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Research Article

Ex vivo and *in vivo* Assessment of Paliperidone Thermal *in situ* Gel as Nasal-to-Brain Delivery System in Rats

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Abstract

Background: Paliperidone (PAL), an antipsychotic drug, has limited brain availability when administered orally due to poor blood–brain barrier penetration and systemic side effects. Intranasal delivery offers a promising strategy for direct brain targeting. ***Objective***: To investigate the pharmacokinetics and brain-targeting efficiency of paliperidone-loaded nanosuspension thermo-responsive *in situ* gel for nose-to-brain delivery. ***Methods***: The optimized NB-IG7 formulation was evaluated for *ex vivo* permeation using a Franz diffusion cell with sheep nasal mucosa, employing simulated nasal fluid. The cumulative drug permeation, steady-state flux (Jss), and permeability coefficient (P) were determined spectrophotometrically. In vivo pharmacokinetic and brain-targeting studies were done on male rats, where NB-IG7 gel administered nasally vs. an IV dose. Over 48 hours, plasma and brain drug levels were measured for pharmacokinetic measurements. ***Results***: The ex vivo tests showed that NB-IG7 had 3.3 times higher permeation across the nasal mucosa than PAL suspension, which confirmed that it had better mucosal penetration. Intranasal administration of NB-IG7 achieved significantly higher brain concentrations of PAL compared with IV administration. The brain C_{max} and $AUC_{0–48hr}$ were 1.89µg/ml and 63.6 hr·µg/ml, respectively, representing 2.66- and 2.68-fold increases over IV administration (C_{max} 0.71µg/ml, $AUC_{0–48hr}$ 23.7hr·µg/ml). Plasma exposure was lower after intranasal delivery (C_{max} 0.19µg/ml, $AUC_{0–48hr}$ 4.66hr·µg/ml) compared with IV dosing (C_{max} 0.87µg/ml, $AUC_{0–48hr}$13.98hr·µg/ml). Brain-targeting assessments showed markedly enhanced values (DTE 807%, DTI 8%, and %DTP 91%), confirming efficient nose-to-brain transport via olfactory and/or trigeminal pathways. ***Conclusions***: The new formula was superior enhanced brain targeting with reduced systemic exposure.

Keywords: Bioavailability, Ex vivo, Nasal-to-brain delivery, Paliperidone, Thermal gel.

تقييم هلام بالبيريدون الحراري الموضعي خارج الجسم وداخله كنظام توصيل من الأنف إلى الدماغ في الجرذان

الخلاصة

الخلفية: البالبيريدون (PAL)، دواء مضاد للذهان لديه توافر محدود في الدماغ عند إعطائه عن طريق الفم بسبب ضعف اختراق الحاجز الدموي الدماغي والآثار الجانبية الجهازية. الأعطاء عن طريق الأنف استراتيجية واعدة لاستهداف الدماغ مباشرة. **الهدف:** دراسة كفاءة استهداف الدماغ للتعليق النانوي المحمل بالبالبيريدون المستجيب للحرارة في الموقع للتوصيل من الأنف إلى الدماغ. **الطرائق:** تم تقييم تركيبة NB-IG7 المحسنة للنفاذية خارج الجسم الحي باستخدام خلية انتشار فرانز مع الغشاء المخاطي للأنف، باستخدام سائل الأنف المحاكاة. تم تحديد نفاذية الدواء التراكمي وتدفق الحالة المستقرة ومعامل النفاذية طيفيا. في الجسم الحي أجريت دراسات الحركية الدوائية واستهداف الدماغ على ذكور الجرذان باعطاء هلام NB-IG7 أنفيا مقابل جرعة IV. على مدار 48 ساعة، تم قياس مستويات البلازما و الدماغ لقياسات الحرائك الدوائية. **النتائج**: أن NB-IG7 كان لديه نفاذية أعلى بمقدار 3.3 مرة عبر الغشاء المخاطي للأنف من PAL، واعطى اختراق أفضل. أدى الأعطاء داخل الأنف لتراكيز دماغية أعلى بكثير مقارنة بالجرعة الوريدية. كان التوافر في البلازما أقل بعد الأعطاء داخل الأنف مقارنة بالجرعات الوريدية. أظهر تقييم استهداف الدماغ قيما محسنة بشكل ملحوظ (DTE 807٪ و DTI 8% و DTP 91٪)، مما يؤكد النقل الفعال من الأنف إلى الدماغ عبر المسارات الشمية و/أو ثلاثية التوائم. **الاستنتاجات**: كانت الصيغة الجديدة تعبر عن استهداف محسن للدماغ مع تقليل التعرض الجهازي.

