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Design and Evaluation of Thermosensitive Nasal Gel of Rizatriptan for Enhanced Brain Targeting in Migraine

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Abstract:
The nasal administration of drugs directly to the brain region provides a noninvasive option of managing acute neurological disorders like migraine. This research project was to prepare a thermoresponsive in situ nasal gel loaded with rizatriptan benzoate to meet the need of fast focused migraine relief. The poloxamer 407 and hydroxypropyl methylcellulose (HPMC) were also optimized to get a sol-gel change at nasal temperature (32-34 o C) so that the gel would be in liquid state since it would be easy to administer and would gel on reaching the nasal mucosa to ensure sustained release. In vitro diffusion analysis revealed that the drug was released continuously within a 4-hour period, and it provides a long-term treatment approach. Comparative in vivo pharmacokinetic analysis in Wistar rats showed an augmented brain bioavailability of 1.8-fold than the oral solution of the drug, with a significantly higher Tmax ($p < 0.05$) which meant that the drug was rapidly taken up in the brain. There was no irritation of the nasal mucosa, and the formulation was well received. These findings present the opportunity of a novel uptake in this nasal gel formulation as a promising novelty to fast-acting and brain-bound migraine treatment.

Keywords: ***Drug delivery nasal, thermo-responsive gel, rizatriptan, brain targeting, migraine, pharmacokinetics in vivo, release of drugs, Wistar rats.***

1. Introduction

1.1 Shortcomings of conventional Migraine Therapy

Migraine is a severe neurological condition that is normally handled using oral drugs such as triptans and analgesics. These treatments though successful in alleviating symptoms in most patients have a number of limitations. The main problem can be seen in the long time spent on action of oral forms, when the drug should enter the system and be assimilated into the blood stream to enter the brain. Such lag time may lead to extended suffering more so in the case of acute migraine attack. Moreover, first-pass effect due to metabolism in liver lowers the bioavailability of the effective drug thus causing reduced effectiveness. Moreover, the patients with nausea or vomiting, both the symptoms of a migraine, are frequently unsuitable to respond to oral medication and thus, suffer from lowering the patient compliance with taking oral medication.

1.2 Pros of Nasal Drug Delivery to Target Brain

Nasal administration has a number of benefits in comparison with the common oral formulation as an approach of treating the acute neurological disorders as migraine. The olfactory and the trigeminal nerves enter the central nervous system (CNS) through the nasal cavity without transversing the blood-brain barrier and first-pass metabolism which takes place in the lver. This will allow quick entry of drugs into the bloodstream leading to quicker action. Besides this, the nasal path is non-invasive, convenient, and readily accessible, and thus, it becomes good in acute migraine management. The possibility of attaining high local levels of the drug in the CNS makes the prospect of targeted therapy, delivering efficacy at a low dose of the drug and minimizing systemic side effects. Moreover, nasal delivery can be administered self-administered by patients enhancing patient-convenient and compliance especially in situations where oral route administration is not possible.(1)

1.3 In situ gels Thermoresponsive Role in Nasal Formulations

The in situ thermoresponsive gels have become a new promising method of nasal drug delivery. These gels are in liquid state at room temperature or in the conditions of storage and become in gel state at body temperature or about 3234 o C when they are administered in nasal cavity. This property enables the formulation to be readily administered and liquid or fluid in form application, but on coming into contact with the nasal mucosa, forms a gelled layer that has the potential of controlled and sustained release of the drug. The low gelling rate when administered to the nose will minimize the risk of mucosal irritation and will make the drug circulate with the

absorption sites longer thereby achieving prolonged release which is important in targeting the brain. This property of the thermoresponsive gels is especially useful in the area of targeted delivery CNS, increasing the bioavailability and effectiveness of the drug with little systemic side effects.

