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Formulation and characterization of intranasal mucoadhesive gel of Rizatriptan

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Abstract

The *in situ* intranasal gel delivery system loaded with rizatriptan was prepared using cold stirring method and evaluated for various parameter. The drug-excipient interaction was studied using FT-IR spectroscopy and no incompatibility was found between rizatriptan and the polymers (poloxamer 407 and carbopol 934). The concentration of poloxamer 407 to be used was optimized by gelation temperature study and it was found that 18% w/v of the same was able to gellify at temperature equivalent to the nasal temperature. Formulations with increasing concentration of carbopol 934 were prepared and evaluated. The higher concentration of carbopol 934 increased the gel characteristics so much that they may not be pleasant for administration. The pH of all the formulations ranged from 6.0 to 6.4, viscosity of the sol ranged between 29 to 82 cps while that of the *in situ* gel ranged between 110 to 211 cps. The drug content ranged from 92.9 to 94.9 %. The flow curve of the formulations indicated that for the all the polymer concentrations, the formulations exhibited the properties of pseudoplastic systems with shear thinning. The *in vitro* release studies of different formulations of drug loaded *in situ* gels were carried out for 20 min in PBS pH 7.2. The maximum drug release from the formulations ranged from 77.1 to 96.7 % over the duration of *in vitro* release study.

Keywords

Intranasal, rizatriptan, pseudoplastic, gelation, poloxamer

Introduction

Migraine is a highly disabling primary headache disorder with a 1-year prevalence of ~15% in the general population[1,2] with prevalence of 20% in female and 8% in male. According to the Global Burden of Disease Study, migraine is the second most prevalent neurological disorder worldwide and is responsible for more disability than all other neurological disorders combined[3]. Migraine manifests clinically as recurrent attacks of headache with a range of accompanying symptoms. Treatments for migraine include acute and preventive medications and a range

of non-pharmacological therapies10. The medications include the use of triptans, ergot alkaloids, anti-emetics like metoclopramide (adjunt therapy), NSAIDs and tramadol. The more recent introduction of intranasal delivery systems for antimigraine drugs has added another therapeutic choice to the existing armamentarium[4]. The clinical rationale for the development of intranasal therapies for migraine was based on factors relating to both the pharmacokinetics of the intranasal route of administration and the physiology of migraine, as well as on considerations related to patient convenience and acceptability[5]. Rizatriptan is 5HT1 receptor agonist widely used for the treatment of migraine and cluster headache. Rizatriptan undergo extensive first pass metabolism with an oral bioavailability of 45% and approximately 14% of an oral dose is excreted in urine unchanged[6]. Direct transport of drug to the central nervous system via the olfactory nerve permits entry into the brain of certain drugs that are normally excluded by the blood-brain barrier[5].

It was therefore hypothesized that utilizing the intranasal mucoadhesive route for delivery of Rizatriptan may be able to overcome the first pass metabolism and increase the bioavailability of the drug.

Material and Methods

Rizatriptan was purchased from Yarrow Pharmaceuticals, Mumbai; Poloxamer 407 from Sigma Aldrich and Carbopol 934P from Oxford Fine Chemicals, Mumbai.

Preformulation Studies[7]

The preformulation studies were carried out for confirming the identity of the drug and to ascertain the compatibility amongst the drug and the excipient (polymers) used in formulation. FTIR of physical mixture of the drug and the used polymers was also performed to observe to any possible interaction between the drugs and excipients (Carbopol 934, poloxamer 407). Calibration curve of rizatriptan was prepared at concentrations 2 to 12 µg/mL in distilled water and phosphate buffer pH 7.2 by measuring the absorbance at 243 nm by UV-Visible spectrophotometer[8].

