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Formulation And Development Of Nasal In-Situ Gel Of Rizatriptan For Treatment Of Migraine

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Abstract

Rizatriptan is a selective 5-HT1B and 5-HT1D receptor agonist that is used to treat migraines. As the plasma half- life of rizatriptan is 2-3 hrs. There is need to increase its bioavailability by incorporating it in suitable drug delivery system. Nasal in situ gel drug delivery systems have ability to directly target the central nervous system while avoiding the blood-brain. Thus this study aims at formulation and development of nasal in-situ gel of rizatriptan for treatment of migraine. Formulation and evaluation of rizatriptan was performed according to standard protocol. Results showed that all the formulations of in situ gel was observed to be transparent. The clarity of gel was observed from F1-F4 while in case of F5 and F6 the gel turned out to be slightly hazy. All the fromulations were viscous as the gel should be without absence of any specific odor. The viscosity among the solution ranged from 936 to 1325 cps while in case of gel the viscocity spanned from 1565 to 2236. The highest mucoadhesive strength was seen to be 74.1 dyne/cm^2 in F6 formulation. The maximum drug content of 99.65% was associated with F3 formulation. Further the gelation temperature varied from 37.12 to 42.23 and accordingly the gel strength varied from 8.5 seconds to 16.4 seconds. As the gelation temperature of F4 is near to body temperature it can be considered as optimized formulation. The % Cumulative Drug Release data suggested that in F4 formulation the maximum drug release of 99.12 % is achieved. From the regression analysis of F4, the R^2 value for zero order and first order was determined as 0.949 and 0.855 respectively. Thus, the release kinetics of in situ gel follows zero order release kinetics. From results it can be concluded that nasal in situ gel will greatly boosts rizatriptan accumulation in the brain and may be a useful substitute for parentral and oral formulations.

Keywords: Migraine, In Situ Gel, Nasal drug delivery, Rizatriptan, Mucoadhesion, Carbapol 934, Poloxamer,

Introduction

Chronic migraine is a frequent headache illness that lasts for four to seventy-two hours. The attacks are characterized by pulsating, moderate to severe severity, and recurrent episodes that are increased by ordinary

physical activity. Additionally, migraine is linked to phonophobia, photophobia, and nausea. Its significant effect on the patient's quality of life (QOL) has led to it being referred to as the seventh disabler. In kids and teenagers, it is the most common cause of headaches. Because migraine affects children and their families so severely and because various phenotypes and potential differential diagnoses make diagnosis and treatment challenging, research on migraine in the pediatric population is essential (Shah and Bartuala, 2018; Stewart *et al*., 1994).

Humans have long suffered from migraines and the discomfort they cause. Charles Darwin, Thomas Jefferson, Julius Caesar, and St. Paul are just a few of the famous persons who have experienced migraines. An unidentified Sumerian poet wrote about a condition in which the patient's headache was so bad that they longed to die in order to be free of the agony three millennia ago (Amiri P et al., 2022; Jones, 1999).

Over-the-counter analgesics (pain medicine) such ibuprofen and paracetamol (acetaminophen) for headache, antiemetics (anti-nausea medication) for nausea, and avoiding triggers are the first recommended treatments for acute episodes. Patients with headaches that don't respond to over-the-counter painkillers may be prescribed certain drugs like triptans, ergotamines, or CGRP inhibitors. Prophylactic medication is advised for those who suffer four or more attacks per month or who may otherwise benefit from prevention (Becker, 2015). Prophylactic prescriptions are often written for antidepressants like amitriptyline, beta blockers like propranolol, anticonvulsants such sodium valproate, and other off-label classes of drugs. Preventive drugs work by decreasing the pathophysiology of migraines through a variety of mechanisms, including matrix metalloproteinases, gap junctions, and the blockage of calcium and sodium channels. Among the non-pharmacological preventative therapies include aerobic exercise, dietary modifications, nutritional supplements, and sleep enhancement (Olesen and Ashina, 2011; Evers, 2008).

Acute migraine treatment can be administered by injection (subcutaneous (SC), intramuscular (IM), or intravenous (IV), transdermal, or inhalation (pulmonary and nasal). Both injection and inhalation (both pulmonary and nasal) provide quick (less than 15 minutes) relief from migraines; however, staff assistance is required for IV injection, which may be quicker and more reliable than SC or IM injection (Aurora, 2009). Although intravenous injection (IV) totally avoids problems with gastric stasis and hepatic first-pass metabolism, certain medications might exacerbate unpleasant effects (AEs) such as nausea and vomiting because of a sudden spike in plasma and brain concentrations. Patients who have a needle phobia may also have issues with injections (Rapoport, 2010; Marmura, *et al*., 2015).

