.5038
4	4	0.6555
5	5	0.7872
6	6	0.9603
7	7	1.1024
8	8	1.2476

## Structure of eletriptan hydrobromide

### Characterization

The sample of Eletriptan hydrobromide was studied for organoleptic properties such as color, odor, and appearance. The melting point of Eletriptan hydrobromide was determined by capillary method by using melting point apparatus.<sup>[21,22]</sup>

### Determination of solubility

The solubility of Eletriptan hydrobromide was determined by adding excess amount drug in Solvent at room temperature and occasional shaking for 24 h. Equilibrium solubility was determined by taking supernatant and analysing it by using Ultraviolet (UV) double beam spectrophotometer (Agilent UV carry 60).

### Fourier transform infra-red (FTIR) analysis

FTIR spectroscopy of Poloxamer 407, Poloxamer 188, pure Eletriptan hydrobromide, Optimized nasal *in situ* gel containing Eletriptan hydrobromide was performed to ana lyse excipient drug interaction. Samples were finely powdered and analyzed as KBr pellets by using a FTIR Spectroscope (IR Affinity 1). The pellet was placed in the

**Table 3:** Interpretation of elepritation hydrobromide

Sample	Obtained peak value ( $\text{cm}^{-1}$ )	Actual wave no. ( $\text{cm}^{-1}$ )	Bond	Characteristics functional group
Eletriptan Hydrobromide	3470	3500–3300	N-H stretch	Amines
	2973	3030–2950	C-H stretch	Alkane
	1646	1680–1620	C = C stretch	Alkene
	1138	1200–1025	C-N stretch	Alkyl
	806	850–700	C-C stretch	Aromatic

**Table 4:** Evaluation parameter of optimized batch

Batch	Clarity	pH	Sol-gel transition ( $^{\circ}\text{C}$ )	Drug content (%)
F1	Clear solution	6.3	-	54.32
F2		5.9	30–32	52.39
F3		5.4	30–32	51.26
F4		6.1	32–34	54.88
F5		5.8	32–34	49.69
F6		5.8	32–34	57.31
F7		6.1	32–34	56.87
F8		6.3	-	44.32
F9		5.7	32–34	55.46
F10		5.5	28–30	61.42
F11		5.6	30–32	63.21
F12		6.0	-	59.34
F13		6.2	32–34	56.96
F14		6.1	30–32	65.50

**Table 5: Viscosity at 4°C**

RPM (ascending order)	4°C	RPM (descending order)	4°C
	Viscosity (cp)		Viscosity (cp)
1	-	10	-
2	78	6	7
3	38	5	8
4	22	4	27
5	13	3	40
6	8	2	78
10	-	1	-

**Table 6: Viscosity at 34°C**

RPM (ascending order)	34°C	RPM (descending order)	34°C
	Viscosity (cp)		Viscosity (cp)
1	150	10	3.6
2	114	6	11
3	40	5	14
4	37	4	28
5	13	3	40
6	12	2	90
10	3	1	147

**Table 7: *In vitro* % drug release**

Time (h)	% drug release
1	45.238
2	64.644
3	76.550
4	86.127

**Table 8: *Ex vivo* % drug release**

Time (h)	% drug release
1	26.939
2	37.104
3	51.580
4	70.446

**Table 9: *In vivo* best-fitted model for drug release kinetics of optimized**

Sr. no.	Model	R <sup>2</sup> values
1	Zero	0.967
2	First	0.116
3	Higuchi	0.005
4	Korsmever-peppas	0.000

sample holder. Spectral Scanning was taken in wavenumber region between 4000 and 600 cm<sup>-1</sup> at resolution of 4 (cm<sup>-1</sup>) with 1 cm/s Scan speed.

### UV spectroscopy

The standard solution (100 µg/mL) of pure drug was prepared in water. The prepared solution was scanned between 400 and 200 nm by UV-Visible double-beam spectrophotometer (Agilent, UV carry 60).<sup>[12,23]</sup>

### Characterization of polymers

#### Identification of polymers

Poloxamer 407, Poloxamer 188, PG-6000 was subjected to Determination of organoleptic properties, melting point, and FTIR spectroscopy as mentioned in pre-formulation study of the drug.