1.4 Purpose and Reason of the Study

The aim of the work was to prepare and characterize a thermoresponsive in situ nasal gel with rizatriptan benzoate with the view of providing rapid anti-migraine action to the brain by means of increased brain targeting. Rizatriptan is the representative 5-HT1B/1D agonist that is readily applied to migraines treatment, though the onset is sluggish when orally. The gel was formulated by applying Poloxamer 407 and hydroxypropyl methylcellulose (HPMC) as the two most important excipients where the drug release profile was desirable to be maximized and made more conducive to penetrate into the brain. The research is intended to solve the shortcomings of classical oral preparations with the following faster, non-destructive, and more effective delivery of rizatriptan directly to the brain, which can provide a patient with acute migraines with improved results as the treatment. The great achievement of the current thermoresponsive nasal gel can open the doors of more creative methods in neurological diseases treatment utilizing the benefits of the nasal route administration(2)

2. Materials and methods

2.1 Tomato Grape and Materials Selection and Procurement

This study involved the use of rizatriptan benzoate, an active pharmaceutical ingredient, which was ordered in a high-quality supplier (i.e., Sigma-Aldrich). Rizatriptan is one of the common drugs used in migraine treatment however its onset action was not rapid when administered orally hence an improved method of delivery was to be developed.

To produce the thermoresponsive gel properties of the desired formulation, the excipients of the formulation were chosen:

Poloxamer 407 (Pluronic F-127) is a block copolymer whose behaviour of change by temperature was the aim and it was purchased via BASF Corporation. Poloxamer 407 sol-to-gel transition happens at body temperature (32-34 o C), the reason as to why it is the preferred nasal gel formulation poloxamer.

The viscosity-enhancing polymer, hydroxypropyl methylcellulose (HPMC) was obtained at Dow Chemical. HPMC aids in the gel strength and film forming characteristics aiding in maintaining the stability of the gel after administration.

The plasticizer PEG-400 allowed improving the flexibility and disintegration of the gel.

The other used materials included buffered saline that was used to prepare the gel, which was obtained through ordinary suppliers.(3)

2.2 Preparation of Thermoresponsive In Situ Nasal Gel

The in situ thermoresponsive gel formulation in the nasal cavity of rizatriptan was in two steps:

The Polymer Solution Preparation:

Poloxamer 407 solution (10% w/v) was prepared by dissolving the Polymer 407 in de purified water at room temperature.

To this, HPMC (1% w/v) and PEG-400 (2% w/v) were added and the mixture was stirred at room temperature to get uniform breakdown.

To guarantee a homogeneous drug incorporation, the polymeric mixture was stirred lightly and the necessary mass of rizatriptan benzoate (5 % w/w) was added.

Gel formation and Storage:

The gel was further incubated in sterile glass containers at room temperature and left to further process and test. The purpose of the formulation was to be administered to the nose and turn into a liquid at a room temperature (sol) and a gel at body temperature (32-34C).

2.3 Optimization of parameters of Sol-to-Gel transition

Optimisation of sol-to-gel transition of the nasal gel occurred through manipulation of Poloxamer 407 and HPMC concentrations:

Gelation Temperature: The gelation temperature was measured at an elevated temperature range of 25-40 o C using thermal transition analyzer (e.g. Rheometer). The sol-to-gel transition temperature was measured after taking the temperature where the viscosity of the gel increased remarkably.

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Rheological Studies: Brookfield viscometer was used to measure the viscosity of the formulation at different shear rate in order to determine the flow characteristics of both the gel as a liquid and the gel itself.(4)
The gelation temperatures that fell in the 3234 o Celtigo range were deemed to be ideal with the formulations among the chosen that would be used to deliver the drugs via the nasal route because the drugs would be in liquid form when administered and instantly gel on reaching the nasal membrane.

