





Frovatriptan Succinate Intranasal Delivery for Brain Targeting – *In Vivo* Study

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A B S T R A C T

Muco-adhesive gel formulations are advantageous in extending the stay at the nasal absorption place, promoting drug absorption. Frovatriptan succinate (FVT) exhibits a 35% oral bioavailability and undergoes hepatic metabolism, making it a viable candidate for nasal delivery. This study aimed to assess novel FVT intranasal formulation for brain targeting in rat animal models. A total of 78 female rats (*Rattus norvegicus domestica*, Wister albino rats) were randomly divided into three groups: group A (considered a negative control), group B (includes 36 rats given FVT IV solution), and group C (includes 36 rats given FVT binary ethosome in situ gel intranasally). Drug levels in plasma and brain tissue were measured using HPLC methods. In all periods, for both brain tissue concentrations of FVT and the brain-to-plasma ratio of FVT, it was significantly higher in Group C compared to Group B. Nasal administration of FVT showed higher brain T_{max} , C_{mac} , and AUC compared to IV administration, with 239.83% higher accumulation of FVT when nasal formulation used compared to IV administration. In conclusion, in situ gel has demonstrated its efficacy in facilitating the delivery of frovatriptan succinate via the nasal route. The convenience of the administration process, combined with reduced frequency of administration, contributes to improved patient adherence.

Keywords: frovatriptan, intranasal, brain, in situ gel

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INTRODUCTION

The prevalence of migraines is estimated to impact approximately 12% to 15% of the population (1, 2). This condition's prevalence is higher among females than males, with annual incidence rates of up to 17% in females and 6 percent in males (3, 4). The most prevalent kind of migraine is migraine without aura, which constitutes around 75% of reported instances (5). Migraine is a significant contributor to disability and is recognized as the 2nd most prevalent condition globally in terms of years lived with disability, following low back pain (6). The prevalence of migraines is highest among individuals between the ages of 30 and 39. Within this age range,

migraines are reported to be 7% in males and 24% in females (4). There is a hereditary component associated with the occurrence of migraines (7). The condition leads to substantial declines in overall well-being and is more incapacitating compared to episodic migraine (8). Furthermore, persistent migraine incurs a significant financial burden on society (9).

Based on existing literature, it is widely accepted that a fundamental malfunction in neuronal activity initiates a series of intracranial and extracranial alterations that contribute to the manifestation of migraine (10). These alterations encompass the premonitory symptoms, aura, headache, and postdrome phases (11). The vascular theory of migraine, previously widely accepted, posited that the

expansion of blood vessels triggered migraine headaches, while the accompanying aura was attributed to the constriction of blood vessels. However, this explanation is now deemed untenable. The occurrence of vasodilatation during spontaneous migraine attacks, if present, is likely to be an epiphenomenon that arises from instability in the central neurovascular control mechanism (12-15).

There are several migraine treatment formulations, but the limitations of drug delivery systems have hampered development (16). While intranasal (IN) drug delivery is an attractive option, its main disadvantages are small nasal cavity capacity (0.2 mL), anterior leakage, and mucociliary clearance, which might impair the effectiveness of the nasal medication delivery system (17, 18). Migraine is defined by intense pain and increased sensitivity to sensory stimuli, leading to a decrease in regular daily activities. Migraines are challenging to investigate in laboratory animals due to the occurrence of pain without tissue damage and the constraints of current behavioral tests (19). Several studies have employed the reduction of activity (such as locomotor activity, eating, and rearing) to evaluate discomfort caused by headaches in rodents (20-23). In addition, migraines are present in other animal models like dogs (24). There are three groups of animal models for migraines: vascular, neurovascular, and molecular/genetic animal models (25, 26). The vascular models use vasoconstriction or vasodilation of relevant vessels (carotid arterial bed, arteriovenous anastomoses, and other meningeal arteries) to study vascular changes during a migraine attack and the effect of drugs on them. Pig and dog models have been used to constrain the external carotid artery (27). The major limitation of these animal models is that they do not reflect the complexity of migraine and focus only on the vascular changes, which, as aforementioned, are an epiphenomenon and not the main cause (25, 28). The current study instead focuses on the drug level in the rats' brain tissue.