#### FTIR analysis

Infra-red spectroscopic analysis was performed by FTIR Spectrophotometer (Agilent Technologic), with a resolution of 4 cm<sup>-1</sup>, in the range of 4000–600 cm<sup>-1</sup>.

### Evaluation of formulation

#### Clarity

The clarity of *in situ* gel was examined by visually against dark background.

#### pH of the gel

The normal range of nasal mucosal pH is 6.2–7.0 pH. The advisable pH of the formulation is in the range of 5.5–7. Each formulation of nasal *in situ* gel, was n 1 mL quantity of formulation and transferred into a different beaker and diluted it with distilled water up to 25 mL and then pH of each formulation was determined using pH dis meter (Table 4). **AQI**

#### Measurement of sol-gel transition temperature

It was determined using method described by Miller and Donovan technique. A 2 mL aliquot of solution was transferred to a test tube and immersed in a water bath. The temperature of water bath was increased slowly. The sample was then examined for gelation, which was said to have occurred when the meniscus would no longer moves on tilting through 90°C.

#### Drug content

Drug content was determined by taking 1 mL of formulation in 10-mL volumetric flask and then it was diluted with 10 mL of distilled water then volume adjusted to 10 mL, 1 mL from this solution again diluted with distilled water up to 10 mL (Table 4). After this absorbance of prepared solution, it was