The widely agreed-upon objectives of quick and reliable pain relief may be attained with nasal administration. For some triptans, rates of early pain relief and pain independence favor nasal delivery over oral delivery; relief from nasal delivery can occur as soon as 15 minutes after dosage. Furthermore, compared to oral delivery, nasal delivery may cause fewer symptoms linked with migraines and headache-related disabilities. Consistency in headache response and long-lasting, robust pain relief are provided via nasal administration. Finally, nasal delivery gives patients discretion over when and when they get therapy using portable, easy-to-use devices, thus empowering them to take charge of their condition (Tepper *et al*., 2015; Cady, 2015).

In situ gels are suspensions or solutions that can undergo a sol-to-gel transformation, which is typically triggered by a stimulus such as ion presence, pH, or temperature. Put another way, they start out as a solution and transform into a gel inside the body. The use of in situ gels has a number of benefits. They can be employed for controlled and sustained release medication formulations because of their characteristics (Vigani *et al*., 2020). They don't need to be used frequently, which effectively lowers the frequency of drug doses and increases patient comfort and compliance. In situ gels also require less doses overall because of their method of distribution, which increases their bioavailability and reduces overall toxicity. They can even be given to patients who are asleep because they are simple to administer. They can be made to be bioadhesive, which enables non-invasiveness and aids in the medication's targeting (Chand et al., 2016; Agrawal *et al*., 2012).

Another advantage of nasal in situ gel drug delivery systems is their ability to directly target the central nervous system while avoiding the blood-brain barrier. Thanks to this feature, medications can enter the nasal cavity's olfactory area and swiftly and directly reach the brain. This renders them a potentially appealing substitute for the management of disorders pertaining to the central nervous system (Vibha, 2014). Drugs' bioavailability and therapeutic efficacy can both be enhanced. The formulations can gel upon contact with the nasal mucosa, increasing the drug's residence duration in the nasal cavity and facilitating greater absorption and longer release. As a result, the stability and shelf-life are increased and the risks of negative effects and enzymatic degradation are decreased. In conclusion, nasal in situ gel drug delivery systems have the potential to enable the development of efficient and effective drug delivery systems, which justifies the extensive study that has been done on them (Ban *et al*., 2018).

Rizatriptan is a selective agonist of the 5-HT1B and 5-HT1D receptors and a second-generation triptan. Rizatriptan was initially authorized in the United States in 1998 for the purpose of treating migraines. Oral pills, oral disintegrating tablets (wafers), and oral film forms are all available for rizatriptan. Rizatriptan functions as a selective agonist at intracranial blood vessel and trigeminal sensory nerve 5-HT1B and 5-HT1D receptors. It binds highly affinitively to these receptors (Pascual, 2004). Though its precise mode of action is still unknown, rizatriptan has a number of known pharmacological properties that may be linked to its antimigraine benefits. Intracerebral extracerebral blood arteries constrict when exposed to rizatriptan; this effect is mostly attributed to 5-HT1B receptors. In the trigeminal pain pathways, rizatriptan also decreases nociceptive neurotransmission. It reduces the trigeminal nerve's release of vasoactive neuropeptides, which is assumed to happen through neurogenic and central 5-HT1D receptors. In investigations on animals, rizatriptan decreased neurogenic dural vasodilation and plasma protein extravasation (McCormack and Foster, 2005; Dahlof *et al*., 1999).

An appealing substitute delivery method is nasal administration since it can prevent first-pass hepatic metabolism, eliminate GI tract absorption, and possibly lessen the frequency of GI side effects. The nose's vast surface area and high vascularity may allow medications to enter the systemic circulation quickly and take effect right away. Thus this study aims at formulation and development of nasal in-situ gel of rizatriptan for treatment of migraine.

Materials and methods

Chemicals and reagents

Carbopol934, Poloxamer, NaCl, Propyl Paraben, Propylene Glycol, Distilled water were obtained from S.D Fine chemicals Mumbai. All chemicals and reagents were of analytical laboratory grade.