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INTRODUCTION

Intranasal administration is a recognized method for delivering active pharmaceutical ingredients that can produce either local or systemic effects. It has attracted substantial attention due to its distinctive anatomical connection with brain [1]. The olfactory and trigeminal nerves, situated in the olfactory and respiratory regions, respectively, facilitate the nose-to-brain absorption of medications intended to exert effects at the central nervous system (CNS) level [2]. Consequently, direct access to the brain enables drugs to circumvent the first-pass effect and bypass the blood-brain barrier, leading to enhanced bioavailability, greater accumulation in the central nervous system, and expedited onset of action, which is crucial in the management of acute seizure episodes [3]. *Ex vivo* and *in vivo* methods represent critical tools in pharmacological research, each offering distinct advantages and limitations. *In vivo* methods involve evaluating pharmaceuticals within living organisms, typically using animal models. The combination of *ex vivo* and *in vivo* methods offers a comprehensive insight into the effects of drugs. *In-vivo* methods are employed to identify potential new pharmaceuticals, whereas *ex vivo* methods facilitate the study of drug

mechanisms of action and the optimization of their dosage and delivery [4]. Paliperidone PAL is an atypical second-generation antipsychotic medication. It acts as an antagonist to both dopamine D_2 and 5-tryptamine 5-HT_2 receptors in the brain, leading to its therapeutic effects in managing psychotic symptoms [5]. Therefore, it is extensively employed in the clinical management of both positive and negative symptoms of schizophrenia. PAL belongs to the class of benzoxazole derivatives and is the primary active metabolite of risperidone. PAL (Figure 1) has a molecular weight of 426 g/mole; it is practically insoluble in water (30 mg/L), is a class II, and has an oral bioavailability of 28% [6].

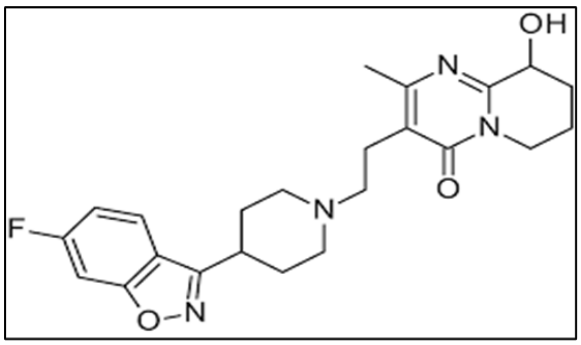

Figure 1: Chemical structure of paliperidone PAL molecular formula: C23H27FN4O3 [6].

PAL's marketed pharmaceutical products primarily consist of oral formulations, including tablets and capsules. After oral administration, the preparations frequently experience significant first-pass metabolism, leading to a delayed onset of action and comparatively low bioavailability. Moreover, the absorption and subsequent transport of orally administered paliperidone (PAL) into the central nervous system (CNS) are greatly limited by the blood–brain barrier (BBB). This restriction reduces the amount of drug reaching the brain, often leading to an inadequate therapeutic response. Therefore, oral administration of PAL is not considered an optimal route for achieving effective management of schizophrenia [7]. Nanosuspension enhances drug solubility and dissolution rate through particle size reduction and increased surface area, promoting rapid absorption across the nasal mucosa. Meanwhile, the thermoresponsive in situ gel, which transitions from sol to gel upon exposure to nasal temperature, prolongs mucosal residence time and ensures sustained drug release. This dual strategy is expected to improve PAL bioavailability and brain uptake following intranasal administration. The objective of the present study was to investigate the pharmacokinetics and other parameters intended for this delivery, like the drug targeting index (DTI), drug targeting efficiency (%DTE), and direct transport percentage (%DTP) of the previously prepared PAL thermal in-situ gel-based as a selected formula coded *(NB-IG7),* which contains lyophilized PAL in Soluplus® polymer as nano suspension NPs incorporated in HPMC K4M as mucoadhesive thermal in-gel [8], intended to be used in rats as a nasal-to-brain delivery system, using *ex-vivo* and *in-vivo* technique designs.