Determination of gelation temperature

Temperature at which the liquid (sol) phase converts to gel form is termed as gelation temperature. The sol–gel transition temperature of the prepared *in-situ* gel formulations was determined by visual inspection method[9]. Briefly, the solutions of poloxamer 407 in the concentrations (15–20 % w/v) were prepared by stirring on a magnetic stirrer in a transparent 10 ml glass bottle sealed with paraffin. The vial was heated at constant rate with an increment of 1°C and the temperature at which the magnetic bead stopped moving due to gelation was considered as gelation temperature. Gels which showed gelation temperature very close to nasal temperature (32-34°C) were selected for further evaluation. Effect of Carbopol 934 on phase transition temperature was evaluated by dispersing different concentration (0.1–0.5 % w/v) in optimized poloxamer 407 solutions.

Formulation of *in situ* nasal gel

Poloxamer 407 gel was prepared by dissolving the optimized poloxamer 407 concentration in cold (4°C) water. The hazy solution formed was kept in refrigerator (2–4°C) overnight for complete dissolution resulting in a clear solution. Carbopol 934 (0.1 to 0.4 % w/v) concentration was added slowly to the optimized poloxamer 407 solution[10] containing drug with continuous stirring at 4°C (Table 1). Formulated gels where then finally stored at 4°C for further evaluation.

Table 1 Composition of intranasal gel formulations

Formulation Code	Drug (% w/v)	Poloxamer 407 (%w/v)	Carbopol 934 (%w/v)
RNS	Pure drug solution (0.5%)	--	--
RNG	0.5	18	--
RNGF1	0.5	18	0.1
RNGF2	0.5	18	0.2
RNGF3	0.5	18	0.3
RNGF4	0.5	18	0.4
RNGF5	0.5	18	0.5

Evaluation of the gel formulations[11]

Determination of pH

The pH of each formulation was determined by pH meter. Initially, the pH meter was calibrated using standard buffer solutions of pH 4 and pH. 1 mL of the formulation was diluted with distilled water and the pH of the solution was recorded by dipping the electrode in the solution.

Clarity testing

The clarity was checked visually by viewing the formulation alternately against white and black background and was graded as turbid (+), clear (++) and very clear (+++).

Drug content

Drug content was determined spectrophometrically using UV at 243 nm. 1 mL of the formulation was dissolved in 10 mL PBS 6.8 and suitably diluted. The absorbance of the resulting dilution was recorded on UV spectrophotometer.

Viscosity Determination

Viscosity of *insitu* gel system was determined using Brook field viscometer DV-1. Temperature of 37±0.5ºC was maintained and the spindle was lowered perpendicularly into both *insitu* sol and gel formulations which were placed in a beaker. The viscosity of each formulation was determined by applying 100rpmspeed.

Rheological Studies

The measurement of viscosity of prepared *insitu* gel was done with Brookfield viscometer. The *insitu* formulations were rotated for 2 minutes at different speeds (10-100 rpm) for selected spindle. At each speed the corresponding dial reading was noted. The viscosity of different *insitu* gel formulations was measured at different speeds at room temperature.

Gel Strength

Gel strength was determined by placing a standard weight of 35 g onto 50 g of thermoreversible gel (placed in 100 ml beaker) maintained at gelation temperature using controlled water bath. The time in seconds by the weight to penetrate 5 cm deep into the container was recorded as gel strength.

***In-vitro* drug release study**

Drug release from gel was determined by using Franz diffusion cell. Artificial dialysis membranes were soaked in receptor medium for 2h prior to use. Phosphate buffer saline (12 ml) pH 7.2 was added into the receptor chamber maintained at 34 ± 1°C. Gel equivalent to 2.5mg of drug was placed into donor compartment and the setup was kept on stirring. Aliquots of 1ml were withdrawn at predetermined time intervals from receptor compartment and replaced with fresh buffer till 12 h. The samples were diluted suitably and analyzed spectrophotometrically at 243 nm and the amount of drug released was determined using calibration curve.

Stability Study

Stability studies of the formulations were carried out at 40 ± 2°C, 75 ± 5% RH at an interval of one month for 3 consecutive months. The results were compared with respect to gelation temperature, pH, viscosity, drug content and drug release to indicate stability for optimized formulation[12].