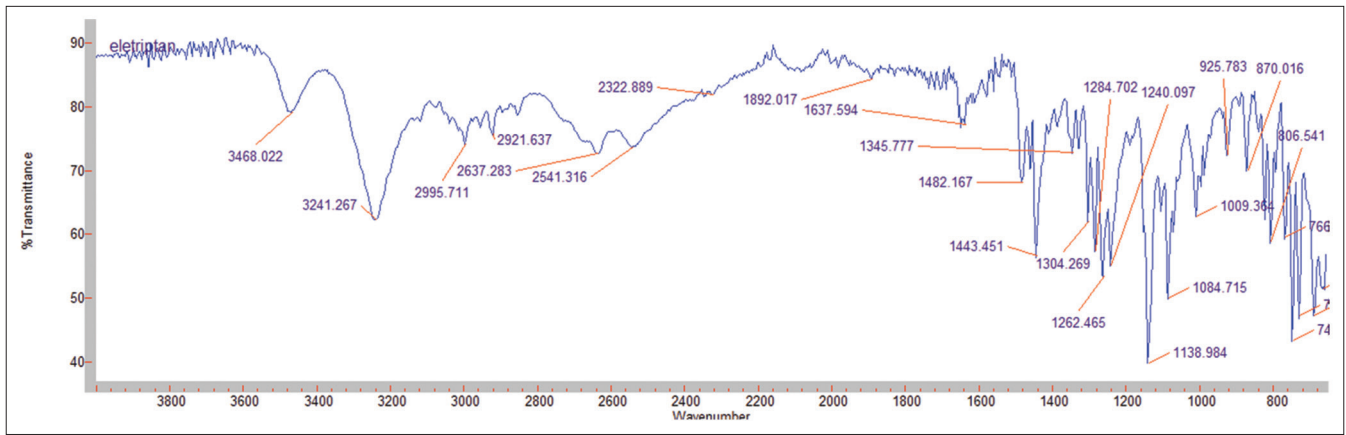


Figure 5: Fourier transform infra-red spectrum of pure eletriptan hydrobromide

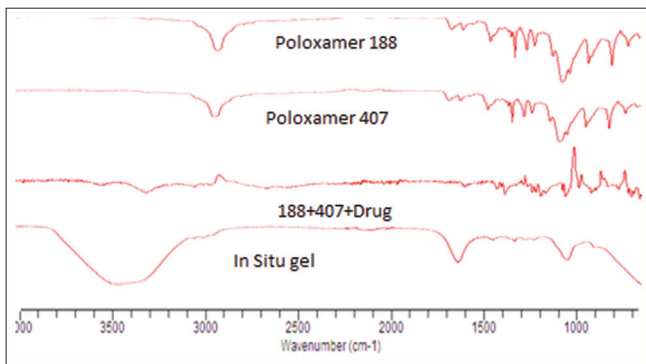


Figure 6: Fourier transform infra-red study

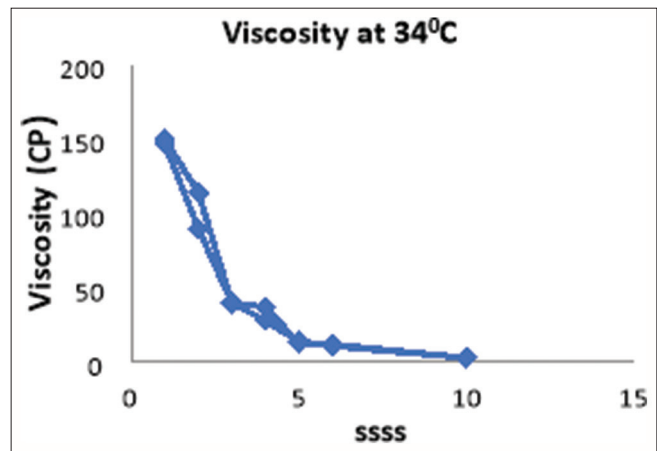


Figure 8: Graph of viscosity at 34°C

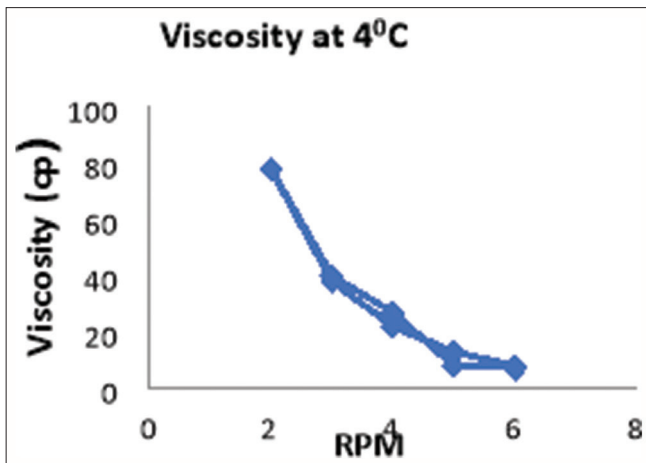


Figure 7: Graph of viscosity at 4°C

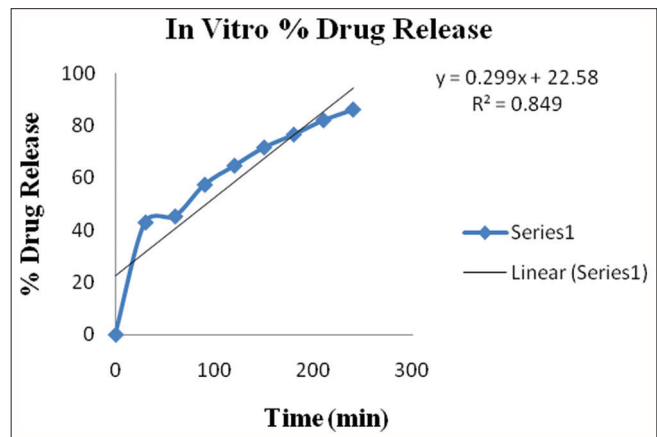


Figure 9: *In vitro* % drug release of nasal *in situ* gel

measured at particular wavelength of the drug using U.V visible spectrophotometer.

### Viscosity studies

Viscosity of nasal *in situ* gel was measured by using Brookfield dv2<sup>nd</sup> model viscometer. The gel was exposed to spindle (S-61), rotated at various speed ranging from 1 to 10 rpm. The apparent viscosity values of studied gels were carried out at 4 10°C and 37 + 10°C temperatures (Figure 7,8 and Tables 5,6).

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### Determination of gel strength

Gel strength was measured by dropping Iron ball (6 mm diameter and 1.045 g weight) on the surface of preformed gel (5 mL) in a 10 mL measuring cylinder. The distance traveled by ball for specific period of time was measured (Table 4).