METHODS

Materials

PAL powder was purchased from Heowns Biochem Technologies, LLC, Spain. Hangzhou Hyper Chemicals Ltd of Zhejiang, China, provided Soluplus®, HPMC KM4. HPLC-grade acetonitrile and water were purchased from Chem-Lab, Belgium. Kolliphor®P 407 was obtained from D-BASF Co., Ltd., and Benzalkonium chloride was obtained as generous gift from Al-Hayat company, and Nimodipine was purchased from Hyperchem in China. All remaining chemicals and solvents were of analytical reagent-grade quality.

Preparation of intranasal mucoadhesive nano-in situ gel (NIG)

The paliperidone nanosuspension was prepared using the anti-solvent precipitation technique. Briefly, 6 mg of PAL was dissolved in 2 ml of ethanol to form the solvent phase. The anti-solvent phase consisted of 10 ml of distilled water containing 18 mg of Soluplus® as a stabilizer. The organic phase was slowly added dropwise through a needle attached to a plastic syringe and directly into a water solution at room temperature [9]. The cold method was employed to prepare the paliperidone nanosuspension-based in situ gel (NB-IG7) for nose-to-brain delivery [10]. First, the previously prepared nanosuspension was combined with the mucoadhesive polymer HPMC K4 to obtain a clear solution. The mixture was then cooled and stored in a refrigerator at 4 °C. Subsequently, 20% w/w of Poloxamer 407, a thermoresponsive polymer, was added to the cold dispersion. Benzalkonium chloride was included as a preservative, and the resulting mixture was stirred continuously at 500 rpm for 2 hours [11,12]. Finally, the in situ gel was stored overnight at 4 °C to ensure complete polymer hydration and gel formation. The compositions of the optimized *in situ* gel formula NB-IG7, which is intended for the current *ex vivo* and *in vivo* study, were depicted in Table 1.

Table 1: Composition of the PAL NB-IG7 formula

Ingredient	NIG
PAL(mg)	3mg
Soluplus® (mg)	18 mg
Poloxamer 407% w/v	20%
HPMC K4 % w/w	1%
Benzalkonium chloride % w/w	0.01

Ex vivo permeation study

The sheep nasal mucosa was employed to conduct the permeation. The sheep nasal mucosa was affixed to the Franz diffusion cell between the donor and receptor sections. The donor section's location was modified to ensure the mucosa contacts the permeation medium. The donor section, which was connected to the nasal mucosal surface of the membrane, was filled with NB-IG7 selected formula equivalent to 6 mg of PAL. The receptor section was filled with 12 ml of simulated nasal fluid (SNF) maintained at a temperature of 34 ± 1°C and stirred at a rate of 50 rpm with magnetic rods. Afterward, a 1 ml sample of the media was removed

from the receptor section at appropriate intervals and replaced with the same volume of fresh medium [13]. The samples were analyzed by UV spectrophotometer at its confirmed λmax, and the cumulative amount of drug permeated through nasal mucosa was quantified; the study was repeated in triplicate. The results were quantified as the quantity that arrived at the receptor chamber. The steady-state flux (Jss) was established by calculating the slope of the line that resulted from graphing the drug's permeation rate (µg/cm^2) against various time intervals (min). By dividing the resulting slope value (Jss) over the initial PAL concentration (Co or Cd) in the donor compartment, then after determining the permeability coefficient (P) [14], as shown in equations 1 and 2 listed below.

