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Rizatriptan Benzoate Mucoadhesive Nasal Delivery for Targeting the Brain Pharmacokinetics of Nasal Delivery and Intravenous Solution in Wistar Rats

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Abstract

Owing to the restricted oral bioavailability of antimigraine drugs Rizatriptan Benzoate (RNB), nasal delivery was employed in lieu of enhancing the bioavailability and brain targeting through utilizing spanlastics nanovascular. This work sought to formulate RNB as mucoadhesive spanlastics nanovesicles and assess the pharmacokinetic parameters and histopathological effects of the formulations on the nasal mucosa of rats. RNB was formulated as mucoadhesive spanlastics nanovesicles; the study comprised ٦8 Wistar rats, each weighing 200±35 g, divided into three groups (control, IN, and IV). RNB is quantified in rat plasma and brain using reverse-phase high-performance liquid chromatography (RP-HPLC). The pharmacokinetic studies on rats indicated that the brain Cmax of intranasal mucoadhesive RNB spanlastics was approximately two times greater than that of intravenous RNB – solution. No damage to the structure of the mucosal membrane was seen during the histological analysis. Consequently, the developed and optimized intranasal mucoadhesive RNB formula demonstrated outstanding potential for safe and effective administration of RNB.

Keywords: Rizatriptan benzoate. Mucoadhesive spanlastics, Nasal delivery ,Brain targeting

Introduction

Migraine is a complex disorder influenced by genetic factors. It is characterized by recurrent bouts of severe headache, usually unilateral, accompanied by symptoms like nausea and increased sensitivity to light and sound. Migraine episodes are intricate cerebral events that occur over hours to days in a recurrent manner. The most common type of migraine is the non-aura variant, comprising 75% of all cases [(1,2)].

Rizatriptan benzoate (RNB) is a potent and selective agonist of the 5-HT1B/1D receptors. It is utilized to manage acute migraines with and without aura and to alleviate the intensity of migraine symptoms such as pain, nausea, and photophobia or phonophobia (3,4).

Rizatriptan is metabolized in the liver through oxidative deamination, facilitated by MAO-A. When administered intravenously, 89% of the parent compound and its metabolites are eliminated in the urine, whereas 82% are excreted when taken orally [(5,6)] .

Intranasal dosing is less intrusive than alternative drug administration methods and is widely accessible for both adult and pediatric patients. Intranasal drug administration is generally more efficacious than the oral route for the same medication. The intranasal route have several advantages over intravenous route and can achieve therapeutic drug concentrations, rendering it an effective delivery strategy for various applications [(7,8)] . Tahar S and Kinani K found that nasal administration of Dolutegravir Sodium appears to improve pharmacokinetic parameters as compared to intravenous route [(9)] .

The oral and parenteral routes are the most commonly used medication delivery methods. The advantages of these pathways are widely recognized. Still, both tactics have several constraints, particularly regarding brain disorders. A developing and innovative non-invasive technique for delivering therapeutic compounds to the brain uses new drug delivery systems via the intranasal route. The nasal passage provides a direct pathway for medication administration to the brain, due to the distinct link between the nose and the brain [(10,11)].

Consequently, nanocarriers like Spanlastics nanovesicles (SPs) have been created to surmount their constraints. The formation of surfactant-structured SPs is attributed to the bilayer membrane

of surfactant macromolecules encasing a drug solution in water, which consists primarily of a Span® and an edge activator (EA) that augment their flexibility and deformability, facilitating the translocation of medicines across biological membranes [12]. Gupta et al. improve that intranasal delivery of piperine SPs is an excellent route for the drug administration and management of epilepsy [13] .

Furthermore, SPs may effectively transport hydrophilic and hydrophobic pharmaceuticals encapsulated inside internal hydrophilic and external lipid layers. Additionally, SPs exhibit osmotic activity, biochemical stiffness, prolonged shelf life, and high customer satisfaction. Notably, SPs are non-toxic nanovesicles compared to other vesicles made of cationic surfactants. Furthermore, they have been documented to improve drug penetration across many pathways, including transdermal, ocular, and intranasal routes. The possible function of RNB-loaded SPs in managing migraine via the nasal route has not yet been investigated [14].

The present study aims to develop and assess a brain-targeted mucoadhesive intranasal drug delivery system utilizing RNB SPs carriers to enhance nasomucosal adhesion and promote direct brain targetability. The intranasal method may be considered a viable alternative to intravenous RNB treatment for migraines.

Materials and Methods

Materials

RNB was supplied from Baoji Guokang Bio-Technology CO., LTD,China , Soluplus® was purchased from Hyper-Chem LTD CO, China , Span®60 and ethanol from Thomas Baker, India . Hyaluronic acid and HPMC K4M) was supplied from Hyperchem LTD CO, United Kingdom.

Methods

SPs were synthesized using an ethanol injection technique. Ten milliliters of ethanol dissolved 7.265 mg RNB and 50mg Span®60. The alcoholic solution was heated and gradually injected into a preheated (70°C) water solution (10 mL) containing dissolved Soluplus® 12 mg (edge activator). Stirring was sustained on a magnetic stirrer for one hour till the total evaporation of ethanol was achieved. The generated dispersion was sonicated for 8 minutes to achieve a fine SPs dispersion and inhibit aggregation. Ultimately, the resultant SPs (10mg) underwent four successive freeze-thaw cycles at -8 °C for 8 hours and at 25 °C for 1 hour, to improve the trapping of RNB within the nanosystem [15,16] .