The olfactory route seems to bring benefits over other modes of administration, such as a faster initiation of action, greater absorption, and fewer undesirable effects. In previous decades, the nasal route has been regarded as the most noninvasive, practical, safe, and dependable way to target the brain (29). Nasal medication distribution is a complex area of research for modern pharmaceutical scientists (30-32). Oral administration of some medications causes an adverse reaction; administration via the nose is an excellent alternative (33). Intranasal administration boosts bioavailability by avoiding first-pass metabolism and postponing partial absorption in the digestive system (34, 35). Several mechanisms facilitate transport through the nasal mucosa, including passive diffusion, carrier-mediated transcytosis, and the passage of molecules via specialized intercellular gaps. Nasal delivery has restrictions that reduce its application, such as the delivery of a small amount of drug molecules and their quick

expulsion from the nasal canal. By paying greater attention to the drug molecules, formulation matrix, nasal mucosa, and drug delivery systems, nasal medicine absorption can be improved (36, 37).

Frovatriptan (FTV) is classified as a second-generation triptan, which is a group of medications that function as selective serotonin 5-HT_{1B/D} agonists. Its mechanism of action is similar to that of sumatriptan (38, 39), the first triptan to be introduced and considered the prototype for this pharmacological class. FTV is indicated for the acute management of migraine attacks. Minor differences in efficacy, headache recurrence, and adverse effects can be observed when comparing the pharmacologic profile of FTV to sumatriptan. Currently, the only approved formulation of FTV is an oral tablet, which was approved in 2001 (40).

The challenge for the formulator is great when attempting to find a method to infiltrate the mucus lining of the nasal canal without inflicting irreversible tissue damage. Nasal treatments quickly rid the nasal cavity of the most persistent ailments. The elimination half-life is 15-20 min for non-muco-adhesive liquid and powder formulations. Thus, mucoadhesive gel formulations may decrease muco-ciliary clearance and increase residence duration close to the point of nasal absorption, facilitating medication uptake. To increase nasal bioavailability, viscosity-enhancing polymers or gel may be utilized; this maintains the medication in contact with the nasal surface for an extended duration, increasing bioavailability. In situ gel is a drug delivery system that undergoes a sol-to-gel phase transition when physicochemical parameters like ionic strength, temperature, or pH vary (29, 41, 42).

In situ gelling systems that are ion-activated include gellan gum and sodium alginate, whereas temperature-dependent methods include Pluronic, Tetronic, and polymethacrylates (e.g., Carbopol and cellulose acetate phthalate) (18, 43, 44). In situ, gels provide several advantages over typical gels, such as being simpler to produce, injectable as a liquid, and able to remain on the surface of the nasal cavity for a longer time owing to gelling (45-50). In this study, the polymer poloxamer 407 and the mucoadhesive polymer Carbopol 934 were used to develop in situ gel formulations of FTV for intranasal distribution, to extend the drug's residence time in the nasal cavity and enhance its absorption across the nasal-mucosal barrier. This study aimed to assess the novel FTV of intranasal formulation for brain targeting in rat animal models.

MATERIALS AND METHODS

Ethical Statement

The local Research Ethical Committee, College of Pharmacy, University of Baghdad reviewed and approved all procedures in this study (Approval Number: RECAUBCP532022G, dated May 2, 2022).

Chemicals

Frovatriptan succinate (CAS Number: 158930-17-7) was purchased from Pharmaffiliates (Catalogue number: PA 06 83000, India), Tween 80® [polysorbate 80] (CAS Number: 9005-65-6) was purchased from Innovative Chemical Interchange Pvt. Ltd. (ID: CH-PTY6DXH, India), phospholipon® 90H [Phospholipids, hydrogenated, with 70% phosphatidylcholine] was purchased from Pharma Excipients™ (CAS-No. 97281-48-6), the remaining chemicals and reagents were of analytical grade and procured from local vendors.