Jss = dM/(S. dt) …… Eq. (1)

Jss = steady-state flux of the drug through the nasal mucosa (µg/cm²·min), dM = cumulative amount of drug permeated into the receptor compartment over a time interval (µg), S = effective surface area of the nasal mucosa exposed to the formulation (cm²), and dt = time interval over which permeation is measured (min).

P= Jss /Cd …… Eq. (2)

Where:

P = permeability coefficient of the drug across the nasal mucosa (cm/min), Jss = steady-state flux as defined above (µg/cm²·min), and Cd = initial concentration of the drug in the donor compartment (µg/ml).

In vivo pharmacokinetic study

The selected formulation of paliperidone (PAL) mucoadhesive in situ gel (NB-IG7) and the intravenous solution were used to establish the pharmacokinetic and brain distribution profiles of PAL for nose-to-brain delivery. The study involved 78 male Wistar albino rats weighing between 180 and 220 g and aged 2–3 months. The animals were maintained in the animal facility of the Research Centre for Cancer Research and Medical Genetics, Mustansiriyah University (Baghdad, Iraq), under controlled environmental conditions (25 ± 1°C; 12-h light/dark cycle) for one week of acclimatization before experimentation. The rats were randomly divided into three groups: Group A (n= 3): Negative control animals euthanized early to obtain plasma and brain tissue for HPLC calibration. Group B (n= 36): Received intravenous (IV) administration of PAL solution at a dose of 0.308 mg/kg. Group C (n= 36): Received intranasal administration of the NB-IG7 mucoadhesive in situ gel at the same dose (0.308 mg/kg) (Figure 2). A total of 13 time intervals were used for sample collection, with six rats sacrificed at each time point per treatment group to obtain statistically reliable pharmacokinetic data while minimizing inter-animal variability. This sampling design followed previously published pharmacokinetic protocols and ensured adequate data density for accurate parameter estimation. The number of rats was scientifically justified to achieve robust brain distribution analysis. All procedures were conducted following ethical standards and in compliance with the principles of the 3Rs (Replacement, Reduction, and Refinement).

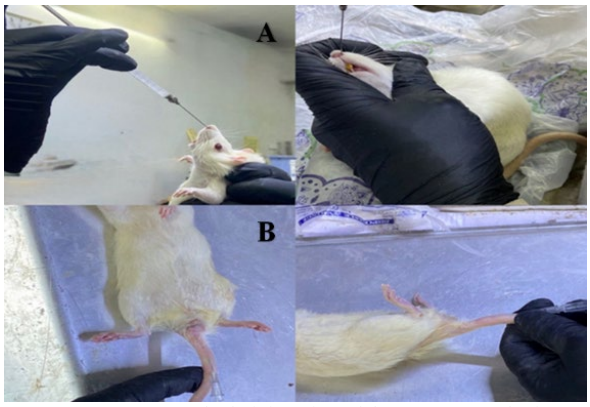

Figure 2: **A**) Intranasal administration of the PAL nose to brain *in situ* Gel NB-IG7, and **B**) IV PAL-solution.

All animals were anesthetized intraperitoneally with ketamine (80 mg/kg) and xylazine (10 mg/kg) before sample collection. After treatment, rats were sacrificed by cardiac puncture under deep anesthesia [15]. Plasma and brain tissues were immediately collected, weighed, and stored appropriately for subsequent analysis.

Dose calculation

The standard human dosage of PAL is 3 mg per 60 kg daily, which is converted to an equivalent dosage for rats using the following equation.

HED (mg/kg) = AED (mg/kg) x (Animal Km)/(Human Km) Eq. (3)

HED represents the effective human dosage, AED indicates the animal effective dose, and Km represents the conversion factor for human adults, which is 37, whereas for rats, it is 6. The animal dose was determined to be 0.308 mg/kg, calculated as follows [16,17].

The dose administered to rats is approximately equivalent to 60 µg.