The mucoadhesive RNB SPs formulation was prepared by incorporating a specified amount of hyaluronic acid (HA) and Hydroxypropyl methyl cellulose (HPMC K4M) into specified volume of the prepared SPs dispersion corresponding to 7.265 mg of RNB, stirred continuously for one hour, and then stored in a refrigerator (4ºC) to allow the mucoadhesive components to dissolve fully. Moreover, benzalkonium chloride at a concentration of 1 mg w/v was incorporated into the final formulation to prevent the growth of microorganisms. The final compositions of the mucoadhesive RNB SPs formulations were depicted in Table (1) [17,18].

Table 1.Formulations of mucoadhesive RNB SPs

Form. No.	RNB mg	Span® 60 Mg	Soluplus® mg	HA mg	HPMC K4M mg	Benzalkonium chloride mg	D.W. q.s. 10 ml
1	7.265	50.0338	12.7543	50		1	10
2	7.265	50.0338	12.7543	100		1	10
3	7.265	50.0338	12.7543	200		1	10
4	7.265	50.0338	12.7543		50	1	10
5	7.265	50.0338	12.7543		100	1	10
6	7.265	50.0338	12.7543		200	1	10

In-Vitro Evaluation of Mucoadhesive RNB Spanlastics Formula

pH and Osmolarity Investigation

The pH and osmolarity of the nasal formulation were measured to assess whether they were within the permitted ranges to avoid harming the nasal mucosa. The pH was measured at room temperature using a digital pH meter [19].

The osmolarity of the formulations was measured using an osmometer. A micropipette was utilized to extract 100 µL from each mucoadhesive SPs formulation (F1-F6), which was subsequently transferred to Eppendorf tubes for analysis in the osmometer. The freezing point depression was subsequently quantified to evaluate osmolarity [20] .

Mucoadhesive Test

The mucoadhesive characteristics of mucoadhesive RNB SPs formulations were evaluated to ascertain their capability for mucin adsorption. Utilizing a UV spectrophotometer, all six formulations (F1-F6) were subjected to mucoadhesive investigations to provide the maximum possible contact duration between the formulations and the nasal mucosal layer cavity. The muco-adhesion characteristics of mucoadhesive formulations were evaluated by combining 5 mL of each formulation with 5 mL of a mucin solution (1 mg/mL). Following a 2-hour incubation at 37 ± 0.5°C, the mixture was centrifuged at 3000 revolutions per minute for 60 minutes. The concentration of free mucin was assessed by extracting the supernatant, diluting it, and conducting spectrophotometric analysis. The subsequent equation (1) can be employed to determine the efficacy of muco-adhesion [21].

$$\text{Mucoadhesive efficiency } \% = \frac{Co - Cf}{Co} \times 100 \quad (1)$$

Where C_0 = initial mucin content and C_f = free mucin content

Field Emission Scanning Electron Microscope (FESEM)

A drop from an optimized SPs formula was applied and air-dried onto aluminium stubs. The slide was affixed to the specimen holder using double-coated adhesive tape. A sputter coater was subsequently employed to deposit gold onto the slide during a ten-minute vacuum period. This was executed to provide a uniform coating that would facilitate high-quality scanning electron microscope photographs; multiple magnifications were employed to obtain the images with FESEM [22].

Selection of the Optimum Mucoadhesive RNB SPs Formula

The optimal formulation of mucoadhesive RNB SPs was determined based on the findings obtained from the assessment tests. The parameters include pH, osmolarity, mucoadhesion testing, and morphology by utilizing Field Emission Scanning Electron Microscope (FESEM). The optimized formulation may be chosen and utilized for *in-vivo* study.

In-Vivo Pharmacokinetics Study

Pharmacokinetic and brain drug distribution experiments were conducted for intranasally administered mucoadhesive RNB SPs (selected formula) and RNB IV solution. The research included 68 female Wistar albino rats, weighing between 180 and 220 gm, aged 2 to 3 months. The rats were randomly allocated into three groups: Group A consists of two rats designated as a negative control, which will be euthanized early to procure plasma and brain tissue for HPLC calibration to quantify drug concentration. Group B comprises 33 rats divided into 11 groups, each containing three rats, corresponding to each time point of drug delivery [23,24] .

Group B received RNB IV solution at a dosage of 0.7474 mg/kg at 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 3 hours,4 hours, 6 hours,8 hours,10 hours, and 24 hours. Group C, comprising 33 rats divided into 11 groups of three rats each, received mucoadhesive RNB SPs intranasally at the exact dosage of 0.7474 mg/kg, equivalent to 100 µl of the mucoadhesive formulation, at the aforementioned time points, as depicted in Figure 1. Upon conclusion of therapy, all animals were anaesthetized intraperitoneally with 80 mg/kg of ketamine and 10 mg/kg of xylazine. After complete anesthesia, all rats were euthanized by heart puncture [25,26] . After the experimental phase for each group, the euthanized rats were autopsied, and their brain tissues were extracted and weighed for further examination (Figure 1) .

The College of Pharmacy at the University of Baghdad provided the animals with a regular pellet diet and unrestricted access to water.