Study Design and Settings

The study included a total of 78 female rats (*Rattus norvegicus* domestica, Wister albino rats), weighing 180–220 g, aged 2-3 months (51, 52); these rats were randomly divided into three groups: group A (6 rats considered a negative control, and plasma and brain tissue used to calibrate the HPLC to measure the drug concentration), group B (includes 36 rats, divided into six groups each contain six rats at each time of administration of the drugs (the drug was given IV via Tail vein injection), after 30 minutes, after 1 hour, after 3 h, after 6 hours, after 12 h, and after 24 h) given FVT IV solution at dose 0.257 mg/kg, and group C (includes 36 rats, divided into six groups each containing six rats at each time of administration of the drugs, administered the same times as in group B) given FVT binary ethosome in situ gel intranasally (IN) at dose 0.257 mg/kg. Following completion of therapy, all animals were anesthetized intraperitoneally (IP) with 80 mg/kg of ketamine (Ketamine 10%, Alfasan Nederland BV, Holand) and 10 mg/kg of xylazine (XYL-M2, VMD® Livestock pharma, Belgium). In the current study, we focused on 24 h and divided the times to mimic its normal effect (first few hours after administration, then every 6 hours till 24 hours). Following total anesthesia, all rats were sacrificed by carbon dioxide (53, 54). After the end of each group's experimental period, dissection was done for the euthanized rat, and the plasma and brain tissue were removed and weighed for further analysis.

The rats were obtained from the (Animal Facility of the College of Pharmacy –University of Baghdad, Baghdad, Iraq), housed in polypropylene cages under a temperature-controlled environment (25 °C), with an inverted light-dark cycle (12/12 h), and acclimated for ten days before starting the experiment at the same center where the rats were obtained (Animal Facility of the College of Pharmacy, University of Baghdad, Baghdad, Iraq). The animals were maintained on a standard pellet diet and free access to water ad libitum supplied by the Animal Facility of the College of Pharmacy, University of Baghdad.

Dosing

The usual human dose of FVT is 2.5 mg (per 60 kg) per day; based on the Reagan-Shaw study (55), this dose is

converted to animal dose (rat) based on the following equation.

$$\text{HED (mg/kg)} = \text{AED (mg/kg)} \times \frac{\text{Animal } K_m}{\text{Human } K_m}$$

Where, HED is the human effective dose, AED is the animal effective dose, and K_m is the conversion factor (for human adults, it is 37, and for rats, it is 6) (55). Based on this equation, the animal dose was 0.257 mg/kg. Under shallow ether anesthesia, rats from the test group were administered FVT binary ethosome in situ gel intranasally with an insulin syringe attached to a small cannula (1 mL). They inserted the required dose into each nostril.

Preparation of the FVT Formulation

In the preparation of IV FVT formulation, dry powder of FVT was dissolved in Tween 80® [polysorbate 80] and buffer solution (pH 6.8). While the IN FVT was prepared as binary ethosome gel [BEG] (BEG was prepared first by mixing the dry powder of FVT and 1% v/v phospholipon® 90H and 1 mg of cholesterol, then the mixture was dissolved in ethanol 30 mL, and ten w/v propylene glycol, finally the obtained BEG formula was introduced into in situ gel form.

Sample Preparation for Analysis

Plasma Treatment

Utilizing a cooling centrifuge (Z216MK, Hermie Labortechnik GmbH, Germany). The blood sample was centrifuged for 10 minutes at 4000 rpm to separate the plasma, then stored at 80 °C. For the sake of analysis, 500 µL of each of the plasma samples was combined with 100 µL of the "internal standard DILT solution" (1000 ng/ml) and 1 mL of "acetonitrile." The mixture was vortexed for 30 seconds (Vortex, IKA MS3 Digital, Germany) and then centrifuged for 15 minutes at 6000 rpm. HPLC was used to determine the amount of FT in the supernatant (56).

Brain Treatment

Each piece of the obtained tissue from the rat brain was homogenized (Heidolph DiAx 900, Germany) for one minute at 25,000 rpm with three times the volume of ordinary saline. Brain homogenates underwent the same processing steps as plasma samples to determine their FTV content (57).