Brain and blood sampling

The sampling was timed, and a calculated dose equivalent to 60µg. was administered to both groups B and C in order to evaluate the pharmacokinetic and distribution parameters in plasma and brain of PAL established for nose to brain. The chosen formula NB-IG7 of PAL serves as a mucoadhesive in situ gel and intravenous solution, utilizing anesthetic ether for group B to sedate the animals before intranasal administration. Each group of animals received 100 µL of PAL mucoadhesive in situ gel (50 µL per nostril) under general anesthesia, administered via a yellow cannula (24 gauge) connected to a 1 cc syringe. While the PAL solution was injected intravenously into the tail of the rats in group C, samples were withdrawn at time intervals of 0, 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 10, 12, 24, and 48 hours. One milliliter of blood was

centrifuged in microcentrifuge tubes (precoated with EDTA to prevent clotting). For 10 minutes at 4000 rpm, blood samples are centrifuged to collect the clear supernatant. followed by component separation using a micropipette. At each time point, six animals from each group were sacrificed simultaneously. Their brains were extracted, rinsed with normal saline, and homogenized with normal saline in a 1:9 (w/w) ratio, followed by blotting for brain kinetics studies [18]. Brain and plasma specimens were obtained and preserved at -20°C for subsequent examination.

PAL concentration in the brain and plasma

Utilizing the reversed high-performance liquid chromatography (RP-HPLC) as a validated technique that was previously established and confirmed according to Rudragangaiah *et al*. [19] and displayed in Table 2.

Table 2: HPLC conditions and criteria for samples *in vivo* analysis (n=3)

Parameter	Condition
Mobile phase	Methanol: acetonitrile: 0.15% v/v triethylamine in water (pH 6) in the ratio of 50:20:30 v/v
Stationary phase (Column)	C18(4.6 x150mm, 5µ)
Column temperature	30°C
Flow rate	1 ml/min
Retention time	7.83 min
Run time	20 min
Wavelength	237 nm
Injection volume	20µl

Pharmacokinetic analysis

A non-compartmental pharmacokinetic approach was employed to assess the drug concentration–time profile of PAL in both brain and plasma tissues. Analyzing the concentration-time curves allowed us to quickly ascertain the maximal concentration (C_{max}) and the time required to attain it (T_{max}) for both the intravenous and intranasal routes. Utilizing the linear trapezoidal method, the area under the concentration–time curve from 0 to 48 hours ($AUC_{0–48}$) was computed. Pharmacokinetic parameters from Group B and Group C were statistically compared using the PKSolver software program (Version 2.0, developed by Zhang *et al*., China Pharmaceutical University, Nanjing, China), which is an add-in tool for Microsoft Excel designed for pharmacokinetic and pharmacodynamic data analysis. The software was employed to perform non-compartmental analysis (NCA) and to determine key parameters such as Cmax, Tmax, t½, AUC, and mean residence time (MRT). Furthermore, the AUC values obtained from brain and plasma samples were used to calculate the drug targeting efficiency (DTE%) and related brain-targeting indices. and direct transport percentage (DTP%) of intranasally delivered PAL-loaded nanoparticles in situ gel. These outcomes were compared with those of the intravenous administration route, and equations 2 and 3 were used to derive the DTE and DTP values [20].

$$DTE\ \% = \frac{[AUCbrain\ \backslash AUCplasma]IN}{[AUCbrain\ \backslash AUCplasma]IV} * 100 \quad \text{Eq } \ldots. (4)$$

A %DTE value exceeding 100% indicates effective targeting of the brain. %DTP represents the proportion of a drug that reaches the brain through direct pathways, such as the olfactory and trigeminal routes, and is described as shown below.

$$DTP\% = \frac{AUC\ brain\ IN - \left(\frac{AUC\ brain\ IV}{AUC\ plasma\ IV}\right) * AUV\ plasma\ IN}{AUC\ brain\ IN} * 100 \text{ Eq .. (5)}$$

A positive value of %DTP signifies that direct pathways substantially contribute to the overall drug delivery to the brain [21].