Preparation of samples for analysis

Chen J. et al. developed a concise, specific, and precise RPHPLC methodology for quantifying RNB in bulk pharmaceuticals and dosage forms. The chromatographic conditions were optimized, as shown in Table (2) below [27].

Table 2. Chromatographic conditions optimized by Chen J. et al.

Parameters	**Method**
The stationary phase (column)	Phenomenex Luna C18 (250 x 4.6 mm, 5 µ)
Mobile Phase	triethylamine: acetonitrile (92:8 v/v)
Flow rate (ml/min)	1.2 ml/min
Run time (minutes)	9 min
Column temperature (°C)	Ambient
Volume of injection loop (µl)	20
Detection wavelength (nm)	225 nm
Drug RT (min)	6.08 min
Internal Standard	Sumatriptan (SUM)

Figure 1. Graphical diagram of the *in-vivo* study experiment

Validation of HPLC Method

Specificity/Selectivity

Specificity refers to the analytical method's capacity to differentiate between the analyte(s) and other constituents within the sample matrix. The HPLC approach guarantees perfect separation of analyte peaks from other peaks originating and resolved in the mobile phase, with suitable concentrations of each component. Overall selectivity was obtained by determining drug purity and resolution peak each time [٢٨].

Lower Limit of Detection (LLOD) and Lower Limit of Quantification (LLOQ)

The limits of detection and quantification were determined by injecting a 100 µL sample and utilizing the dilution method with a signal-to-noise (S/N) approach. In establishing the lower limit of quantification (LLOQ), a minimum concentration was established where the signal-to-noise ratio (S/N≈3) was at least three. Correspondingly, the LLOQ was determined at the lowest concentration where the signal-to-noise ratio (S/N≈10) was at least ten [29].

Accuracy

The accuracy was evaluated by calculating the percentage recovery of injected RNB solutions at three concentrations (50, 100, and 150 ng/ml), while keeping the internal standard concentration constant at 50 ng/ml of SUM in each sample. The samples were injected into the HPLC apparatus in triplicate. The recoveries of RNB from the extracted samples were determined by calculating the percentage recovered from the injected sample by using equation 1:

$$\% \text{ Recovery} = ([A] / [B] \times 100) \quad \textbf{(1)}$$

Where [A] is the peak area of the drug in the spiked sample, and [B] is the peak area of the drug in a standard mixture (mobile phase) [30].

Precision

The relative standard deviation (RSD) of intra-day (analysis was carried out on the same day (n = 3) using the same instrument) and repeatability (injection and analysis) with inter-day reproducibility (using the same instrument on three separate days (n = 3 × 3). The RNB standard solution and spiked plasma samples were made separately at 50 ng/ml each with a corresponding constant IS concentration of 50 ng/ml. They were injected three times into the HPLC system per day and over three consecutive days. The relative peak areas (RPA) were expressed as mean ±SD and %RSD calculated from data obtained [31].

Pharmacokinetic analysis

After the collection of the supernatant, we filtered and injected 100 µL of the resultant filtrate into a reverse-phase high-performance liquid chromatography (RP-HPLC) system for analytical mass spectrometry RNB analysis.

The pharmacokinetic parameters Cmax, AUC, and Tmax, and the duration to achieve Cmax in the brain or plasma were analyzed using the PK-Solver software tool [32]. The percentage of targeting efficiency (% DTE), percentage of drug targeting potential (%DTP) were computed for nasally administered mucoadhesive RNB SPs using their AUC values in the brain and plasma. [33], as illustrated in the equations below:

$$\%\mathbf{DTE} = \frac{[\mathbf{AUC_{Brain/}\ AUC_{Blood}}]\ \mathbf{Intranasal}}{[\mathbf{AUC_{Brain/}\ AUC_{Blood}}]\ \mathbf{Intravenous}} \times \mathbf{100} \qquad \mathbf{2}$$

$$\%\mathbf{DTP} = \frac{[\ \mathbf{B_{Intranasal}} - \mathbf{B_X}]}{\mathbf{B_{Intranasal}}} \qquad \mathbf{3}$$

$$\boldsymbol{B_X} = \frac{\boldsymbol{B_{Intranasal}}}{\boldsymbol{P_{Intravenous}}} \times \boldsymbol{P_{Intranasal}} \qquad \mathbf{4}$$

Where:

B Intranasal = AUC_{0-24} of brain resulting through intranasal administration.

B Intravenous = AUC_{0-24} of brain resulting through intravenous administration.

P Intranasal = AUC_{0-24} of plasma resulting through intranasal administration.

P Intravenous = AUC_{0-24} of plasma resulting through intravenous administration

Statistical analysis

Various statistical methods, such as one-way ANOVA (analysis of variance), were employed to analyze the data. For the results to be statistically significant, the p-values must be below 5% ($p < 0.05$). Non-compartmental analysis was utilized to calculate various pharmacokinetic parameters, including Cmax, Tmax, and AUC0-24, employing PK-Solver software [34] .

Results and Discussion

The *in vitro* characterization of the mucoadhesive RNB SPs Formulations illustrated in Table 3.