Brain-to-Plasma Ratio

Based on the levels of FVT in the brain and in the plasma, their ratio will be used to indicate drug accumulation in the brain compared to its levels in the plasma.

HPLC Analysis of FTV-Succinate

The HPLC system (Agilent Technologies 1200 series, Germany) consisting of a G1315D diode array detector, an

LC-G 1311A solvent delivery pump with a 20- μ L loop, and a rheodyne sample injector was employed. The mobile phase, which was composed of "acetonitrile and potassium phosphate buffer" (10 mM) 35:65 (v/v), was adjusted to pH 5.5 with orthophosphoric acid and ran on an Agilent® TC-C18 column (250 mm 4.6 mm ID, particle size 5 μ m) at 30 °C. The injection volume was 50 μ L, and the elute was seen at 255 nm with a 1 mL/min flow rate.

Sample Size and Randomization

For sample size computation, [program G Power](#) was utilized (58) based on Cohen's principles (59). A table of random integers was used to construct the groupings at random; the animals were placed in labeled containers and given tail tags to minimize misunderstanding (60). Six animals were enough for kinetics studies (we needed to minimize the number of animals; the usual sample size was between 5 - 10 animals per group, which was common in animal studies; from the statistical point of view, this was related to large effect size (0.5 in this study)(61)

Statistical Analysis

The current study used GraphPad Prism version 10.0.1 for statistical analysis. The descriptive statistics were reported as mean \pm standard deviation (SD). The independent t-test was applied to verify the significance of the difference between the studied groups, followed by the post hoc Tukey test. The differences between the groups were considered significant statistically when the P-value was ≤ 0.05 .

RESULTS

During the first 30 min, there was no significant difference in plasma levels between groups B and C; after

60 min, 3, 6, 12, and 24 h, the plasma level of FVT was significantly higher in group B compared to group C. At all times, but for both brain tissue concentrations of FVT and the brain-to-plasma ratio of FVT, it was significantly higher in Group C compared to Group B, as illustrated by Table 1 and Figures 1, 2, and 3.

Table 1. Change in plasma, brain, and plasma-to-brain ratio of Frovatriptan levels according to the study groups

Time	Group B	Group C	P-value
Plasma			
30 min	10.8 \pm 2.99	14.7 \pm 8.39	0.3110
60 min	28.8 \pm 2.00	15.3 \pm 3.81	<0.001
3 h	40.4 \pm 2.61	25.6 \pm 7.82	0.004
6 h	89.2 \pm 7.91	60.6 \pm 12.4	0.001
12 h	35.2 \pm 7.43	49.6 \pm 8.88	0.013
24 h	9.82 \pm 2.98	30.3 \pm 3.55	<0.001
Brain			
30 min	2.66 \pm 0.46	30.8 \pm 22.5	0.028
60 min	7.56 \pm 1.62	35.9 \pm 8.34	<0.001
3 h	8.85 \pm 2.92	69.2 \pm 26.7	0.002
6 h	23.2 \pm 6.56	123 \pm 21.3	<0.001
12 h	8.30 \pm 2.40	121 \pm 37.1	0.001
24 h	2.31 \pm 1.04	83.2 \pm 15.6	<0.001
Brain to plasma			
30 min	0.26 \pm 0.07	1.98 \pm 0.46	<0.001
60 min	0.26 \pm 0.06	2.40 \pm 0.50	<0.001
3 h	0.22 \pm 0.07	2.68 \pm 0.48	<0.001
6 h	0.26 \pm 0.08	2.07 \pm 0.43	<0.001
12 h	0.24 \pm 0.05	2.43 \pm 0.46	<0.001
24 h	0.23 \pm 0.04	2.78 \pm 0.65	<0.001

Nasal administration of FVT showed higher brain Tmax, Cmac, and AUC compared to IV administration, with 239.83% higher accumulation of FVT in the brain tissues when nasal formulation was used compared to IV administration, as illustrated by Table 2 and Figures 4 and 5.