Ciliotoxicity to the nasal mucosa.

By using sheep nasal mucosa similar to that of the ex-vivo diffusion study, histopathological studies were used to evaluate nasal toxicity of developed NIG formulations. Three samples of uniformly thick sheep nasal mucosa (N1, N2, and N3) were chosen and put on Franz diffusion cells. For just one hour, N1 received 0.5 mL of PBS (pH 6.5), N2 received 0.5 mL of isopropyl alcohol (positive control), and N3 received NB-IG 7. After passing the exact determined time, the mucosa was rinsed with PBS (pH 6.5) subsequently, the specimens were subjected to histological analysis and photographed using a microscope [22].

Ethical considerations

The study was conducted in accordance with the institutional rules of the Animal Ethics Committee of the College of Pharmacy, University of Baghdad (certificate ID: RECAUBCP532022G).

Statistical analysis

The results were presented as mean ± SD. A difference was considered statistically significant if the *p*-value was less than 0.05. The pharmacokinetic parameters, including C_{max}, T_{max}, and $AUC_{0\text{-}48hr}$ were evaluated using an unpaired student's *t*-test.

RESULTS

In this research, the ex vivo permeation study revealed that the optimized selected formula, NB-IG7, significantly enhanced the nasal delivery of paliperidone (PAL), achieving a 3.3-fold increase compared to the PAL suspensions shown in Figure 3. Table 3 presents the mean plasma and brain drug concentration *vs*. time curves that were observed after the administration of the PAL nano formula (NB-IG7) by intranasal and intravenous routes (Figures 4 and 5). Intranasal delivery of the PAL-loaded nanoparticle in mucoadhesive in situ gel as an intranasal formula showed a higher brain concentration than intravenous administration of PAL.

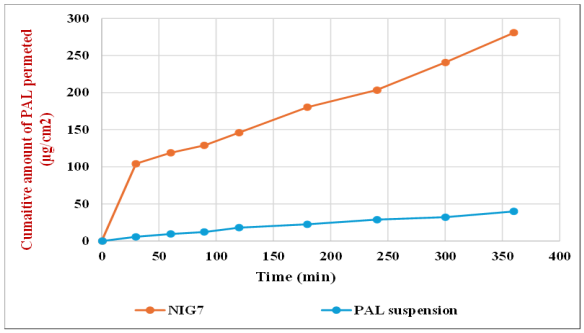

Figure 3: A comparison of *ex-vivo* permeation of PAL from (NB-IG7) formula with PAL suspended dosage form in SNF pH6.5 at temperature 34°C (n=3).

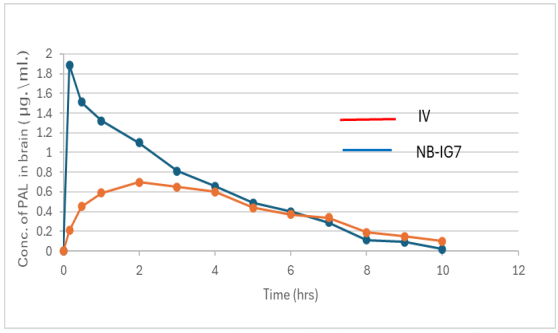

Figure 4: Concentration–time profile for PAL mucoadhesive *in situ* gel NB-IG7 formula, and PAL- (IV) of brain.

According to these results, the pharmacokinetic parameters listed in Table 3 indicate that the intranasal PAL-loaded mucoadhesive nanoparticle as an *in situ* gel formula achieved the highest concentration of PAL in the brain (C_{max} 1.89 µg/ml), T_{max} 0.25 hr, and $AUC_{0\text{-}48hr}$ of 63.6 hr.µg.ml, and the lower concentration in plasma (C_{max} 0.19 µg/ml), T_{max} 8 hr., and $AUC_{0\text{-}48hr}$ of 4.66 hr.µg.ml). Whereas intravenous administration of PAL demonstrated the concentration of PAL in the brain (C_{max} 0.71 µg/ml, T_{max} 2.2 hr, $AUC_{0\text{-}48hr}$ 23.7 hr.µg.ml), and the higher concentration in plasma (C_{max} 0.87 µg/ml) and more AUC0-48hr (13.98 hr.µg.ml).