Table 3. *In-Vitro* Characterizations of the Mucoadhesive RNB SPs

Formulas No.	pH	Osmolarity (mOsmol/L)	Mucoadhesive Efficiency (dyne/cm^2)
F1	6.02±0.026	248.76±3.23	18.26 ± 0.14
F2	7.10±0.012	326.19±2.11	25.86 ± 0.31
F3	6.12±0.0 34	304.07 ± 1.76	23.69 ± 0.05
F4	6.42± 0.019	297.63±3.02	17.03 ± 0.19
F5	5.40 ±0.057	301.38±1.02	24.59 ± 0.28
F6	6.09±0.031	323.12±2.79	25.72± 0.08

Values are expressed as mean ± SE.

The standard pH range for nasal secretions is 4.5 to 6.4 [30]. According to the collected data, hyaluronic acid-based mucoadhesive polymer formulations (F1,F2, and F3) seem non-irritating to the nasal mucosa since their pH values fall within the range of nasal secretions. Preserving an optimal pH level in the nasal cavity facilitates medicine absorption and inhibits bacterial proliferation in the mucosa [35].

The osmolality of nasal formulations is critical since hypertonic and hypotonic solutions can impair proper ciliary activity, resulting in diminished nasal medication absorption. Nasal formulations should preferably be isotonic and should possess an osmolarity ranging from 285 to 310 mOsmol/L . The osmolality of nasal formulations is critical since hypertonic and hypotonic solutions can impair proper ciliary activity, resulting in diminished nasal medication absorption. Nasal formulations should preferably be isotonic and should possess an osmolarity ranging from 285 to 310 mOsmol/L [36].

The formulations containing hyaluronic acid generally exhibited enhanced mucoadhesion, indicating a strong interaction between mucin and HA. Since F3 presents a higher concentration of HA (2%), more interactions with the mucin were possible. HA is a hydrophilic polymer capable of swelling and interpenetrating glycoprotein chains in mucin, forming hydrogen bonds that improve mucoadhesion. This impact is advantageous since it extends the formulation's adherence to the administration site, resulting in improved drug absorption [37]. HPMC K4M also has a hydrophilic nature, which allows it to swell upon contact with moisture, creating a gel-like matrix that adheres strongly to the mucosal surface. This prolonged contact time facilitates drug absorption [38] .

Demonstrated that F3 has the most accepted pH, osmolarity , and mucoadhesive efficiency values, so it was selected as an optimum formulation for nasal drug delivery [39].

Field emission scanning electron microscope (FESEM) exhibits morphology of F3, showing that the vesicles had a spherical morphology and a smooth surface (Figure 2) [40] .

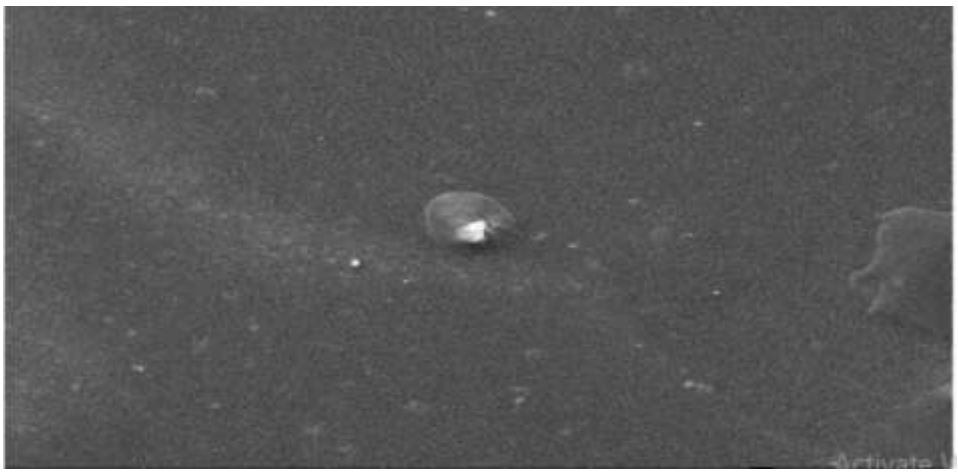
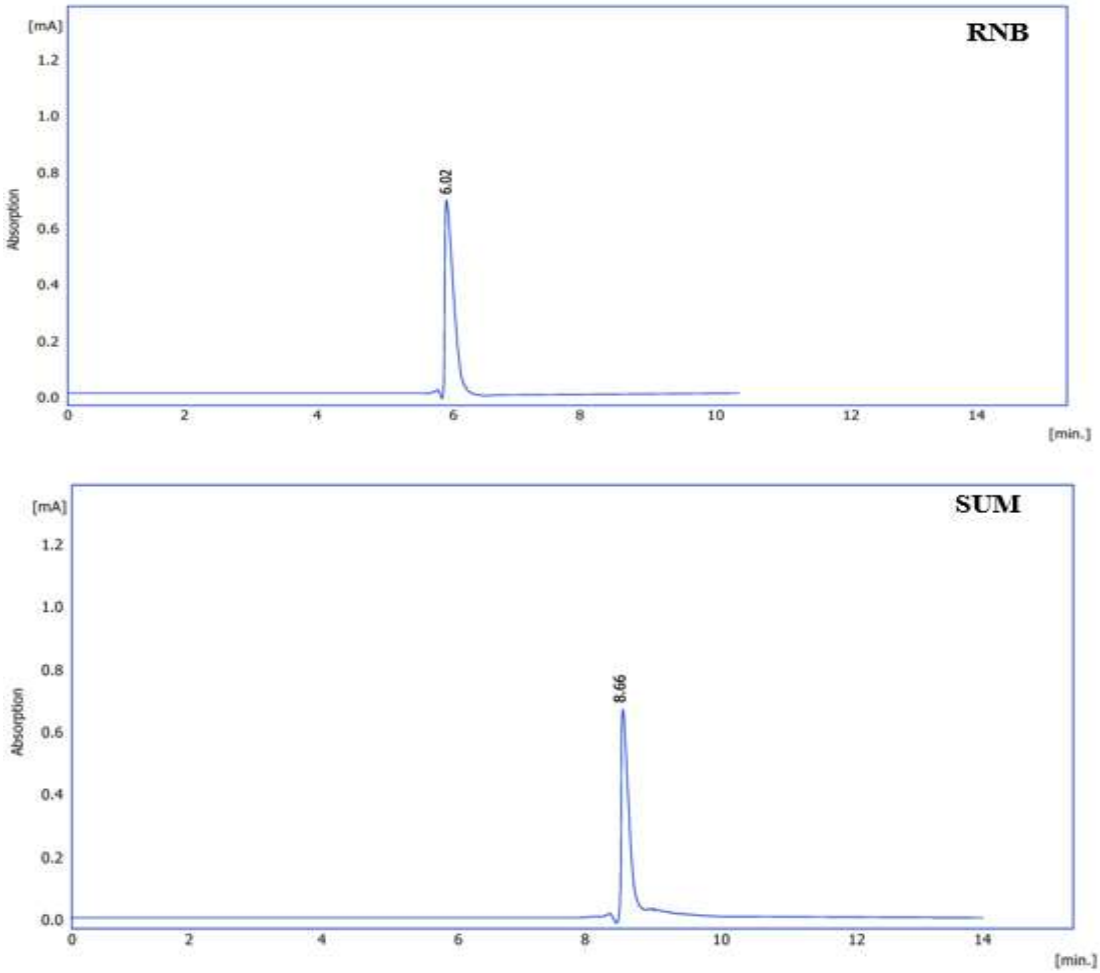