Results and Discussion

Rizatriptan was off-white in color with no odor and a melting point of 178-180°C. The data was in tandem with the reported properties of the drug[13]. The calibration curve was prepared in distilled water as well as phosphate buffer pH 7.2 (Figure 1a, 1b).

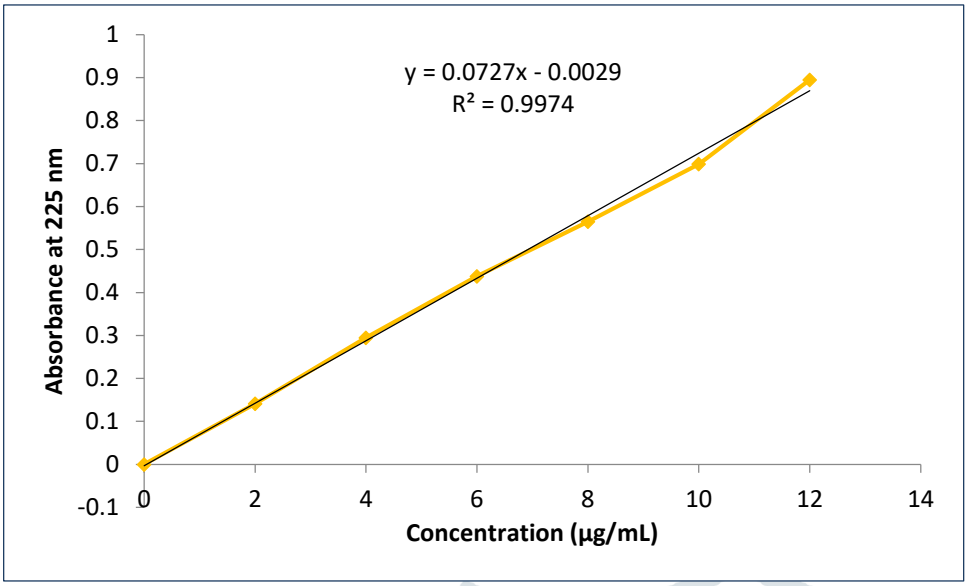

Figure 1a. Calibration curve of rizatriptan in distilled water

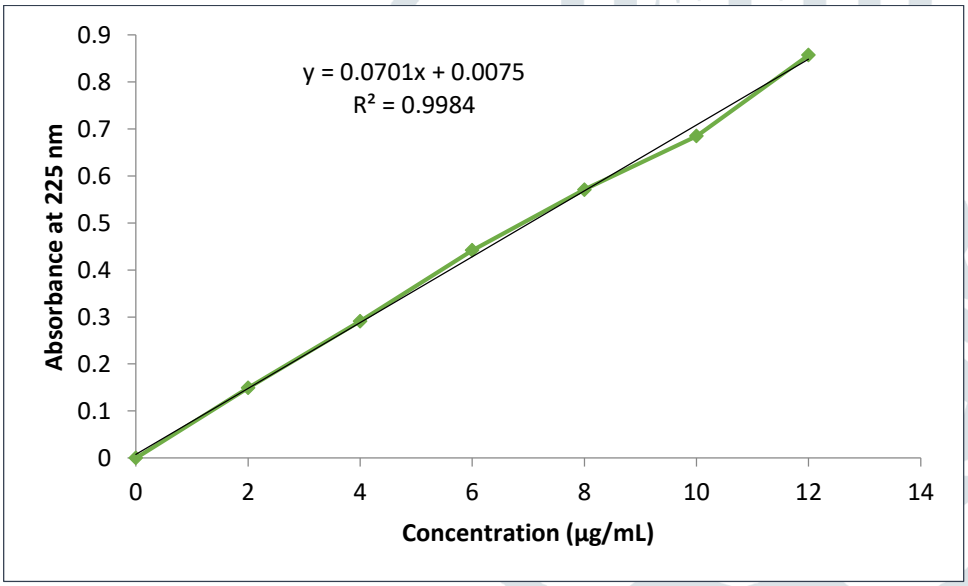

Figure 1b. Calibration curve of rizatriptan in phosphate buffer pH 7.2

The FT-IR spectra exhibits the major peaks of the functional groups present in Rizatriptan. All these peaks were observed in the FT-IR spectra of the physical mixture of drug and excipients also providing evidence for the absence of any chemical incompatibility between pure drugs with the excipients.