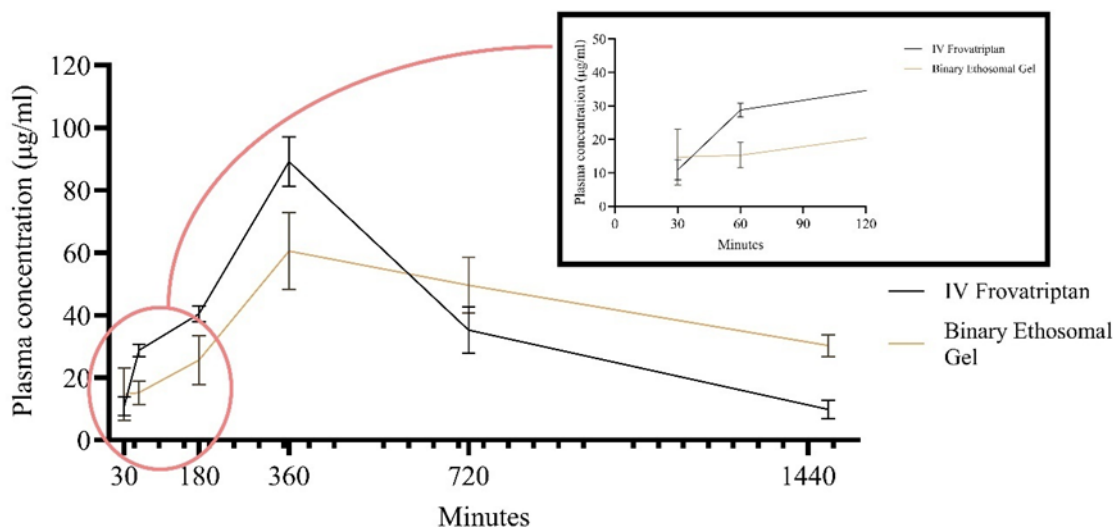


Figure 1. Assessment of plasma concentrations of IV and intranasal frovatriptan

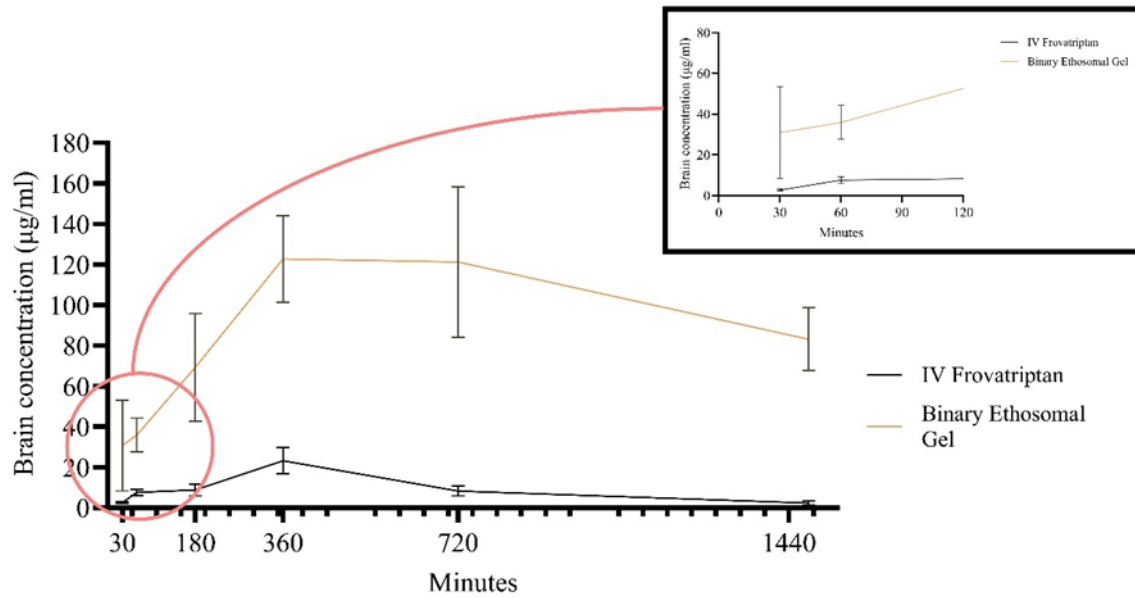


Figure 2. Assessment of brain tissue concentrations of IV and intranasal frovatriptan