Figure 2: Field Emission Scanning Electron Microscope (FESEM) of the Selected Formula

Specificity/Selectivity

Figures (3-a,3-b,3-c and 3-d) illustrate the retention times and peak chromatograms of RNB (standard solution), Sumatriptan (SUM) (internal standard solution), plasma sample (control), and brain sample (control), which are 6.02, 8.66, 2.06 and 3.55 minutes, respectively.

In all assessed plasma samples, no endogenous peaks were detected during the retention time of the analytes of interest [41].



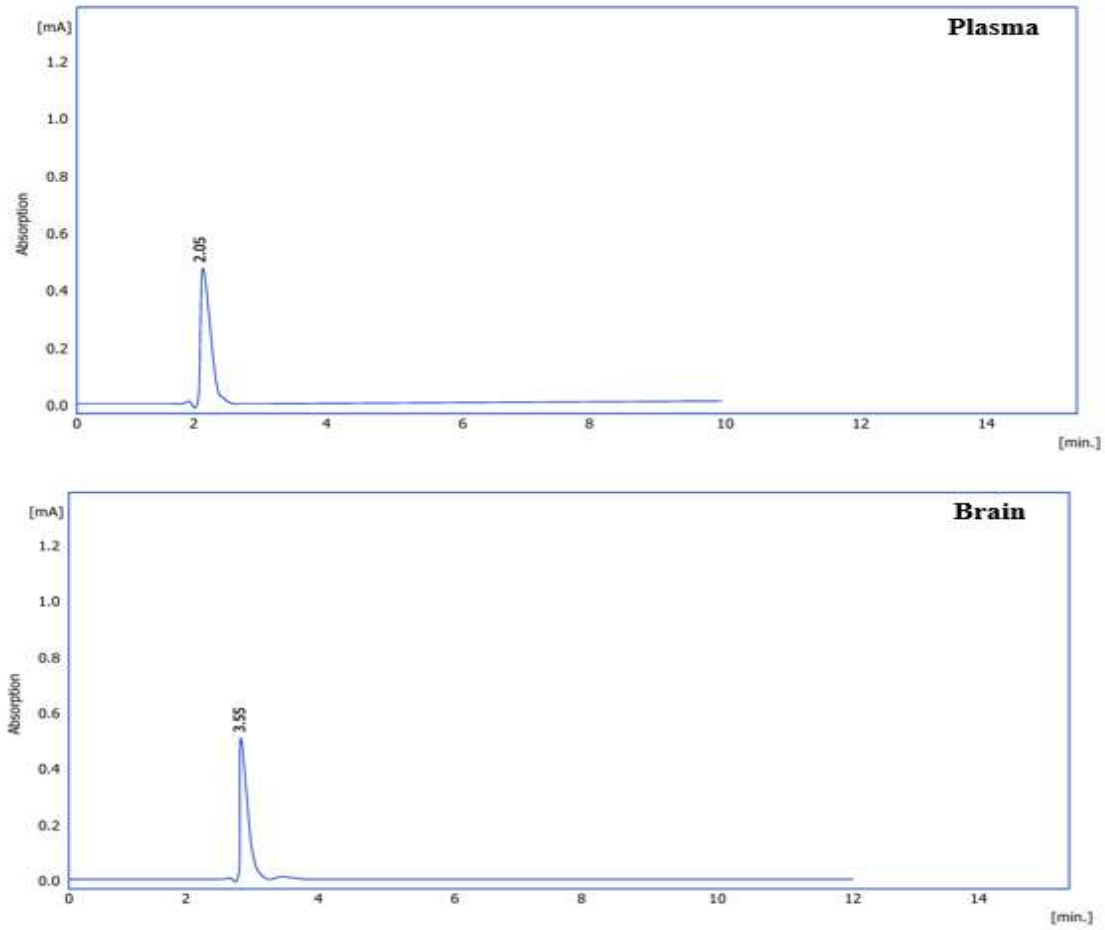
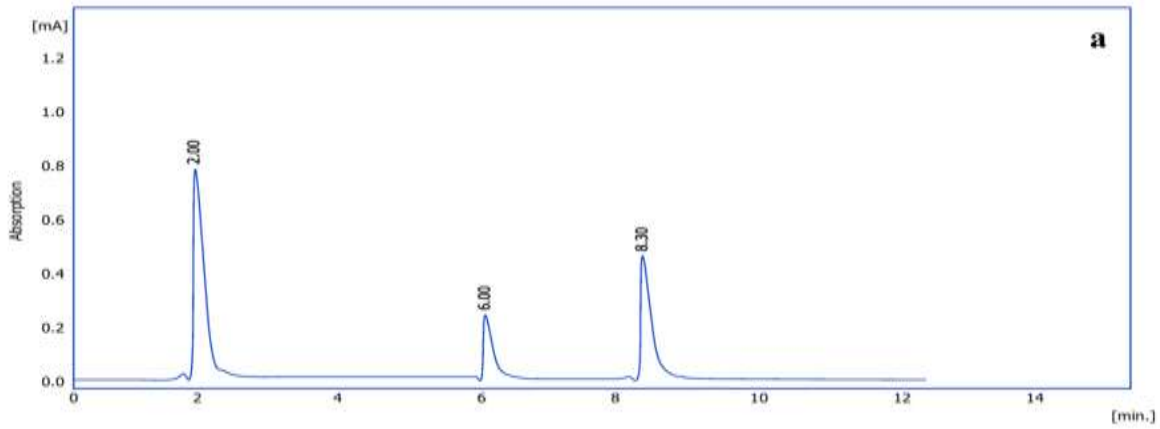