Determination of gelation temperature

Phase transition temperature determination is a preliminary step in the formulation of the *in situ* gel. Gelation temperature of gel formulations suggests that Poloxamer in the concentration of 18% w/v showed best results for phase transition at 32-34°C. As the concentration of poloxamer increased from 18 to 20 %, transition temperature decreased from 34 to 25 °C.

The addition of carbopol 934 also affected the gelation behaviour of the formulations. The effect of varying concentration of carbopol 934 on gelation temperature revealed that all the formulations were able to transform to gel form at temperature from 25-32°C. Increasing the concentration of carbopol 934 led to a decrease in gelation temperature of the formulations (Figure 2). A concentration of 0.4% and higher of carbopol 934 decreased the gelation temperature to 25°C making the concentrations unsuitable for *in situ* intranasal gel delivery.

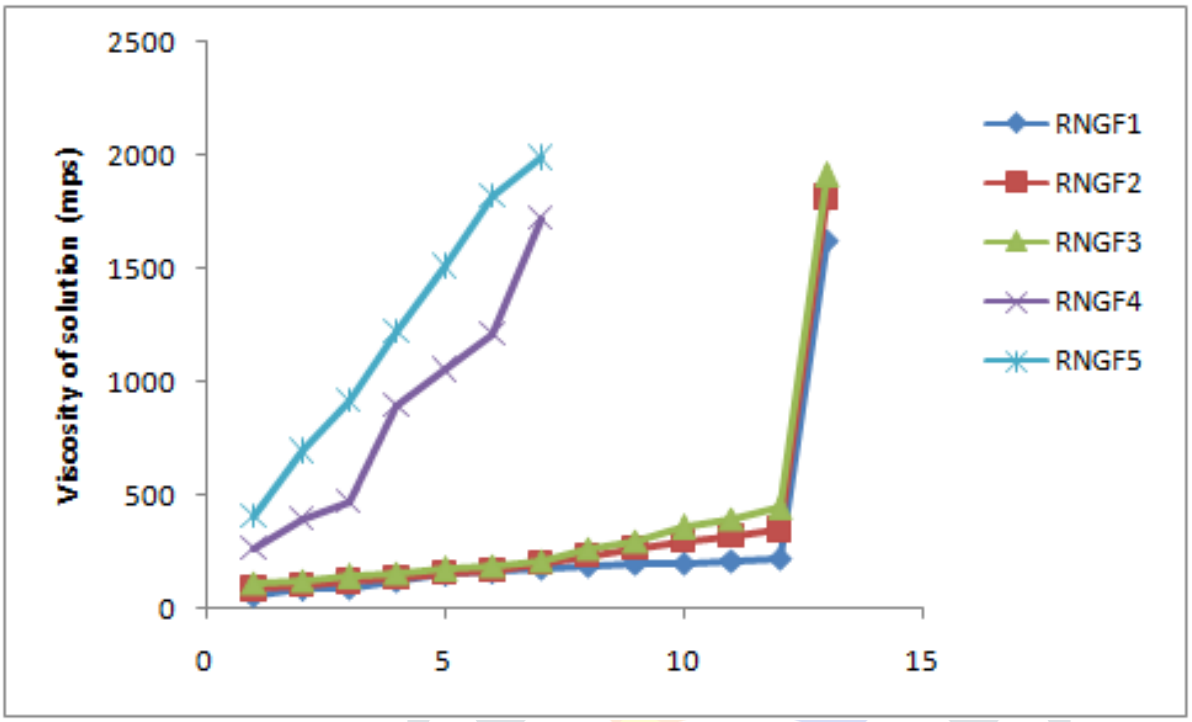

Figure 2 Effect of carbopol 934 on gelation temperature

Evaluation of the gel formulations

The pH of all the formulations was found to be between 5.9 to 6.3 which lies in the range of nasal pH (5.5 to 6.5). This ascertains that all the formulations are compatible with nasal mucosa. The formulations RNGF1, RNGF2 and RNGF3 were found to be clear while RNGF4 and RNGF5 were turbid in appearance revealing that clarity of the gel is inversely proportional to the concentration of Carbopol. The results of pH, clarity, drug content, viscosity, gelling time and gel strength are presented in Table 2.

