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Formulation, development and characterization of frovatriptan succinate in situ gel for nasal administration

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ABSTRACT:

Introduction: *One of the most common conditions in the world is migraine. This is the second most common reason why non-manual workers miss work for a short time. This study created new in situ-gel forms of FVT for intranasal administration. These forms help the drug pass through the nasopharyngeal barrier more easily and stay in the nose cavity longer.*

Materials and Methods: *A thermoreversible, mucoadhesive in situ intranasal gel was made with frovatriptan succinate. The mucoadhesive properties of the gel make it stay in the nasal cavity longer, and the thermoreversible properties make it easier to work with and give.*

Results: *The best amount of carbopol 934 for mucoadhesive strength and the right temperature for the phase change is 0.2% w/v. Carbopol makes it easier for the drug to be absorbed and works better. This mixture did not do a lot of damage to the nasal membranes.* ***Conclusion:*** *The findings of this study support using Frovatriptan succinate as a new mucoadhesive in situ intranasal gel to treat migraines.*

Keywords: *Intranasal, formulation, in situ gel, frovatriptan succinate.*

INTRODUCTION:

A case of migraine, a neurological disorder, usually includes headaches, gastrointestinal, neurological, and sometimes auditory symptoms that happen over and over again. One of the most common conditions in the world is migraine. It's the second most common reason why non-manual workers miss work for a short time [1-3]. Many different types of medicines have been made to treat migraines, but one big problem has been the lack of effective ways to give these medicines. The nasal drug transport system can be changed by things like the drug volume capacity of the nasal cavity, anterior leakage, and mucociliary clearance. The drug comes in film-coated pills or fast-dissolving films [2-4].

However, it is considered a low-efficacy triptan because it takes a while to start working, even though it is strong and has a long half-life. There are some major problems with the current dose forms. They take a while to start working, aren't bioavailable because they're not very well dissolved and break down in the digestive system, and cause side effects like chest tightness, pain, and numb fingers [3-5]. One problem with film-coated tablets is that they need to be taken by mouth more than once because they have to go through the mucosal lining of the nasal canal without damaging the tissue permanently [4-7].

The main problems with the nasal drug delivery system are anterior leakage, poor mucociliary clearance, and a small nasal cavity. All of these problems may make the system less effective. In situ gels are better than standard gels in a number of ways. For example, they are easier to prepare and stay in the nasal mucosa for longer because they stick to it and gel [8-11]. This study created new in situ-gel forms of FVT that can be used for intranasal administration. These forms help the drug pass through the nasopharyngeal barrier more easily and stay in the nose cavity longer [12-15].

MATERIAL AND METHODS:

An approved Indian supplier gave us Frovatriptan succinate. HiMedia Laboratories Limited gave us Dialysis Membrane. Loba Chemicals Limited in Mumbai, India, gave us Poloxamer 407 and Carbopol 934. Each of the extra solvents used in this study was all are pure analytical grade.

Formulation of in situ nasal gel:

To make the fake nasal fluid, potassium, calcium, and sodium chloride were mixed with 250 ml of pure water. This was done after the binary ethosome was prepared. Adding Pluronic F127 to the in situ nose gels using a cold method made them even better, and the in situ gel was left to soak up water overnight. The poloxamer dispersion was mixed with a binary ethosome dispersion of FVT that had different amounts of carbopol and a stabilizer [16,6,8].

Table 1: Ingredients for in situ nasal gels

Sr. No.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Drug	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml
2	Pluronic F127	20	20	20	20	20	20	20	20	20
3	Carbopol	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	0.4

4	Methyl paraben	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
5	SNF q. s.	15ml	15ml	15ml	15ml	15ml	15ml	15ml	15ml	15ml

Evaluation of in-situ gel:

Many tests were done on the formulations that were looked at, such as particle size analysis, clarity measurements, pH assessments, checks to see how uniform the FVT content was, spreadability tests, in vitro diffusion through nasal mucosa, gel strength assessments, stability studies, mucoadhesive force measurements, histopathological examinations, and ex vivo permeation analyses [17].

Visual Appearance:

The composed substances were looked at to see how well they worked. Before gelling, an Abbes refractometer could be used to check the purity of sols or formulas by measuring their refractive indices. During the testing process, D.W. was used as the refractometer's reference standard. By changing the refractometer scale, the cross wire of the telescope was placed exactly where the bright and dark parts met. By using the same method for each composition from F1 to F9, the results were compared to the refractive index of water [18].

pH:

To set up the electrical pH meter, pH buffer solutions of 4.0 and 7.0 were used. Each mixture was put into a beaker, which was then used to submerge the glass electrodes. After that, the solution's pH was checked three times [19].