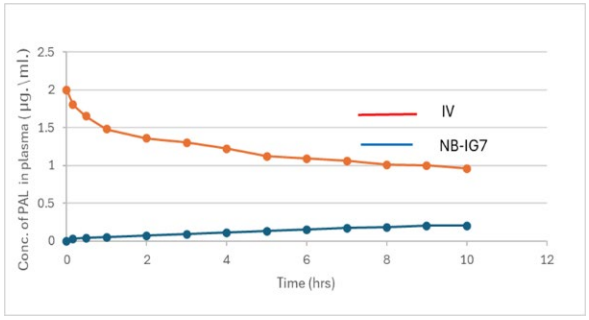

Figure 5: Concentration–time profile for PAL mucoadhesive *in situ* gel NB-IG7 formula, and PAL- (IV) of plasma.

Table 3: Comparison of pharmacokinetic parameters of PAL samples in brain and plasma of selected NB-IG7 formula and IV administration in rats

Formula	Brain			Plasma			Brain targeting parameters		
	C_{max} (µg/ml)	T_{max} (hr)	$AUC_{0\text{-}48}$ (µg\ml.hr)	C_{max} (µg/ml)	T_{max} (hr)	AUC0-48 (µg\ml.hr)	DTE (%)	DTI (%)	DTP (%)
PAL (NB-IG7)	1.89	0.25	63.6	0.19	8	4.66	807	8	91
PAL (I.V)	0.71	2.2	23.7	0.87	zero	13.98	-----	-----	------

So that the intranasal delivery of the PAL nano formula (NB-IG7) gave a significant ($p< 0.05$) 2.66-fold higher brain C_{max} of PAL than the intravenous PAL concentrations and a 2.68-fold higher AUC of PAL than the intravenous PAL available in rats. The direct delivery of drugs from the nasal cavity to the brain was assessed using DTE, DTI, and % DTP. Table (3) indicates that the PAL nano formula (NB-IG7) exhibited the highest values for DTE, DTI%, and DTP%, with ranges of 807%, 8%, and 91%, respectively. DTE values exceeding 100 suggest that intranasal drug administration is more effective than intravenous administration as an alternative route. Values of % DTI and % DTP exceeding zero signify the activation of PAL brain targeting via the olfactory and/or trigeminal pathways. The nasal ciliotoxicity experiments were conducted after three days to assess the possible harmful effects of excipients included in the (NB-IG7) formula on the nasal mucosa. The nasal mucosa treated with PBS (pH 6.5, negative control) exhibited no evidence of inflammation, erosion, or damage to the nasal ciliary region, as shown by Figure 6A, where the nasal membrane remained intact. In contrast, positive control showed significant damage to the nasal mucosa, along with the loss of nasal cilia (Figure 6B). However, no damage was observed with the PAL-loaded nanoparticle as a mucoadhesive in-*situ* gel, as seen in Figure 6C.

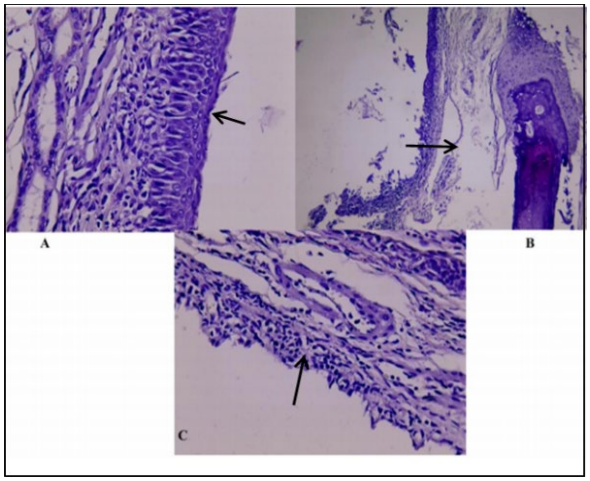

Figure 6: Histopathological examination of nasal mucosal section. **A**) control mucosa showing intact epithelial lining; **B**) positive mucosa showing epithelial disruption, and inflammatory infiltration; and **C**) PAL mucoadhesive *in situ* gel treated mucosa showing preserved epithelial architecture with minimal inflammatory changes.