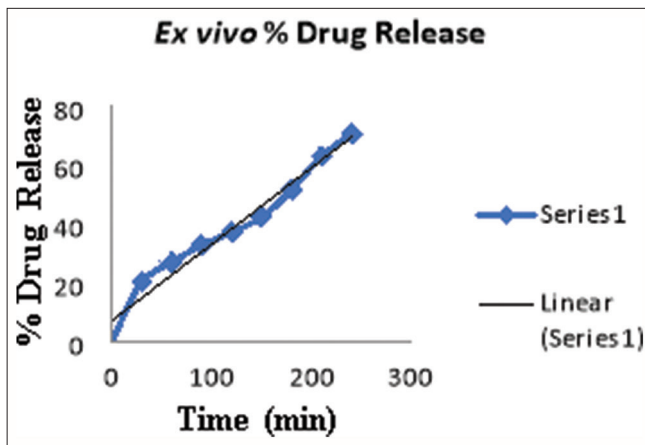


Figure 10: Ex vivo % drug release

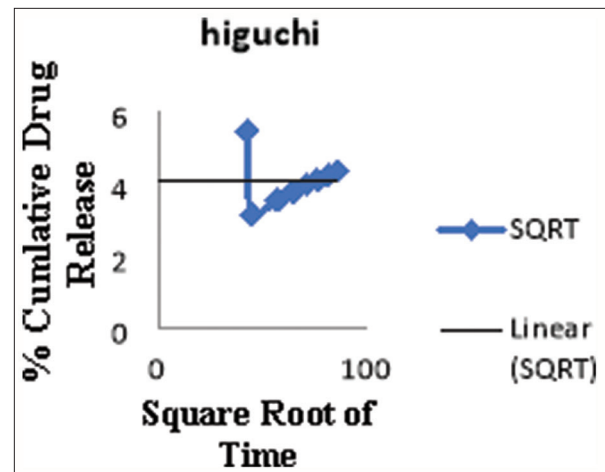


Figure 13: Higuchi order drug release

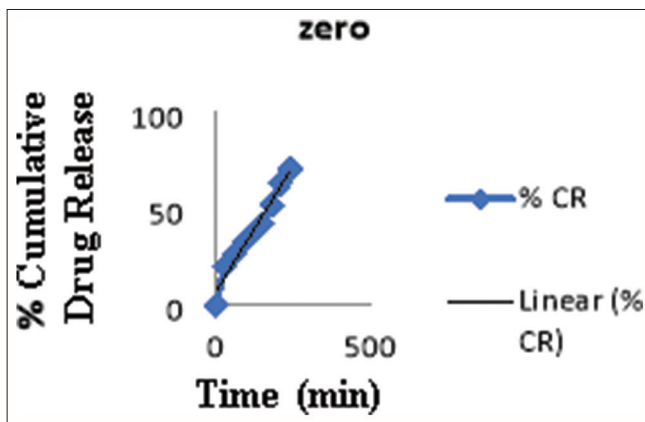


Figure 11: Zero order drug release

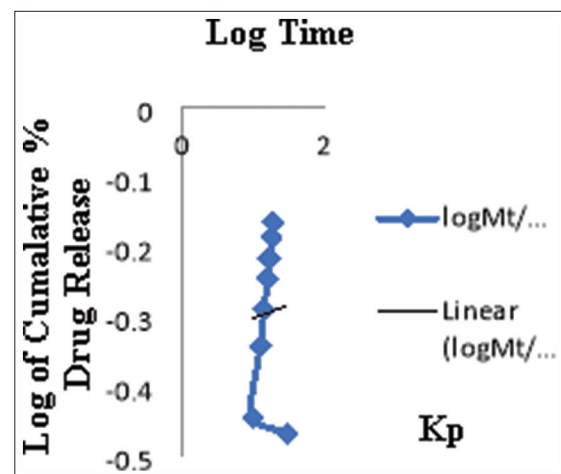


Figure 14: Kp order drug release

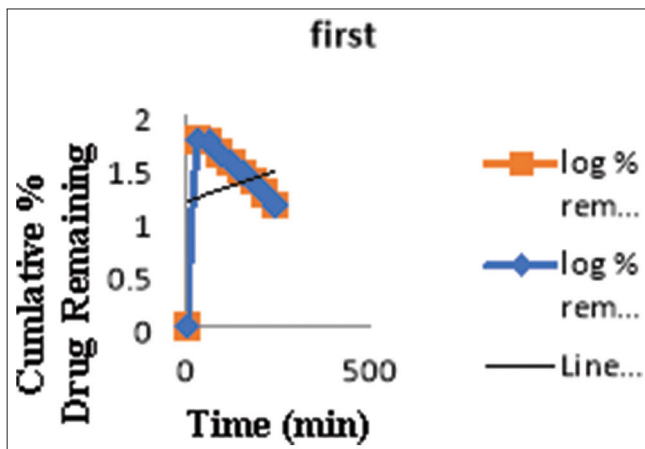


Figure 12: First order drug release

### *In vitro* diffusion study of *in situ* gel

Franz diffusion cell having capacity of 2.4 diameter and 15 mL diffusion cell was used for *in vitro* diffusion study of *in situ* gel. Dialysis (22  $\mu$ m pore size) or cellophane membrane (12000–18000 mol wt.) with diffusion area 8 cm<sup>2</sup> was used. 60 mL of phosphate buffer (pH 5) was prepared and membrane was soaked with phosphate buffer (pH 5), after this temperature was maintained at 37°C–0.5°C phosphate buffer placed into

the receiver chamber, and gel containing drug equivalent to 20 mg was placed in donor chamber, At predetermined time interval, 1 mL sample was withdrawn from receiver chamber and then replaced the sample volume with equal amount of phosphate buffer after each sampling process, for a period of 300 min, after each sampling, the samples were suitably diluted and measured spectrophotometric ally at specific wavelength of drug. The concentration of drug was determined with the help of previous calibration curve.

### *In vitro* permeation study of *in situ* gel

To check permeation of drug and efficiency of permeation enhancer, it was added into formulation. Fresh nasal tissue section of goat obtains from slaughter house. Tissue was inserted in the diffusion cell. Gel containing drug equivalent to 20 mg was placed in donor chamber, at predetermined time point, 1 ml of sample was withdrawn from acceptor chamber and replacing the sampled volume with same amount of phosphate buffer for 300 min, after each sample, the sample was suitably diluted and measured using UV-visible spectrophotometrically at specific wavelength of drug.