Spreadability:

To test spreadability, the slip-and-drag method was used. A very carefully measured amount of FVT in situ gel was put on a clear glass plate. A clear slide was put on top of the gel-coated slide that was attached to a block of wood. A 100-gram weight was briefly put on the upper slide to make sure that the gel was spread out evenly. Because of this, the gel spread out evenly between the slides, leaving no residue on the edges. The weight was taken off, and then it was put on the wooden block [20].

Drug content:

A double-beam ultraviolet-visible spectrophotometer was used three times to check how much drug was in the mixtures. Nine milliliters were double-distilled water, and one milliliter of the mixture was put into a 10-milliliter volumetric flask. To make a 1 mL sample, 10 mL of double-distilled water were added to the first solution to thin it out. This was the last step: after the solution was made, its absorption was measured with a UV-visible spectrophotometer [21].

Viscosity:

For viscosity testing, the Brookfield viscometer was used. For checking viscosity, a miniature volume adaptor was used. At temperatures between 32 and 34 °C and spinning speeds between 3 and 100 rpm, the apparent viscosity values of the mixtures were recorded [22].

Mucoadhesiveness:

We used a custom-made mucoadhesive force testing tool to check the mucoadhesive force and detachment stress of the formulation. A modified balance method was used in the experiment, with two glass jars and ovine nasal mucosa. The temperatures of the bottles were between 32 and 34 degrees Celsius for a total of 10 minutes. On one side of the scale, a bottle was attached. At the same time, a 0.5 ml gel sample was placed between the two membranes that were attached to the bottom of the jars [23-25].

Gelling time:

The method that Miller and Donovan came up with was used to find out. Two milliliters were taken from each mixture and put into a test tube. The test tube was then put in a water bath. One degree Celsius at a time, the temperature of the water bath was raised, with a five-minute break between each rise. In order to see if gelation happened, the specimens were tilted 90°, which stopped the meniscus from moving. The gelling time was found by counting the number of minutes that passed since the first notice of gelation [26-28].

SEM Study:

Using SEM, the shape of F5 was looked at. On a sample stand, a drop of the F.T. in situ gel mixture was mixed with double-distilled water and left to dry in the air. The sample was looked at more closely using different magnifications and energies that went up to 15,000 volts. A high vacuum was used by the experts to get good pictures [29,30].

Compatibility Study:

At room temperature, the compatibility of excipients and medicines was tested. Infrared spectroscopy with Fourier transform. We used Fourier transform infrared spectroscopy to look at plastics and pure FVT (1:1). The KBr pellet method was used to look at the samples. For testing reasons, DSC was used. A rate of 10 degrees Celsius per minute was used to heat the samples from 50 to 300 degrees Celsius. In this material investigation, an empty metal pan was used as a standard to look at the DSC profiles of FVT, Carbopol, and in situ gel. A lot of people use Differential Scanning Calorimetry (DSC) to figure out the physical and energetic qualities of different materials and combinations of materials [31-33].

***Ex-vivo* drug permeation study:**

Five to ten minutes were set aside for each wash run. The clean nasal tissue was carefully placed on a sterile plate after the process was over. The nose mucosa tissue was carefully cut out with ophthalmic scissors and tweezers. A piece of the nasal tissue is carefully cut out and placed on a new, clean plate so that the surface faces upward. To fix the nasal mucosa, a tissue sampler is used, which produces 8 mm diameter circular pieces of tissue that are all the same shape. After being cleaned, the mucosal membrane was put into a 12-well transwell device so that the mucosal surface faced upwards. The pores in the filter membrane in the upper part are 0.4 µm in size. The whole transwell setup had about 600 µL of growth media in it, which is only half the thickness of the mucosal tissue. At 37°C and 5% carbon dioxide, the tissue was grown in an atmosphere. On the entertainment media, there were regular updates [34-37].

RESULTS AND DISCUSSION:

Physical characterization study:

Refractive index:

Table 2 and figure 1 showed that F5 had the highest refractive index (ARI), which was about 1.33 and was about the same as water. The other formulas, from F2 to F9, did not vary significantly from one another.