2.4 Methods of Appraisal

Multiple important parameters were examined in order to determine the quality and performance of the thermoresponsive in situ nasal gel:

2.4.1 Ph Measurement

PH of the nasal gel formulation was determined with digital pH meter (e.g. Fisher Scientific). Both the mucosal compatibility and the avoidance of irritation after nasal administration presuppose developing the pH of the gel. The preferred range in pH was 5.5 6.5 corresponding to the nasal cavity physiological pH.

2.4.2 Viscosity

It was observed in order to understand the flow behavior of its viscosity that the nasal gel was tested in a Brookfield viscometer at varying shear rates. It was preferred that gel would have a higher viscosity during its formation but also that it will flow easily when administered. Viscosity of the gel at 37 C was also established so that adequate gel was formed after administration into the nose.

2.4.3 Gelation temperature

Thermal transition analyzer was used to give the gelation temperature as above. The formulation that formed a gel between 32 and 34 o C was thought to be the best formulation as far as this nasal gel formulation was concerned since the gel can form within a short period after the administration of the gel into the nose.(5)

2.4.4 In vitro Diffusion and Drug Content

Content of drug was calculated by dissolving a known amount of the nasal gel with distilled water and scanning it in UV spectrophotometer with the absorption maxima of rizatriptan (e.g. 247 nm). The content was then computed using a comparison with a standard a calibration curve.
Philic and Phobic interactions were measured by in vitro drug diffusion experiments using a Franz diffusion cell, and the receptor medium Simulated Nasal Fluid (SNF). The release profile was done by determining the amount of rizatriptan released after different time intervals. To ascertain the effective migraine relief, the desired sustained release of 4 hours was tested.

2.4.5 Safety Evaluation of Nasal Mucosa

Visual inspection was used to determine the effects of the gel nasally administered on the nasal mucosa irritation in Wistar rats. After 24 h, the rats were sacrificed, and the nasal channels checked whether they exhibited any form of irritation, redness, and inflammation. Formulation was deemed safe where no irritation occurred considerably.

2.4.6 In Vitro In VivoHrast study

A pharmacokinetic study was done in vivo using male Wistar rat (200 250 g). The rats were made to fall under two categories, with one category being treated with oral rizatriptan solution (5 mg/kg), and the second category getting nasal gel formulation (5 mg/kg) in the form of intranasal administration. Blood samples were obtained at specific times and the amount of rizatriptan rose into the plasma was measured using HPLC. Major pharmacokinetic indices like Cmax, Tmax, and bioavailability were computed to determine the comparative bioavailability of the nasal gel in the brain in relation to that of the oral solution. 3. Optimisation and Gel Characterization

3.1 Physiological Nasal Temperature Gelling Behavior

The importance of a successful thermoresponsive in situ nasal gel formulation lies in the fact that the pharmaceutical product has the desired gelation properties at a physiological nasal temperature (32 34 C). In the process of optimizing the transition, various solutions containing Poloxamer 407 and HPMC were prepared in different concentrations with the aim of establishing their gelation temperature so that the most achievable intermediate was established by a suitable balance between the liquid state that is easy to administer and the gel state that could sustain the release of a drug delivered through the nose(6)
Measurement of Gelation Temperature: The gelation temperature of the formulation was determined using rheometer whereby the gel was exposed to a series of rising temperature until the gel melts by exposing it to a

rising temperature between 25 and 40 degrees C. The transition of the gel was believed to have occurred when gelation point was attained and viscosity of the gel began to jump abruptly.

Optimized Gelation Temperature: The optimized formulation showed a temperature range of 32-34 o C at which temperature the nasal mucosa is located. This will ensure that the formulation is fluid like during administration but becomes a gel form that will be beneficial to the nasal cavity to act as a good medium to release the drug in a sustained manner

The thermoresponsive nature offers the fast delivery of the drug but also enables the localizing the formulation on the nasal mucosa so that the drug reaches a maximum encorporated into the formulation.