Figure 3. Representative HPLC chromatograms of a. standard (RNB), b. internal standard (SUM), c. chromatograms of the plasma sample, d. chromatograms of the brain sample.

Chromatograms of spiked plasma samples and spiked brain samples at different concentrations of RNB with their respective IS (SUM) at constant concentration, confirming that the peaks were separated and there is no interaction or overlap; the previously listed effects were shown in Figures (4- a, and b) listed below:



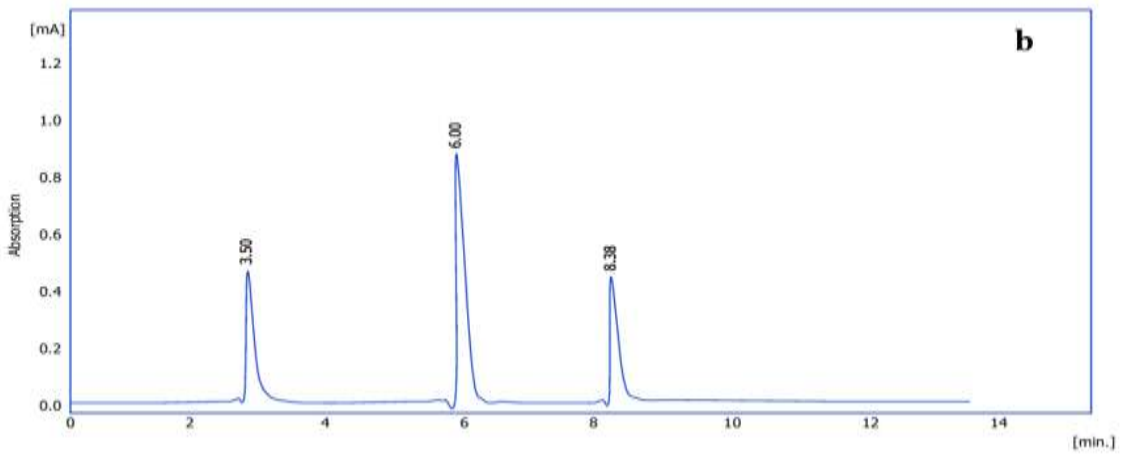


Figure 4 . a. spiked plasma sample at 15 min , b. spiked brain sample at 15 min

Lower limit of detection (LLOD) and lower limit of quantification (LLOQ)

The determined LLOD and LLOQ were (11.01 ng/mL) and (36.33 ng/mL) in spiked plasma samples, respectively, and (13.66 ng/mL) and (40.98 ng/mL) in spiked brain samples, respectively.

LOD and LLOQ assess a method's ability to detect and quantify substances at low concentrations. The findings indicated that the concentrations employed in the standard curves are suitable and align with prior validation investigations [42].