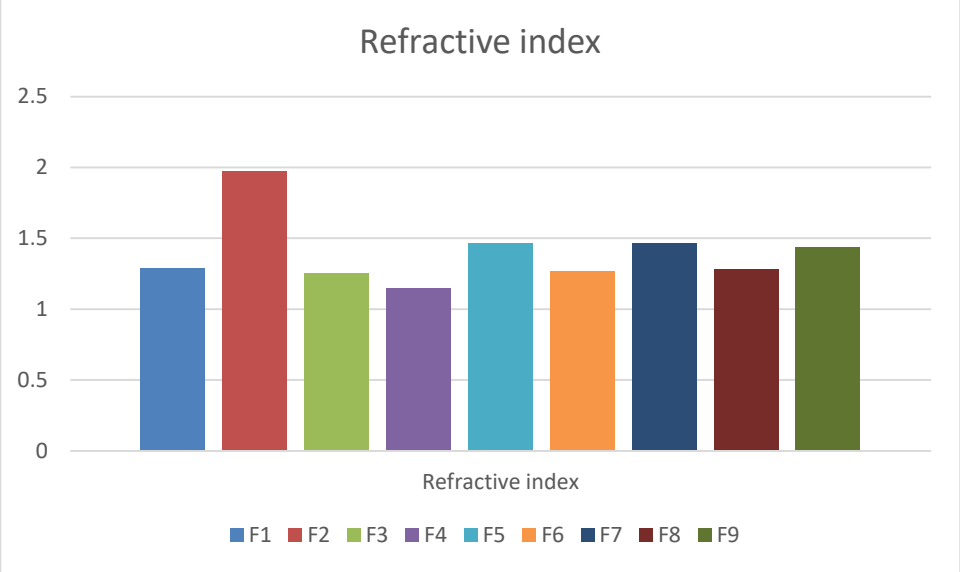

Figure 1: Refractive index of the prepared batches

pH:

It was checked to make sure that the pH of each mix was safe for the nasal passages. Compared to the other formulas, F5 had pH readings that were much higher (figure 2 and table 2).

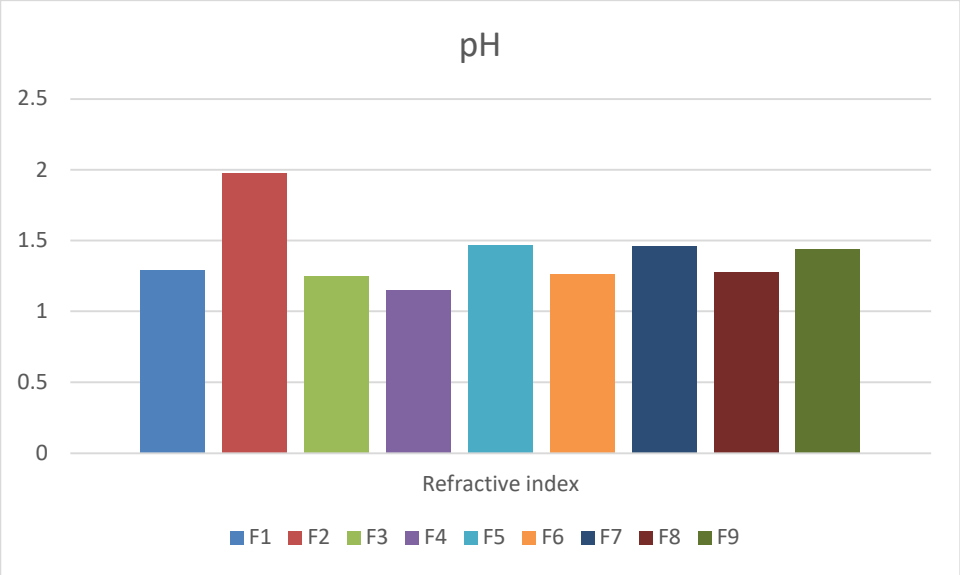

Figure 2: pH of the prepared batches

Drug content:

Table 2 shows that there wasn't a big difference between the formulas in the average percentage of active medicinal ingredients, which was between 92.33±0.36% and 99.68±0.34%. The mixture with the best release, F5, had a value of 99.68±0.34.