Preparation of nasal insitu gel formulation by (Temperature induced in situ gelling system)

It is prepared by dispersing polymers in distilled water with continuous stirring (Thermostatic hot plate with magnetic stirrer, Remi) until completely dissolved and allowed to hydrate overnight. The preparation of solution, first poloxamer was added in distilled water and allowed to hydrate. Then carbopol was sprinkled over the solution and allowed to hydrate overnight. After complete hydration of polymers a separate solution of Rizatriptan and sodium chloride was added to the polymeric solution (Sadhna *et al*., 2015; Vydehi *et al*., 2016). The resultant solution was thoroughly mixed, Propylparaben was added and mixed until a uniform and clear solutions were formed. Finally volume was makeup to required volume of distilled water. All the formulations were adjusted to pH 4.5 to 5.5 by using freshly prepared 0.5 M sodium hydroxide solution. Accurately weighed amount of polymers mixed with 10ml of distilled water, preheated to 60ºC followed by addition of propylene glycol (5ml). To this 0.15gm of Rizatriptan was added and mixed thoroughly to get an homogeneous solution 500c and then add drop wise Propyl paraben (0.02%w/v) then pre heated at 600c with magnetic stirrer until to get an homogeneous solution. Then sodium chloride was added drop wise for an 1hour with continuous stirring at room temperature and it is kept stabilize to get in situ gel. Then the mixture was left to cool at 5 to 100c for 30mins to enhance the settling of insitu gel. Several batches namely (F1, F2, F3, and F4, F5, F6) were formulated by changing the drug and polymer (carbopol934p and poloxamer) ratio.

Table 1: Composition of nasal in situ gel formulation of Rizatriptan

Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Rizatriptan	50	50	50	50	50	50
Carbopol934p	0.2	0.3	0.4	0.2	0.3	0.4
Poloxamer	0.3	0.3	0.3	0.4	0.4	0.4
Nacl	180	180	180	180	180	180
Propyl paraben	0.02	0.02	0.02	0.02	0.02	0.02
Propylene glycol(ml)	5	5	5	5	5	5
Distilled water	q.s	q.s	q.s	q.s	q.s	q.s

Characterization of Rizatriptan nasal *insitu* gel

Appearance

The developed formulations were inspected visually for clarity in sol and gel form.

Viscosity and rheological behavior studies

Viscosity of formulations before and after gelation are measured by Brookfield R/S CPS + Rheometer with software Rheo 3000 and using spindle CP-75 at 100 rpm shear rate (Inayat *et al*., 2013).

pH of the formulation
The pH of the each formulation was determined by using pH meter.

Drug content
To 1 ml formulation taken in a 50 ml volumetric flask phosphate buffer pH 6.4 was added for dilution and shaken to dissolve the drug. The solution was filtered through 0.45µ PVDF syringe filter,1ml of above filtrate was pipette out and diluted to 10 ml with phosphate buffer pH 6.4. The drug content was estimated spectrophotometrically by using standard curve plotted at 234nm.

Gelation temperature
Gelation Temperature, defined as the temperature at which the liquid phase makes the transition to a gel, determined by using method described by Miller and Donovan technique. A 2ml aliquot of gel was transferred to a test tube, immersed in a water bath (Ahiwale *et al*., 2014). The temperature of water bath was increased slowly and left to equilibrate for 5 min at each new setting. The sample was then examined for gelation, which was said to have occurred when the meniscus would no longer move upon tilting the test tube to 90º.

Gel strength determination
It is expressed in time (in seconds) required by a 35 g piston for penetration of 5 cm distance, through the 50g gel formulation. Test was performed using 'Gel strength apparatus' modified in laboratory (Madan *et al*., 2009). Formulation (50g) was placed in a 100 ml measuring cylinder and gelation was induced by Simulated Nasal Fluid. The apparatus i.e. piston for measuring gel strength (35g) was then placed onto the gel. The gel strength was measured as the time (in seconds) required for moving the apparatus 5 cm down through the gel. In cases, that take more than 5 min to drop the apparatus into the gel, suitable weights were placed on top of the apparatus and gel strength was described by the minimal weights that pushed the apparatus 5cm down through the gel.

Mucoadhesive strength study
Mucoadhesive force of nasal phase transition system was determined using sheep nasal mucosa and phosphate buffer pH 6.4 as the moistening fluid at the time of testing, a section of tissue was secured, keeping the mucosal side out, onto each glass vial using a rubber band and aluminium cap. The diameter of each exposed mucosal membrane was 1.1 cm. On glass vials, tissues were fixed in a manner that the mucosal side became outer part and properly fixed. A vial with a section of tissue was connected to the modified balance and suitable height was maintained. The gel was applied to the exposed tissue of lower vial. The height of the vial was adjusted so that the gel could adhere to the mucosal tissues of upper vial. After applying constant weight for several minutes, suitable weights were added to the modified balance. Minimum amount of weight that detached two vials expressed as mucoadhesive force (dyne /cm^2).
Detachment stress (dynes /cm^2) =M+G/A
Where,
Mis the weight added to balance in grams;
G is the acceleration due to gravity taken as 980 cm/sec2;
A is the area of the tissue exposed and is equal to πr2 (r, the radius of the circular hole in the aluminum cap).