Accuracy

The accuracy of the proposed analytical method was demonstrated through % recovery at three concentration levels: 50, 100, and 150 ng/ml for RNB. The average percent recovery for RNB in spiked plasma samples was determined to be 99.308 %, while for spiked brain samples, it was 99.027 %. The accuracy data are presented in table 4 . A recovery study was conducted to assess the method's accuracy. Three replicates exhibited 5, 10, and 15 µg/ml concentrations. The outcomes were presented as a percentage of drug recovery. Due to the superior separation efficacy of RNB, the proposed analytical approach was considered accurate, following the standard guidelines [43].

Table 4. Accuracy (% recovery) of RNB in spiked plasma and spiked brain sample, and mobile phase

Concentration (ng/ml)	RPA in Spiked Plasma Sample	RPA in Spiked Brain Sample	RPA in the Mobile Phase	%Recovery in Spiked Plasma Sample	%Recovery in Spiked Brain Sample
٥0	٠.4895	0.4790	0.4966	98.570	96.455
١٠0	0.9415	0.9702	0.9750	96.564	99.507
١٥0	1.2711	1.2503	1.2720	99.929	98.294
Average				**98.354**	**98.085**

Precision

Intra-day precision was assessed by analyzing the same drug concentration three times within a single day. In contrast, inter-day precision involved analyzing the same drug concentrations across three distinct days. The precision was indicated by the relative standard deviation (RSD). The inter- and intra-day repeatability data of a standard sample are illustrated in table 5. The suggested analytical approach is precise, as the %RSD values for all measurements were below 2.0% [44].

Table 5 . Precision of RNB in the mobile phase, spiked plasma, and brain sample

Sample Type	RPA in Spiked Plasma Sample		RPA in Spiked Brain Sample		RPA in the Mobile Phase	
	Mean RPA ± SD	RSD%	Mean RPA ± SD	RSD%	Mean RPA ± SD	RSD%
Repeatability	0.4911 ± 0.0012	0.2443	0.4109±0.0027	0.6570	0.5031 ± 0.0023	0.4571
Intra day	0.4721± 0.0026	0.5507	0.4514± 0.0021	0.46521	0.4771± 0.0025	0. 5239
Inter day	0.4°12± 0.0031	0.6870	0.4864± 0.0035	0.71957	0.4255± 0.0019	0.4465

Analysis of RNB Concentration in Brain and Blood Plasma Samples

Figures 5-a and 5-b illustrate the mean brain and plasma drug concentration versus time curves following intranasal and intravenous administration of RNB as mucoadhesive SPs. The data indicated that, compared to intravenous injection of RNB solution, the nasal delivery of mucoadhesive RNB SPs formulation achieved a higher concentration in the brain.

The formulation of the mucoadhesive RNB SPs attains the highest brain concentration of RNB and the lowest plasma concentration. In contrast, the intravenously administered RNB solution demonstrates the contrary, as indicated by the pharmacokinetic results in table 4. Comparative analysis revealed that the brain concentration of RNB following nasal administration of mucoadhesive RNB SPs was significantly higher than that observed in animals receiving intravenous RNB solution ($p<0.05$).

On the other hand, Direct drug administration from the nasal cavity to the brain was evaluated with DTE and % DTP. Intranasal RNB formulation had the highest values for % DTE and % DTP. DTP values above 0 indicate the occurrence of drug brain targeting, whereas DTE values above 100 indicate that intranasal administration of the drug is more successful than intravenous administration.

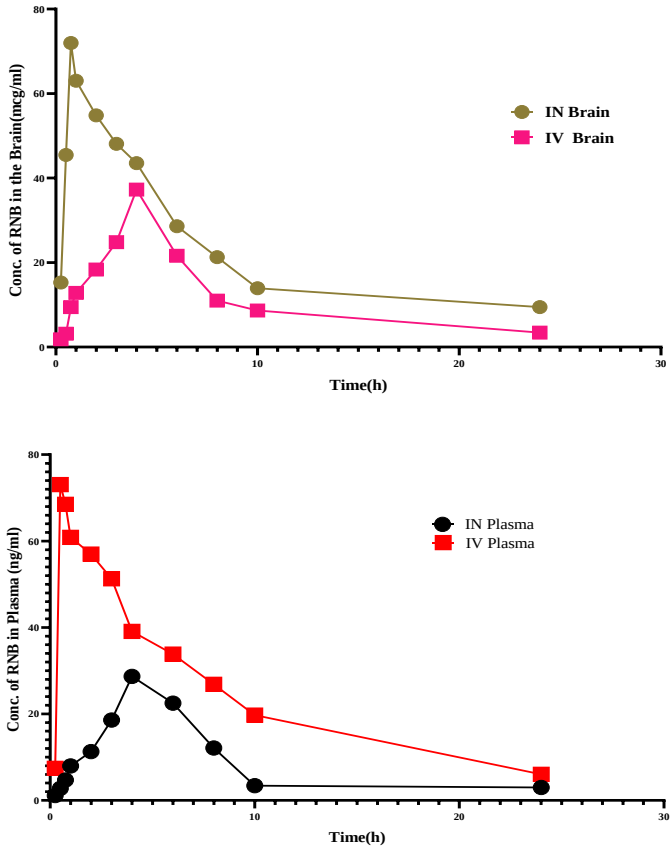


Figure 5. Concentration–time curve for mucoadhesive RNB SPs (intranasal), RNB solution (IV) of a brain, b. plasma