Table 2: Physical characterization study

Batches	pH	Appearance	Refractive index	% Drug
F1	4.50±0.031	Whitish	1.287±0.03	92.33±0.36
F2	5.35±0.045	Whitish	1.975±0.02	93.82±0.14
F3	6.51±0.061	Whitish	1.249±0.02	92.24±0.74
F4	4.40±0.033	Whitish	1.147±0.01	94.45±0.89
F5	6.48±0.084	Whitish	1.468±0.02	99.68±0.34
F6	5.34±0.025	Whitish	1.264±0.02	95.26±0.20
F7	4.25±0.069	Whitish	1.462±0.02	95.34±0.41

F8	4.75±0.037	Whitish	1.278±0.04	97.37±0.32
F9	5.29±0.364	Whitish	1.437±0.04	96.35±0.31

Viscosity:

Time of gelation and temperature conditions Mucociliary clearance is a big problem when it comes to delivering medicine through the nose. Making preparations with thermoreversible gels could be a good way to get around this problem. The current study used poloxamer and carbopol to make thermoreversible gels that were meant to make the drug more bioavailable. Because of this, our goal was to use pluronic F125 to make a thermoreversible gel that would stay gel-like between 24°C and 35°C but turn into a liquid below 24°C. In this study, F5 had the quickest gelation time. For all formulas, its gelation time ranged from 7.35±0.45 seconds to 12.26±0.52 seconds, and its gelation temperature ranged from 30.14±0.36°C to 37.27±0.44°C. This means that all of the formulas show the right temperatures for gelation.

Mucoadhesion:

A strong mucoadhesive force is very helpful for in situ gelling nasal formulations because it keeps the gel in the nose cavity longer before it can be flushed out without leaking. Also, F5 is better because a gel's strong mucoadhesive qualities can hurt the nasal mucosal membrane.

Surface morphology:

Shape optimization, segregation, uniformity, and monodispersity are all signs of a stable nanoformulation (figure 3). The nanoparticles were spread out in a single layer, which suggests that their surface charge may have helped them separate.

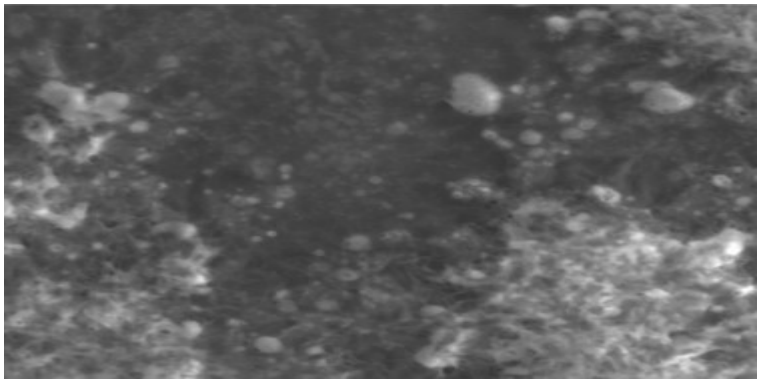

Figure 3: SEM image of an optimized batch of F5

Compatibility studies:

The pure FTIR spectrum of the drug was compared to the FTIR spectrum of the drug mixed with different polymers. The FVT spectrum, which showed a clear peak at 3120.94 and 3497.06 cm-1, confirmed that the main amide group did exist in monohydrate form. There is a C=O bond, as shown by the peak at 1666.48 cm-1, and an aromatic group, as shown by the spectral bands at 827 and 1100 cm-1. FTIR studies of drug-

polymer interactions show that the drug is compatible with pluronic F127 and carbopol, which is a gelling agent. This means that there is only a small amount of physical touch. The FTIR spectrum of the medicine with a physical mix of FVT, poloxamer 407, and carbopol can be seen in Figure 4. Figure 2 shows that the peaks at 1690, 1810, 2530, 2900, and 3300 cm-1 were clear, but the peak at 3500 cm-1 was less noticeable, which means there was only weak physical touch.