***In vitro* diffusion studies**
In vitro diffusion study of formulated in situ gels was carried out on Franz diffusion cell having 2.4 cm diameter and 13 ml capacity. Dialysis membrane having cut off molecular weight12000–14000 kDa was used as diffusion membrane. Pieces of dialysis membrane were soaked in phosphate buffer pH 6.4 for 24 hrs prior to experiment (Sheri et al., 2015; Pandey, et al., 2014; Ranjana *et al*., 2014). Diffusion cell was filled with phosphate buffer pH 6.4; dialysis membrane was mounted on cell. The temperature was maintained at 37 ± 0.5°C. The donor compartment contained 3 ml of artificial nasal fluid. After an equilibration of membrane, formulation equivalent to 1 mg of Rizatriptan was placed in the donor compartment. At predetermined time points (30, 60, 90, 120, 150,and 180 min), 1 ml samples were withdrawn from the acceptor compartment, replacing the sampled volume with phosphate buffer pH 6.4 after each sampling to maintain a constant volume, for a period of 5hr The samples withdrawn were filtered and used for analysis.

Blank samples without Rizatriptan were run simultaneously throughout the experiment to check for any interference. The amount of diffused drug was determined using UV visible spectroscopic method.

Results and Discussion

All the formulations of in situ gel was observed to be transparent. The clarity of gel was observed from F1-F4 while in case of F5 and F6 the gel turned out to be slightly hazy. All the fromulations were viscous as the gel should be without absence of any specific odor.
The viscosity among the solution ranged from 936 to 1325 cps while in case of gel the viscocity spanned from 1565 to 2236.
The gels that contained Poloxamer demonstrated increased mucoadhesive forces. This could be explained by the fact that Poloxamer formulations have higher chain flexibility and viscosity and interact with mucin more. The loading the drug caused a twofold reduction in mucoadhesion, presumably as a result of an improved interaction between the cabapol and polaxamer chains. This increased viscosity of the gel, as shown by the rheological measurements, also decreased the gel's ability to bind to mucin. The highest mucoadhesive strength was seen to be 74.1 dyne/cm^2 in F6 formulation.
Mucoadhesive drug delivery techniques extend the dosage's residence duration at the application or absorption site and limit first-pass metabolism by allowing drugs to dissipate quickly in the circulatory system. In the current investigation, formulations made with a high HPMC K-100 concentration demonstrated stronger mucoadhesion than formulations made with a lower concentration. Therefore, the formulation is largely dependent on the high concentration of carbopol 934.
Three steps are involved in mucoadhesion: soaking, interpenetration, and mechanical interlocking of the polymer and mucin. The nasal passage's unique anatomy and physiology, including its enormous surface area, highly vascularized epithelium, and porous endothelium membrane, have made nasal drug delivery a viable method of delivering medications for systemic therapy. There are two layers of nasal mucus: the bottom, low-viscosity layer and the higher, more viscous one. The presence of glycoproteins (2%) is what gives nasal mucus its viscoelastic characteristics. Moreover, the composition of nasal mucus is as follows: water (95 percent), inorganic salts (1%), lipids (<1%), albumin, immunoglobulins, lysozyme, lactoferrin, and other proteins (1%).
The maximum drug content of 99.65% was associated with F3 formulation. Further the gelation temperature varied from 37.12 to 42.23 and accordingly the gel strength varied from 8.5 seconds to 16.4 seconds. As the gelation temperature of F4 is near to body temperature it can be considered as optimized formulation. The gelling temperature is defined as the temperature at which the liquid phase changes to gel. If the gelling temperature is below the specified period, a gel can form at ambient temperature. On the other hand, when the temperature is raised, the nasal mucosal region does not gel, which results in rapid nasal clearance. All of the formulations, however, demonstrated rapid gelation upon contact with the solution and maintained their integrity for a prolonged duration, allowing for the drug's continuous release. The gelling time is the amount of time needed for a sol form to solidify into a gel.
The % Cumulative Drug Release data suggested that in F4 formulation the maximum drug release of 99.12 % is achieved. The viscosity of the formulation affects how easily the medicine is released from it. The outcomes unequivocally shown that sumatriptan succinate could be retained in the matrix network of the mucoadhesive nasal in situ gel. When cations are present, two COO^- groups on the glucuronic acid molecules in gellan chains form a chemical connection that causes gellan gum to undergo gelation. The medication release continued even at reduced gellan gum concentrations. As gellan concentration rose, drug release appeared to decrease. The medication releases from a high concentration to a low concentration when the formulation gels at the application site.
From the regression analysis of F4, the R^2 value for zero order and first order was determined as 0.949 and 0.855 respectively. Thus, the release kinetics of in situ gel follows zero order release kinetics.
The goal of the current trial is to provide patients with migraines with brain-targeted rizatriptan medication delivery. This study aims to explore the nose-to-brain route of rizatriptan drug delivery through intranasal delivery, which greatly boosts rizatriptan accumulation in the brain and may be a useful substitute for parentral and oral formulations.Longer residency features provided by the nasal ruote will improve the drug's bioavailability. Prolonged drug release characteristics were seen in the nasal cavity during formulation, with little adverse effects on the nasal mucosa. Because of its continuous release capability and convenience of administration, less frequent administration may be necessary, which would improve patient compliance.