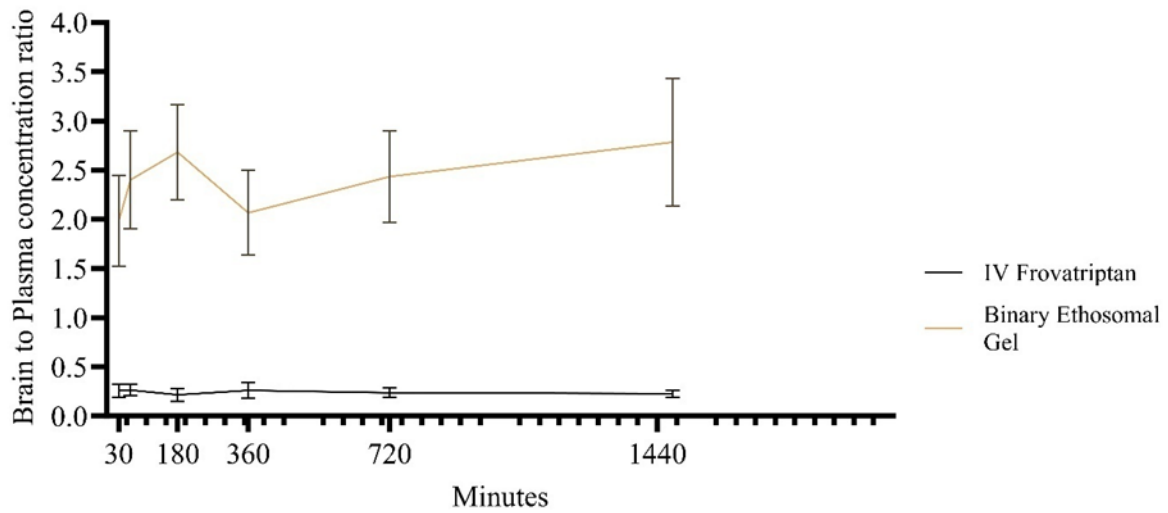


Figure 3. Assessment of brain tissue to plasma concentrations of IV and intranasal frovatriptan

Table 2. Pharmacokinetic parameters, brain targeting efficiency, and direct nose-to-brain transport following administration of FVT formulations

Parameters	Route of administration	Plasma	Brain
T _{max} (min)	Nasal	581.74	643.04
	IV	336.52	336.52
C _{max} (µg/mL)	Nasal	54.16	125.24
	IV	72.67	18.05
AUC 0-24 (µg h/mL), mean ±SEM	Nasal	59234±4625	142058±16780
	IV	55015±3569	13508±1710
Absolute bioavailability (%)		107.67%	-
Ratio of AUC brain tissue/AUC plasma (%)	Nasal	239.83%	
	IV	24.55%	