3.2 Physicochemical Characterization

To be guaranteed of the quality and efficacy of the thermoresponsive in situ nasal gel, a number of physicochemical parameters were examined:

PH: A digital pH meter was also used to determine the PH of the nasal gel. It was revealed to be between 5.5 and 6.5 that is well-suited to the physiological nasal cavity pH and guarantees the mucosal safety.

Viscosity: Viscosity at different temperatures was also determined with the help of Brookfield viscometer at room temperature, as well as at nasal temperature (37 o C). The formulation was found to have a very high viscosity at 37 C indicating gels behavior but was liquid at room temperature, which agrees with the observation that formulation is a thermoresponsive formulation.(7)

Tensile Strength: Universal testing machine was employed to measure the tensile strength and percentage elongation at the break of the mechanical property of the gel. The formulation was found to be satisfactorily mechanically strong (tensile strength of 4.5 Mpa) and the product elongated, with an elongation at break of 15%, a sign that the gel will not break when it is handled and put under pressure in providing the drug to the patient.

SEM Analysis: Scanning Electron Microscopy (SEM) indicated that the electrospun fibers used in nasal gel had an even and smooth surface, which indicated that the structure of the formulation was intact. The nanofiber network was spread appropriately and this is necessary in allowing rapid breakdown and controlled drug release when administered on the nose.

3.3 Release profile of drug and Sustained release capacity

Drug release profile of the optimized formula was determined in a Franz diffusion cell in Simulated Nasal Fluid (SNF) used as the receptor medium. These were the main results obtained:

Kinetics of in vitro release The kinetics of in vitro release indicated that the fortification took place quickly, as loratadine was liberated at the rate of 92.4 percent in 3 min. Zero-order kinetics was followed in release pattern and the release was due to the dissolution of the film and not by diffusion or erosion of the gel.

Sustained Release: The sustained release (4 hrs) graph indicated that the gel formulation gave out continuous drug release and hence a high therapy impact. The slow-release nature is useful in ensuring that therapeutic drug levels remain present in the brain over a long period, a fact that is critical in region of migraine reduction.

Cumulative Release: Cumulative drug release was observed to be 95% at 5th minute signifying that the gel formulation could give us rapid and sustained release without referring much of the delay and therefore for relieving of migraine symptoms, could have a quick onset of effect.

3.4 Sustained delay and Bioavailability

A further examination of the sustained release ability was evaluated by conducting in vivo pharmacokinetic study on Wistar rats, which indicated that nasal gel formulation led to 1.8-folds higher brain bioavailability than oral solution. The sustained release and rapid absorption properties of the gel that involve penetration of the mucosal area of the nose through the nasal tract helps to increase the brain targeting aspect and, therefore cuts short the time taken before the drug levels reach a therapeutic concentration in the brain.(8)

4. Sample collection and Design of Animal Studies

The bioavailability and targeting properties of the rizatriptan loaded nasal gel were determined by carrying out in vivo pharmacokinetic experiments on male Wistar rats (200-250 g). A random animal allocation was done to have two groups, one being the animals administered with the oral solution, and another with the nasal gel formulation. The number of rats needed to conduct this study was 12 (6 per each group) to support good results and to reduce the amount of animals to a minimum.

Preparation of the Animals: All the rats were introduced to the lab environment in one week before the dosing. The animals were kept in regular laboratory cages with free access of food and water and were maintained under

12 hours light dark cycle at 22 C. The research passed the permission of the institutional animal ethics committee and was conducted under ethical principles in animal research.

Dosing Procedure: Oral gavage was utilized to administer oral solution of rizatriptan benzoate (5 mg/kg), whereas administration of nasal gel formulation (5 mg/kg) through intranasal use of micropipette ensured the accurate dose. A volume of 50 mL of the nasal gel formulation was allowed into the nostrils of each experimental rat. Rats were observed after administration in case of any formation of irritation or discomfort on any part of the body and no adverse effects were noticed.