Table 2 Physicochemical properties of the *in situ* gel formulations

Formulation code	pH	Clarity	Drug content (%)	Viscosity (cps)		Gel Strength (g)	Gelling time (sec)
				Sol	Gel		
RNGF1	6	+++	92.9	29	110	5.4	15
RNGF2	6.2	++	93.4	37	124	6.7	12
RNGF3	6.2	++	94.3	49	171	7.3	9

RNGF4	6.4	+	94.1	61	187	8.4	5
RNGF5	6.3	+	94.9	82	211	8.8	4

Viscosity of the both *insitu* sol and *insitu* gel was examined at 100 rpm. RNGF5 formulation was having maximum viscosity. The viscosity of RNGF3 (49 in sol to 171 in gel) was taken as optimum. Viscosity of the sol formulation ranged between 29 to 82 cps while that of the *insitu* gel ranged between 110 to 211 cps.

Rheological Studies

Rheological behaviour study is an important parameter for the *in situ* gels. The viscosity of formulations should be in an optimum range which improves its ease of administration. The flow curve (viscosity against speed / rpm) of the formulations indicated that for the all the polymer concentrations, the formulations exhbited the properties of pseudoplastic systems with shear thinning. The prepared formulations tend to thin when being exposed to shearing force and therefore tend to be easily syringeable and spreadable. The effect of agitation speed on viscosity is presented in Figure 3.