AUC: area under the curve, SEM: standard error mean

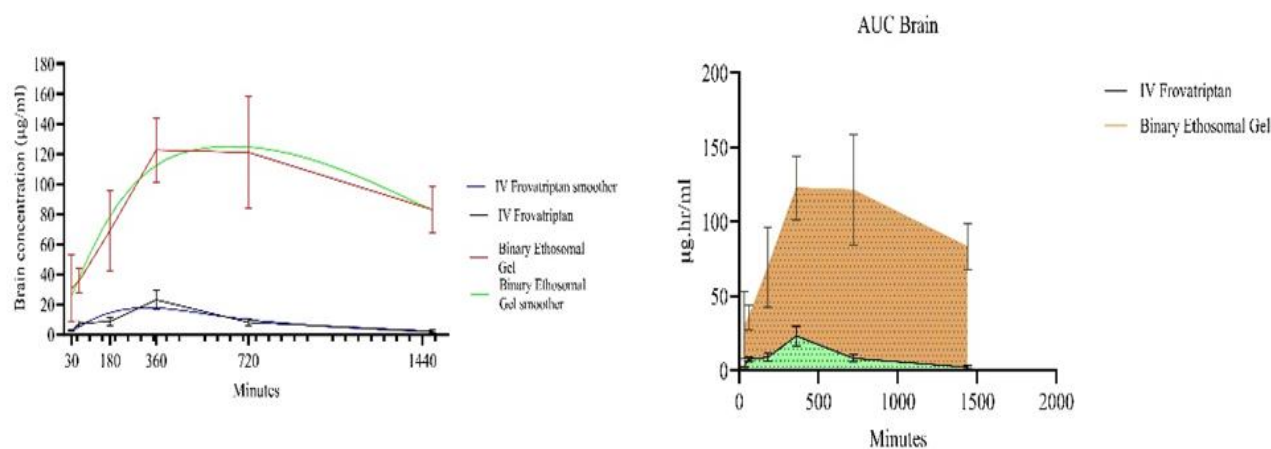


Figure 4. Assessment of pharmacokinetic study of FVT levels in brain tissue by measuring total concentration of the drug according to mode of delivery (AUC)

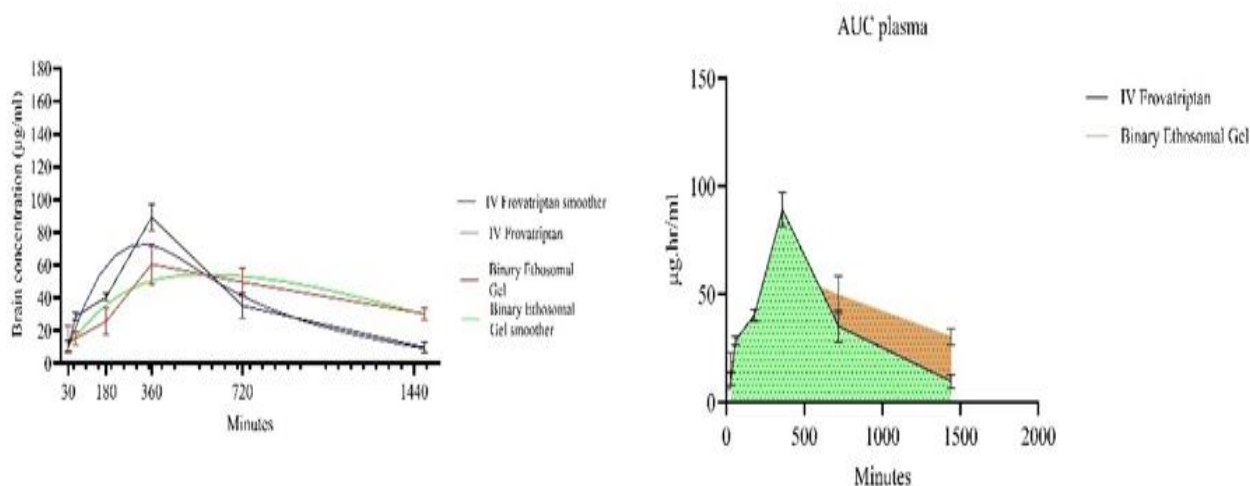


Figure 5. Assessment of pharmacokinetic study of FVT levels in the plasma by measuring the total concentration of the drug according to mode of delivery (AUC)

DISCUSSION

Researchers have created gel-based medication carriers to address the earlier constraints that can be delivered through the nose-to-brain pathways. This methodology was characterized by its noninvasive nature since it effectively improves the absorption of drugs while minimizing systemic adverse effects and circumventing the BBB. In the current study, FVT was successfully delivered intranasal to brain tissue with 239.83% higher accumulation in the brain than in IV administration. The brain's maximum concentration (C_{max}) was higher, 125.24 vs. 18.05 µg/ml, compared to IV administration. This improvement in FVT concentrations in the brain reflects enhanced targeting at lower doses of FVT and less frequent application of FVT, ultimately reducing side effects and enhancing the drug's efficacy.

Treating neurological disorders involves applying medical treatments via topical, oral, and intravenous routes (62). Several techniques encompass the administration of the medicine through direct injection into the brain, cerebrospinal fluid, or intranasal delivery. Several techniques are deemed hazardous, harmful, limited in scope, and have temporary effects (63, 64). The blood-brain barrier (BBB) serves as a physiological barrier that restricts the transport of several medicines to the central nervous system and impedes the passage of medications over the endothelial capillaries to reach the brain (63).