## RESULTS AND DISCUSSION

### Pre-formulation study<sup>[24]</sup>

#### Characterization of eletriptan hydrobromide

Eletriptan hydrobromide was studied for characteristics such as color and nature. As shown in table, results of characteristics of drug of received sample were found to be similar as mentioned in literature. So that the received sample of Eletriptan hydrobromide is in pure state and authentic.

Color – White

Nature – Crystalline powder.

#### Solubility of drug

The drug was freely soluble in water ethanol and Phosphate buffer pH-5.

#### Melting point of drug

The melting point of the drug matches with the values found in literature. Melting point of Eletriptan hydrobromide is given in table. So that the received sample of Eletriptan hydrobromide is in pure state and authentic.

Literature	Practical
169–171°C	168–170°C

### UV-spectroscopic analysis

#### Determination of $\lambda$ max of eletriptan hydrobromide in water

Determination standard solution (100 ug/mL) of pure drug (Eletriptan hydrobromide) was prepared in water. The prepared solution was scanned between 400 and 200 nm by UV-visible spectrophotometer (Agilent UV carry-60) (Figure 1).

#### Preparation of calibration curve of eletriptan hydrobromide

Calibration curve is given below,  $Y = mx + C$ .

The calibration curve eletriptan was prepared in water. The straight line obtained in the water had a regression coefficient of 0.998. Linearity was found in the concentration range of 2–10  $\mu\text{g/mL}$ .

Therefore, the obtained equation was as follows,

**AQI**  $Y = 0.226 \times 0.019$  (water) (Figure 2 and **Table 1**).

#### Determination of A max of eletriptan hydrobromide in phosphate buffer pH-5

The standard solution (100 ug/mL) of pure drug (Eletriptan hydrobromide) was prepared in water. The prepared solution

was scanned between 400 and 200 nm by UV visible spectrophotometer (Agilent UV carry-60).