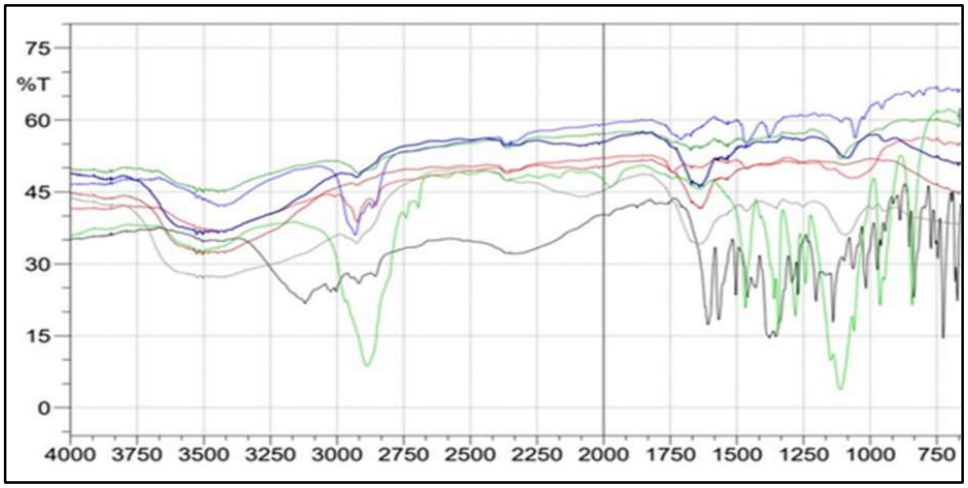

Figure 4: FTIR spectra of formulation and all excipients

The DSC thermogram of the pure FVT drug, the improved binary ethosome formulation, and the FVT-encapsulated in situ gel is shown in Figure 5. The pure FVT medicine showed an endothermic peak at 152.98°C for its melting point and breakdown, which shows that FVT is pure and crystallized. The drug's endothermic peak was measured at 102.75°C in the best FVT binary ethosome formulation. The drug reached its highest temperature at 104.92°C in the FVT-loaded in situ gel (F5). It's possible that the drug's decreased ability to absorb heat was caused by it mixing with other molecules, which made each part less pure in the end product. This doesn't always mean that they probably won't get along.

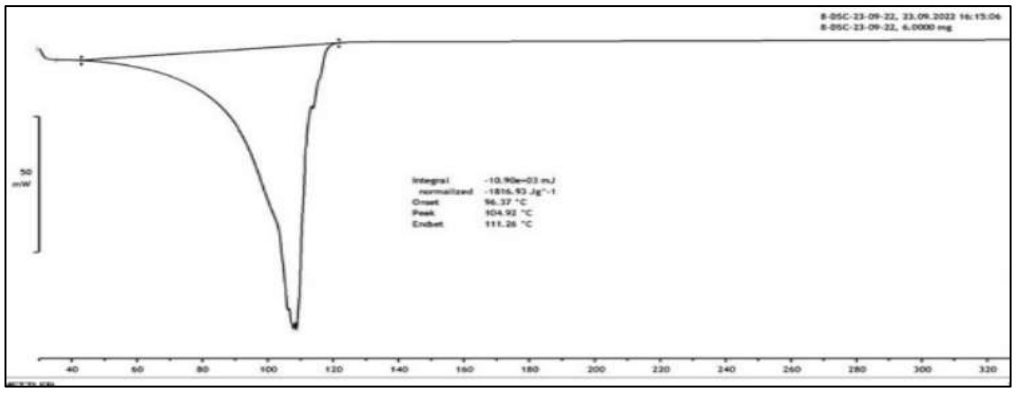

Figure 5: DSC Thermograms of optimized batch (F5) of formulation

Ex-vivo permeation study:

Ex vivo tests on goat nasal mucosa looked at how the drug permeated through an in situ gel that contained FVT. After 48 hours, people who were exposed to the FVT solution took in 150.43±1.55 mg/cm2, while people who were exposed to the F5 solution took in 498.45±1.34 mg/cm2. It took 1.765±0.24 mg/cm²/h for the FVT solution to reach steady state flow, while it took 6.864 mg/cm²/h for the F5 solution. It was about 4.24 times more permeable when FVT was encapsulated in situ gel than when the drug solution was used. This meant that the treatment would reach the nasal mucosa.

CONCLUSION:

Its thermoreversible polymer and carbopol made it possible for better gelation thickness, gel strength, drug release, and mucoadhesive strength. A thermoreversible, mucoadhesive in situ intranasal gel was made with frovatriptan succinate. The mucoadhesive properties of the gel make it stay in the nasal cavity longer, and its thermoreversible properties make it easier to work with and give. The best amount of pluronic F127 for mucoadhesive strength and the right temperature for the phase change is 0.2% w/v. Carbopol makes the drug work better by increasing its entry. This mixture didn't have a big effect on the nasal membranes. This study shows that Frovatriptan succinate works well as a new mucoadhesive in situ intranasal gel for treating migraines. This form makes Frovatriptan succinate more bioavailable and permeable to the brain. Because of this, we suggest using it instead of the commonly sold oral dose form, which is not as bioavailable or permeable to the brain.

Funding:

None

Conflict of Interest:

None

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