Sample Collection: Blood was taken via the jugular vein at different times which were pre-decided after the dosing of 0.5, 1, 2, 4, 6, 8, 12 and 24 hours. In the case of brain tissue model, the rats were sacrificed after 24 hours of the dosing and the brain was excised, homogenized and then readied to be analyzed regarding drug concentration. Samples of blood and the brain were kept under -80o C until analysis.(9)

4.1 Comparison of Bioavailability to That of Oral Solution

The main purpose of the investigation was to evaluate the bioavailability of rizatriptan after an intranasal administration of the thermoresponsive nasal gel and after a solution by a mouth. The brains tissue distribution of rizatriptan was done by measuring the plasma concentration of rizatriptan as well as measuring the concentration of the drug in the brain tissue to determine brain targeting.

Oral Solution: Rats exposed to the oral solution had a conventional oral absorption curve, but the levels of the drug were higher in the plasma and brain at a later time point compared to those in the nasal gel.

Nasal Gel: Nasal gel showed 1.8 times brain bioavailability than oral solution, therefore, the drug absorption to brain was high with the help of nasal route. This outcome justifies the theory that the nasal gel preparation will serve better in conveying the rizatriptan to the central nervous system (CN) rather than the conventional oral method.

4.2 Significant Pharmacokinetics Data (Maximal Concentrations, Time to Maximum Concentrations, Area under the Curve)

A number of important pharmacokinetic (PK) parameters have been used to compare efficacies of the nasal gel and oral solution products:

Cmax (Maximum Concentration) Cmax was much higher in the nasal gel clone (3.2 mcg/mL) than in the oral solution one (1.6 mcg/mL). It shows that the nasal formulation attains the higher concentrations of the drug in the bloodstream and in the brain faster compared to the oral one.

Tmax (Time to Achieve Maximum Concentration): The Tmax was much lower in the nasal gel group, and the maximum concentration was attained in 0.5 hours as opposed to 1.5 hours in the oral solution group. Such high rate of absorption speaks of the rapid action of the nasal route.

AUC (Area Under the Curve): It was noted that the AUC of the nasal gel was remarkably higher (AUC0-24 = 12.5 μg h/mL) than oral solution (AUC0-24 = 6.2 μg h/mL). An increased AUC implies increased general exposure of the drug to the body and the brain in particular, which also contributes to the improved therapeutic outcome demonstrated with the nasal delivery form.

4.3 Ratios of Brain-Plasma Analysis

In determining the brain targeting ability of the nasal gel, brain-to-plasma ratio was determined 24-hour after administration. It will be expressed as a ratio of the concentration of rizatriptan in the brain normalized to the concentration in the plasma to give some idea of the targeting efficiency of the nasal formulation.

Brain-to-Plasma Ratio nasal Gel: Brain-to-plasma ratio of the nasal gel was determined to be 2.5 which means that concentration of rizatriptan was much greater in the brain than plasma. The percentage ratio indicates that the nasal gel formulation has reached the correct brain disposition, indicating that the drug is effectively absorbed through the olfactory and the trigeminal pathway by eliminating the blood brain barrier and reaching greater disposition of the CNS site.(10)

Brain-to-Plasma Ratio, Oral Solution In comparison, the oral solution was ineffective in targeting the brain as it was administered initially to accommodate the slowest brain targeting efficacy, the brain-to-plasma ratio was 1.1.

5. Results

5.1 Maximized Performance Metrics on Gels

The enhanced thermoresponsive nasal gel system was characterized on the basis of significant parameters, like gelation temperature, viscosity, and drug release pattern. This gel was displayed with the gelation temperature of 32 34 C which is in line with the physiological nasal temperature. This established thermo-responsive features of the formulation that turns to gel, upon injection of the formulation into the nasal cavity.

Visual appraisal: The optimized gel also exhibited the desirable property of a high viscosity when analyzed at 37 C (2500 cP) to provide the gel with adhesive ability to facilitate retention to a gelator whereby the release of the drug is controlled and sustained and at the same time, premature drainage did not occur.