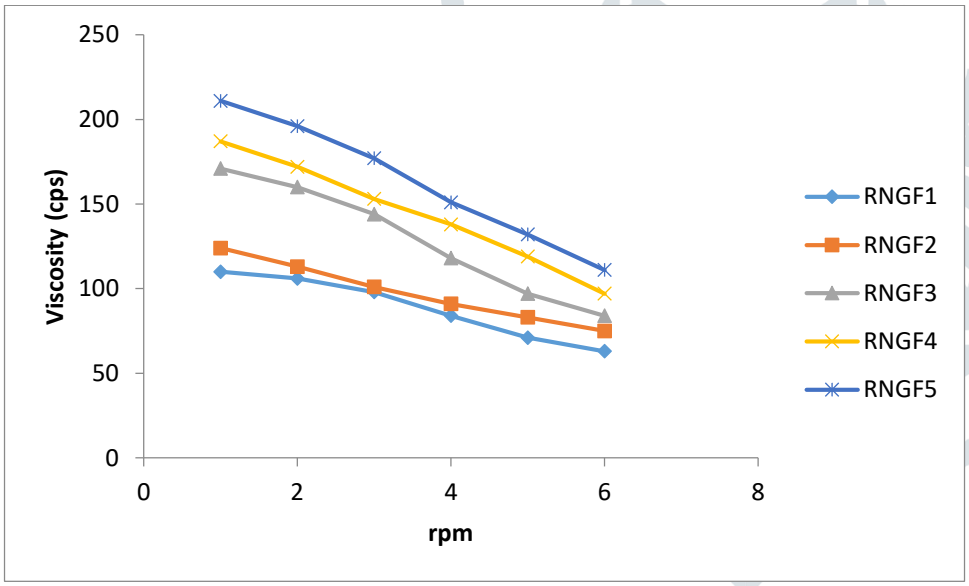

Figure 3 Rheological behaviour of *in situ* gel

***In vitro* drug release from *in situ* gel**

The *in vitro* release studies of different formulations of drug loaded *in situ* gels were carried out for 20 min in PBS pH 7.2. PBS of pH 7.2 was selected as medium for drug absorbance since it resembles nasal pH. Throughout the study the pH and temperature were kept constant. The maximum release was found to be for RNGF2 and RNGF3 with respective release of 94.1 and 94.9%. The polymer concentration plays a vital role in release pattern of drug.

The release of drug mainly depends on the polymer concentration. Polymer concentration was proportional to release to some extent. It was seen that very low concentration of carbopol 934 resulted in very quick release of the drug from the formulation making it unpleasant for administration. Also, it was observed that too high concentration of the polymer can adversely affect the *in vitro* release as in formulation RNGF4 and RNGF5. The RNGF3 formulation was showing highest percentage release and was regarded as the optimised formulation. The result of drug release over time has been presented in Figure 4.

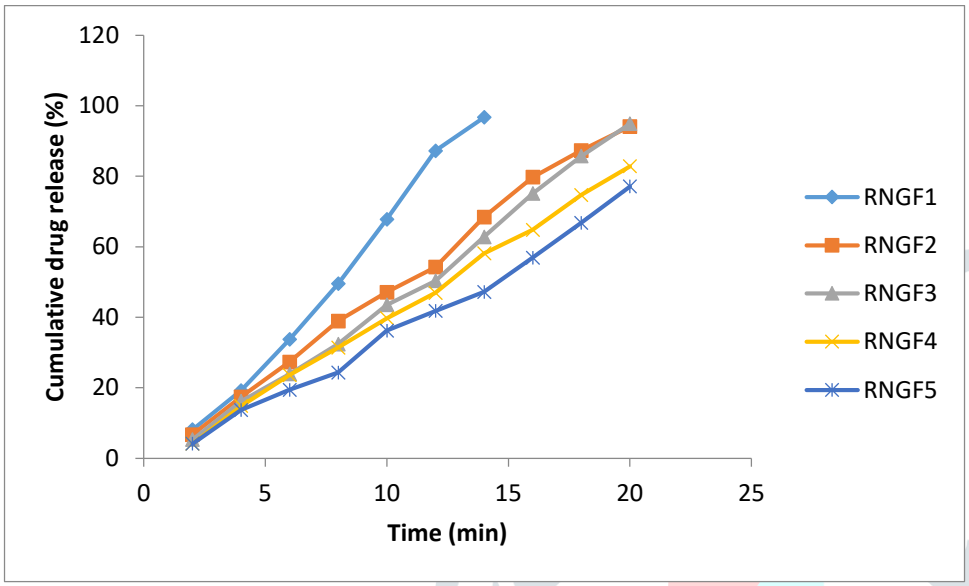

Figure 4 Comparative drug release profile from the formulations

Stability study

Stability studies (ICH guideline Q1A (R2)) of gel formulations were performed with respect to determining factors like gelation temperature, pH, viscosity, drug content and drug release. The analysis after 1, 2 and 3 months exhibited no significant change in all determining factors suggesting stability of gel formulations.

Conclusion

The present study represents formulation of *in situ* intranasal gel for rizatriptan using poloxamer 407 and carbopol 934. Formulation (RNGF3) was found to be optimized due to its desirable gelation temperature, gelling time and gel strength. *In-vitro* release studies suggests that carbopol not only acts as mucoadhesive agent but also as an penetration enhancer where as poloxamer acts as thermoreversible polymer leading to sustained release of drug for longer time. In conclusion, intranasal gel of rizatriptan could be better alternative to existing conventional dosage form to improve drug bioavailability and patient compliance.

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