Table 4. Pharmacokinetics parameters of IN-mucoadhesive RNB SPs and IV-RNB solution

Formulations	Brain			Plasma		
	Cmax (µg/mL)	T max (hr)	AUC_{0-24} (h. µg/mL)	Cmax (µg/mL)	Tmax (hr)	AUC_{0-24} (h. µg/mL)
Mucoadhesive RNB SPs (IN)	71.985 ±3.15	0.75	518.059 ±3.30	28.485 ±0.82	4	250.325 ±3.30
RNB-Sol IV	37.264 ± 2.05	4	269.314 ±4.03	73.485 ±3.08	0. 5	671.420 ±4.32
Formulations	**Brain Targeting Parameters**					
	%DTE			**%DTP**		
Mucoadhesive RNB SPs (IN)	518.201			62.7171		

*DTE (%): Drug targeting efficiency, DTP (%): Direct transport percentage, AUC: Area under the curve.

The data indicate that the formulation of mucoadhesive RNB SPs enhances the bioavailability of RNB when delivered intravenously, compared to the reduced bioavailability of pure RNB medication.

This study's pharmacokinetic evaluations in rats indicated that the intranasal mucoadhesive RNB SPs achieved a brain Cmax approximately two times greater than the intravenous RNB solution. The superior values of % DTE and % DTP derived from the IN SPs formulation demonstrate that a greater percentage of the drug was effectively targeted following nasal administration. At the same time, the circulatory system absorbed a minimal fraction. These results concurred with those reported by Vyas TK et al. and Kumbhar SA et al. [45,46] Ultimately, altering the route of administration, in conjunction with advanced nanotechnology and a mucoadhesive formulation, facilitates the development of acceptable, efficacious, safe, and bioavailable formulations that enhance patient outcomes .

Conclusion

This study explored the efficacy of the mucoadhesive spanlastics nano carrier for the delivery of RNB to the brain via nasal administration. A key aspect of this investigation was the pharmacokinetic assessment of the RNB-loaded mucoadhesive SPs formulation for the nasal administration. The pharmacokinetic and biodistribution studies showed that the optimized formulation led to a much higher concentration of the drug in the brain compared to the drug solution that was given intravenously. A lower Tmax may also mean that the drug is absorbed more quickly, possibly through the olfactory region in the nose. Therefore, the optimized mucoadhesive RNB SPs could be considered a novel and promising approach for the management of migraine.

This study indicates that the intranasal mucoadhesive RNB SPs achieved brain targeting and are considered a promising approach for the safe and effective brain targeting of RNB .

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Conflicts of Interest

The authors declare no conflicts of interest related to this work.

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Ethics Statements

Ethical committee approval was gained from Research Ethics Committee of the University of Baghdad – College of Pharmacy (Approval number: RECAUBCP2952029C on 29/5/2024) .

Author Contribution

Study conception and design: Rajaa A.; data collection: Rajaa A.; analysis and interpretation of results: Rajaa A.and Mowafaq M.; draft manuscript preparation: Rajaa A.and Mowafaq M.; All authors reviewed the results and approved the final version of the manuscript.

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دراسة استخدام ريزاتريبتان بنزوات في التوصيل الأنفي اللاصق للمخاط لاستهداف الدماغ: مقارنة الحركية الدوائية بين التوصيل عبر الأنف والحقن الوريدي في جرذان ويستر

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الخلاصة

بسبب التوافر الحيوي المحدود للأدوية المضادة للصداع النصفي عند استعمالها عن طريق الفم،مثل دواء الريزاتريبتان بنزوات، تم استخدام التوصيل الأنفي من اجل تعزيز التوافر البيولوجي واستهداف الدماغ من خلال استخدام نظام الأوعية الدموية النانوية سعى هذا العمل إلى صياغة الريزاتريبتان بنزويت كحويصلات نانوية لاصقة مخاطية وتقييم المعلمات الحركية الدوائية والتأثيرات النسيجية المرضية للتركيبات على الغشاء المخاطي للأنف لدى الجرذان تمت صياغة الدواء على شكل حويصلات نانوية مخاطية ملتصقة، وتضمنت الدراسة ٦٨ فأر ويستر، وزن كل منها ٢٠٠ ± ٣٥ جم، مقسمة إلى ثلاث مجموعات (المجموعة الضابطة، عن طريق الانف و عن طريق الوريد). يتم قياس كمية الدواء في بلازما الفئران والدماغ باستخدام (RP-HPLC). أشارت الدراسات الحركية الدوائية التي أجريت على الفئران إلى أن اعلى تركيزفي الدماغ من مادة الريزاتريبتان بنزويت ذات اللصقات الأنفية المخاطية كان أكبر بحوالي مرتين من محلول الدواء الوريدي. لم يلاحظ أي ضرر في بنية الغشاء المخاطي أثناء التحليل النسيجي. ونتيجة لذلك، أظهرت صيغة الدواء المطورة والمحسنة للصداع المخاطي داخل الأنف إمكانات كبيرة للاعطاء الآمن وا لفعال .

الكلمات المفتاحية: ريزاتريبتان بنزويت ،سبالاستك لاصقة، اعطاء انفي، استهداف الدماغ .