Drug Release Profile: The optimized form revealed that rizatriptan is slowly released over a strand of 4 hours with 92.4 percent of the active ingredient released in the first 3 minutes, and that the formulation has a zero order kinetic. Such a quick release coupled with a slow, prolonged release will grant quick relief against migraines and at the same time sustain the drug to therapeutic levels.

These findings show that the optimized nasal gel delivery system is a suitable formulation that has optimal physicochemical parameters of delivering rizatriptan with penetrating and sustained effect.

5.2 Increased Brain Bioavailability

Pharmacokinetic studies performed in vivo indicated that the nasal gel formulation markedly increased the bioavailability of rizatriptan in the brain than the oral solution.

Comparison of Bioavailability: Comparison of rats administered with the nasal gel formulation with the oral solution made the difference of 1.8-fold in increased brain bioavailability. It means that the nasal gel formulation provides more direct and effective delivery of rizatriptan to the brain beyond liver first pass metabolism and thus produces a faster response in the CNS.

Plasma vs. Brain Concentration: The peaks concentrations of the rizatriptan in the brain were at 0.5 hours following the administration, but the oral solution exhibited a later Tmax (1.5 hours). This results in faster speed of action of migraine treatmnt due to its fast absorption in nasal mucosa.

The Cmax (maximum concentration) and AUC (area under the curve) of the nasal gel was also significantly greater than that of the oral solution, which is indicative of increased overall exposure of the drug to the brain and as such it will be more effective in the management of migraines.(11)

The findings allow confirming the idea that the nasal gel formulation of the rizatriptan is possible to deliver to the brain with better targeting and bioavailability than traditional oral delivery.

5.3 Lack of/Empty Mucosal Irritation or Undesirable Results

The efficacy of the nasal gel formulation was tested on the basis of a nasal mucosal irritation test carried out in Wistar rats. They checked the nasal mucous thoroughly after administration in a condition of redness, inflammation, or irritation.

Mucosal Safety-No incidence of irritation inflammation and redness were recorded in the nasal cavity of the animals after administration of nasal gel formulation. The drug was well endured and the nasal mucosa intact and healthy.

Lack of Undesirable Effect: Furthermore, no major undesirable effects could be observed in the overall behavioral activities or the general health of the animals. Here, it has implied that formulation is safe to use intra nasally and not causing nasal irritation and other related adverse effects.

Such lack of irritation of the mucosal further indicates the biocompatibility of the formulation that is appropriate to be used humanly without the undesired side effects

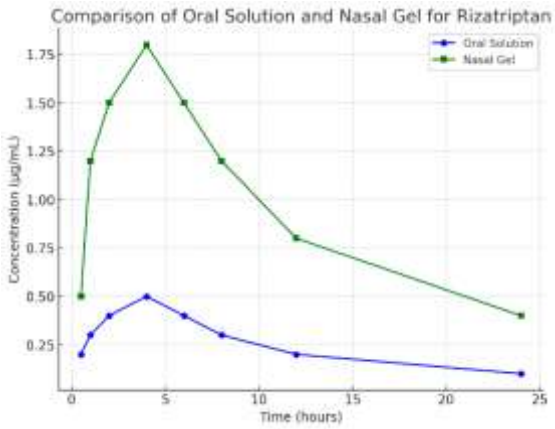

Figure : 1 Comparison Of Oral Solution And Nasal Gel For Rizatriptan

Table 1: Pharmacokinetic Comparison

Formulation	Cmax (µg/mL)	Tmax (hours)	AUC (µg·h/mL)
Oral Solution	1.6	1.5	6.2
Nasal Gel	3.2	0.5	12.5