Several researchers have conducted a study on intranasal nanoparticles containing FVT and have observed that these nanoparticles have the potential to penetrate the brain tissue through the olfactory region when administered via the nasal route. Therefore, the administration of drugs through the intranasal route can

lead to a reduction in systemic circulation, thereby minimizing undesirable effects. Additionally, this method allows for more precise targeting and a faster commencement of action (65), which agrees with the current study. A recent study that examined Poloxamer-Based in Situ Nasal Gel of Naratriptan Hydrochloride showed promising results for brain targeting (66). Othersexamined sumatriptan succinate nasal gel as intranasal delivery and found increased concentration in the brain (67).

Over the latest research, there has been an investigation into the potential utilization of the nasal mucosa as a viable pathway for drug delivery, intending to achieve enhanced levels of drug absorption that are both expedited and elevated. The nasal cavity offers several notable advantages, including convenient accessibility, favorable permeability primarily for lipophilic and low molecular weight medications, limited proteolytic activity, protection against harsh environmental factors and hepatic first-pass metabolism, and the potential for direct administration to the brain (68).

In situ gel has demonstrated its efficacy in facilitating the delivery of frovatriptan succinate via the nasal route. The convenience of the administration process, combined with reduced frequency of administration, contributes to improved patient adherence.

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N/A

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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فروقاتريبتان سكسينات الذي تم توصيله عبر الأنف لاستهداف الدماغ - دراسة داخل الجسم الحي

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الخلاصة

تعتبر التركيبات الهلامية اللاصقة المخاطية مفيدة في إطالة فترة البقاء في مكان الامتصاص الأنفي، مما يعزز امتصاص الدواء. يُظهر فروقاتريبتان توافراً حيوياً عن طريق الفم بنسبة ٣٥٪ ويخضع لعملية التمثيل الغذائي الكبدي، مما يجعله مرشحاً صالحاً للتوصيل عن طريق الأنف. الهدف من هذه الدراسة هو تقييم تركيبة فروقاتريبتان سكسينات الجديدة داخل الأنف لاستهداف الدماغ في نموذج حيواني الفئران. تم تقسيم إجمالي ٧٨ جردي (ويستر البينو) عشوائياً إلى ثلاث مجموعات: المجموعة أ (تعتبر سيطرة سلبية)، المجموعة ب (تتضمن ٣٦ جرذ أعطيت محلول فروقاتريبتان سكسينات الوريدي)، والمجموعة ج (تتضمن ٣٦ جرذ). إعطاء فروقاتريبتان سكسينات ثنائي إيوسوم في الموقع عن طريق الأنف). تم قياس مستويات الدواء في البلازما وأنسجة المخ باستخدام طرق التحليل الكروماتوغرافيا. في جميع الفترات، بالنسبة لكل من تركيزات أنسجة المخ من سكسينات فروقاتريبتان ونسبة الدماغ إلى البلازما من سكسينات فروقاتريبتان، كانت أعلى بشكل ملحوظ في المجموعة ج مقارنة بالمجموعة ب. أظهر تناول فروقاتريبتان سكسينات عن طريق الأنف ارتفاعاً في الحد الأقصى للوقت الأقصى للدماغ، والحد الأقصى التركيز والمساحة تحت المنحنى مقارنة بالإعطاء الوريدي، مع تراكم أعلى بنسبة ٢٣٩,٨٣٪ سكسينات فروقاتريبتان عند استخدام التركيبة الأنفية مقارنة بالإعطاء الوريدي. في الختام، أثبتت الجر في الموقع فعاليته في تسهيل توصيل فروقاتريبتان سكسينات عبر الطريق الأنفي. تساهم سهولة عملية الإدارة، إلى جانب انخفاض وتيرة الإدارة، في تحسين التزام المريض.

الكلمات المفاحية: فروقاتريبتان، عبر الأنف، الدماغ، التركيبات الهلامية اللاصقة المخاطية