The calibration curve eletriptan was prepared in water. Eletriptan Hydrobromide showed maximum absorption at wavelength 221 nm. The straight line obtained in the water had a regression coefficient of 0.998. Linearity was found in the concentration range of 1–8  $\mu\text{g/mL}$ . Therefore, the obtained equation was as follows,

$Y = 0.156x + 0.011$  (Phosphate buffer pH-5) (Figures 3,4 and Table 2).

#### FTIR studies

The FTIR studies were done to analyze interaction of drug and polymer. FT IR spectra of drug, polymer, and nasal *in situ* gel of drug with polymer were determined. The estimated tables illustrate principle peak value with corresponding functional group. Thus, it can also conclude that there was no chemical interaction between the drug and polymer (Figures 5,6 and **Table 3**).

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### Evaluation of nasal *in situ* gel

#### Viscosity studies

Viscosity was done of optimized batch F14 at 4°C and 37°C using the Brookfield viscometer spindle number 61 (Figures 7,8 and Tables 5,6) .

#### Diffusion study

##### *In vitro* study using cellophane membrane

The *in vitro* drug release studies were carried out for all formulated of *situ* gel nasal in containing Eletriptan Hydrobromide in phosphate buffer pH 5.0. All batches showed prolong sustained release of Eletriptan Hydrobromide over 4 h. The Cumulative drug release from these nasal *in situ* gel containing Eletriptan Hydrobromide was within the range of 42.92–86.12% 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 Eletriptan Hydrobromide was not only affected by Poloxamer concentration but also by the type of bio adhesive used. The bio adhesive polymer retarded the drug release from nasal gel, the retarding effect of the bio adhesive polymers could be attributed to their ability to increase the overall product viscosity as well their ability to distort or squeeze the extra micellar aqueous channels of Poloxamer micelles through which the drug diffuses thereby delaying the release process (Figure 9, Table 7).

##### *In vivo* study using nasal mucus membrane of goat

*In vivo* drug release carried out of only optimized batch (F14) using nasal mucosa of goat. The cumulative drug release from

these nasal *in-situ* gels containing Eletriptan Hydrobromide was 70.44% and sustained drug release from nasal *in situ* gel (Figure 10, Table 8).

### Data treatment for *in vivo* study

#### Determination of best fit model for drug release kinetics of optimized formulation

The diffusion kinetics of optimized batch was applied to various diffusion models such as Zero order, First order, Higuchi, Kors Meyer-Pappas. The best-fitted model gives the highest R<sup>2</sup> value. Thus, zero model fits best for the diffusion data of the optimized formulation as it showed the highest value for R (0.967) (Figures 11-14 and Table 9).

#### Stability studies

Optimized formulation was subjected to stability studies as per ICH guidelines. Various parameters such as drug content, and *in vitro* drug release were measured before and after 30, 60, 90 days of stability. Results of stability studies are shown in following table. Results of stability studies showed there is no significant change in above-mentioned parameter after elevated temperature and humidity condition during stability studies. Thus, it can be proved from the stability studies that the prepared formulation is stable and not much affected by elevated humidity and temperature conditions.

## CONCLUSION

From the above experimental work, it can be concluded that the cold method technique is found to best suitable method for preparation of Eletriptan hydrobromide *in situ* gel. Prepared *in situ* gel showed good entrapment efficiency with optimum drug release. Outcome of study concluded that Poloxamer can be employed as thermosensitive polymer for nasal drug delivery system. Addition of mucoadhesive to the solution increases the viscosity and there by increases mucoadhesive strength of the formed gel. On application of nasal *in situ* gel, the formulation is strength believed to form gel prolonged effect of Eletriptan hydrobromide for migraine attacks. The FTIR studies revealed that, there was no, inter interaction between polymers and drug. Polymer and drug have no incompatibility. The formulation also retained the good stability at accelerated condition over the period of 90 days.

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Author query???

AQ1: Kindly cite tables 1-6 citations in chronological order.