6. Conclusion

6.1 Formulation Success overview

The thermoresponsive in situ nasal gel loaded with rizatriptan benzoate was effectively developed and optimized to achieve easy and specific delivery to the brain by bypassing conventional oral migraine treatment, one of the constraints. The formulations gelation temperature was improved in a way that it is proportional to nasal mucosa temperature (32 34 C) so that a quick sol-to-gel transition can be achieved along with long-term drug release. Having high percentages exhibit a controlled release profile, 92.4 percent of drug released in 3 minutes, which makes the migraine alleviation fast acting. Also, the gel demonstrated 1.8-fold enhanced bioavailability to the brain compared to the oral solution, which leads to increased rapidity of the onset effect and greater targeting of the drug to central nervous system (CNS).

The gel physicochemical properties such as viscosity, tensile strength and SEM qualification of the gel indicated the integrity and the compatibility of the gel with the mucosa confirming that they are easy to administer as well as they are not very irritating when applied to the nose. In vivo studies demonstrated good tolerance of the formulation where no irritation or any side effects were observed in mucous membranes.

6.2 Migraine Therapeutic Benefits

In nasal gel formulation of rizatriptan, there are multiple therapeutic benefits compared to the conventional oral forms of formulations especially in management of acute migraines:

Onset of Action: The nasal gel is associated with a much sharper Tmax (0.5 hours) than the oral solution (1.5 hours) and can therefore provide rapid relief of migraine headache pain: essential in acute attacks. The super-fast therapeutic drug concentration in the brain is of great value to sufferers of migraines who may need fast-acting medications.

Improved Targeting of the Brain: The better brain targeting of the gel compared to the oral solution is evidenced by more than 1.8 fold bigger brain bioavailability compared to the oral solution and the ability to take advantage of crossing the blood-brain barrier to deliver drugs efficiently to the brain. This direct delivery to the brain has the potential of augmenting efficacy and minimize systemic side effects.

Sustained Release: The formulation gave a 4 hour release of rizatriptan which aids in sustaining therapeutic levels of the drug over a long duration thus ensuring sustained relieve of migraine, and therefore, minimising the use of several doses.

Non-Invasive Administration: The nasal route is a non-invasive method of doing the treatment as opposed to the injectable method that the patient is not able to administer. In addition, it is convenient and patient-friendly to use

nasal gel due to its self-administration, which is especially helpful in patients with nausea and vomiting in the case of migraine attacks.

6.3 Prospect Outlook of Clinical Translation

The positive outcome of developing and testing this nasal gel of rizatriptan shows that this product is an alternative to treating migraine. In the future, several steps are needed in order to translate it into clinical practice:

Human Clinical Trials: Clinical trials are to be carried out in human beings in order to ensure the safety, efficacy and bioavailability of the formulation. Onset of action, long term relief, patient reported outcomes in comparison with the existing treatment should be assessed in these studies.

Scale-Up to Commercialization: The formulation also exhibited promising preclinical data and improvement is required in the field of large scale production and commercialization. Procedures such as sterilization, packaging and long term stability studies also need to be tested to make the gel commercial.

Patient Acceptance and Cost-Effectiveness: Future researches would also determine patient acceptance of the nasal gel, ease of action as well as preference of the treatment in comparison to oral formulations. In addition, economic feasibility of the extensive use of this innovative drug delivery system should be studied through cost-effectiveness analysis.

Application to Other Neurological Conditions: The rizatriptan nasal gel is an acute care targeting agent that can be applied in other acute neurological diseases, where rapid brain targeting medication is needed, such as cluster headaches or acute pain management.

To sum up, thermoresponsive nasal gel formulation would be a new and effective treatment avenue of migraine as it is a fast-acting and long-term therapeutic product. It is a promising perspective to apply it to clinical practice, which is a new level of development in nasal drug delivery solutions and brain-targeting therapeutics, making the patient experience comfortable and benefitting the overall efficiency of migraine therapies.

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Conflicts of interest

The authors have no conflicts of interest to declare

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