Table 2: Results of appearance of Rizatriptan nasal *insitu* gel

Parameters	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Color	Transparent	Transparent	Transparent	Transparent	Transparent	Transparent
Clarity	Clear	Clear	Clear	Clear	Slightly hazy	Slightly hazy
Consistency	Viscous	Viscous	Viscous	Viscous	Viscous	Viscous
Odor	odorless	odorless	odorless	odorless	odorless	odorless

Table 3: Results of Viscosity and rheological behavior studies

Formulation Code	**Viscosity of solution (cps)**	**Viscosity of Gel (cps)**
F1	936	1565
F2	1032	1723
F3	1065	1965
F4	1132	2013
F5	1263	2155
F6	1325	2236

Table 4: Results of Mucoadhesive strength study and percentage of drug content

Formulation Code	**Mucoadhesive strength (**dyne/cm^2**)**	**Drug content (%)**
F1	63.2	98.78
F2	68.8	97.25
F3	66.6	99.65
F4	72.2	96.45
F5	73.3	98.78
F6	74.1	96.78

Table 5: Results of Gel strength and Gelation temperature

Formulation Code	**Gel strength (Sec.)**	**Gelation temperature (^{0}C)**
F1	8.5	42.23
F2	10.2	38.85
F3	13.3	37.65
F4	14.4	37.12
F5	15.6	37.20
F6	16.4	38.85

Table 6: Results of *In vitro* release studies of formulation F1 to F6

Time (mins)	% Cumulative Drug Release					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
30	36.65	33.36	31.15	30.25	28.85	20.23
60	69.98	65.58	60.12	55.65	36.65	36.65
90	90.23	89.98	78.85	69.98	46.65	46.65
120	96.65	98.85	89.98	83.32	69.98	59.98
150	98.85	99.12	95.65	92.65	73.32	67.74
180	99.12	99.74	99.85	99.12	89.98	79.95

Table 7: In-vitro drug release data for optimized formulation F4

Time (min)	**Square Root of Time(h)$^{1/2}$**	**Log Time**	**Cumulative*% Drug Release**	**Log Cumulative % Drug Release**	**Cumulative % Drug Remaining**	**Log Cumulative % Drug Remaining**
30	5.477	1.477	30.25	1.481	69.75	1.481
60	7.746	1.778	55.65	1.745	44.35	1.745
90	9.487	1.954	69.98	1.845	30.02	1.845
120	10.954	2.079	83.32	1.921	16.68	1.921
150	12.247	2.176	92.65	1.967	7.35	1.967
180	13.416	2.255	99.12	1.996	0.88	1.996

N=6 mean±S.D

Table 8: Regression analysis data

Batch	**Zero Order**	**First Order**
	R^2	**R^2**
F4	0.949	0.855

Conclusion

The development of a successful in situ gel for nasal delivery of an migraine medication can be the study's conclusion. Based on the results, the F4 formulation was determined to be the most optimal. It included carbapol, propylene glycol, Poloxamer increased nasal residence time by increasing viscosity and mucoadhesion characteristics while also improving permeation. The study showed that the nasal residence time and absorption of rizatriptan may be safely and effectively increased by using the mucoadhesive polymer and the in situ thermogelling agent Poloxamer. It has been discovered that the temperature-induced methodology is the most effective way to prepare rizatriptan nasal in situ gel. The gel strength and gelation temperature of the prepared nasal insitu gel were both good. Thus, considering its evaluation criteria such as gelation temperature and drug release, it can be stated that nasal in situ gel having (F4) with carbopol and poloxamer concentration is an excellent gel for regulated and sustained nasal drug delivery system.

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