DISCUSSION

In this research, the ex vivo permeation study revealed that the optimized selected formula, NB-IG7, significantly enhanced the nasal delivery of paliperidone (PAL), achieving a 3.3-fold increase compared to the PAL suspension. This result suggests improved mucosal permeability and potential for direct nose-to-brain delivery. This offers a potentially useful substitute for oral administration, which has limitations

due to first-pass metabolism and plasma level fluctuations. Such a system may improve therapeutic outcomes in CNS disorders by providing more consistent and targeted drug delivery. For effective nasal drug delivery, sufficient permeability is a critical requirement. The enhanced permeation of PAL from the NB-IG7 formula can be attributed to different factors involved during this study, among them nanoscale droplet size and rapid mucosal interaction, besides the mucoadhesive and permeation-enhancing properties of the incorporated polymers [23]. These factors facilitate rapid disintegration and diffusion across the nasal mucosa. The thermal reversible gel matrix ensures intimate contact with the nasal epithelium, promoting sustained and efficient nose-to-brain transport, thereby overcoming limitations of conventional PAL administration [24]. According to the pharmacokinetic investigations, the trigeminal or olfactory pathways may be involved in the direct intranasal distribution of PAL to the brain by intranasal mucoadhesive in-situ gel of PAL-loaded nanoparticle formulation. Pharmacokinetic evaluation in rats from the current study revealed that intranasal administration of the mucoadhesive *in situ* gel of paliperidone-loaded nanoparticles led to a brain Cmax approximately 14-fold greater than that achieved with intravenous PAL solution. The high values of the Drug Targeting Index (DTI), Drug Targeting Efficiency (%DTE), and Direct Transport Percentage (%DTP) observed with the NB-IG7 formula of PAL suggest enhanced direct brain delivery, with only a minimal proportion entering systemic circulation. Notably, a DTP value approaching 100% implies negligible systemic absorption through indirect pathways. These results are consistent with those reported by Ezzat *et al*., who demonstrated that mucoadhesive in situ gels enhance nasal residence time and improve drug bioavailability through the formation of a strong gel matrix upon contact with the nasal mucosa, enabling sustained drug release and efficient absorption via the olfactory pathway. Likewise, Hamzah *et al*. observed successful brain targeting following intranasal administration of frovatriptan succinate, confirming that the nasal route can effectively bypass the blood–brain barrier and achieve higher brain drug concentrations compared to intravenous delivery [25,26]. The nasal ciliotoxicity assessment confirmed that the excipients utilized in the formulation are safe for intranasal administration. The findings indicate that these components exhibit good biocompatibility and are not expected to induce notable histopathological changes in the nasal mucosal tissues, even with extended use [27].

Study limitations

This study has few limitations. The *ex vivo* permeation model cannot fully replicate the complex physiology of the human nasal cavity, and the *in vivo* experiments were limited to rats, and their nasal and brain structures differ from humans. In addition, the work focused mainly on short-term pharmacokinetics and histopathology; long-term safety, neurobehavioral outcomes, and advanced biodistribution studies were not explored. Future research should address these gaps to strengthen the translational potential of this nasal-to-brain delivery system.

Conclusion

Ex vivo permeation studies showed enhanced mucosal penetration, while *in vivo* pharmacokinetics and biodistribution revealed higher brain PAL availability and concentrations via the intranasal route. Moreover, histopathology confirmed the formulation's safety, and stability data supported its robustness over time. This formulation offers a promising non-invasive approach for efficient CNS drug delivery, which may enhance treatment efficacy and patient compliance during treatment of schizophrenia and related neuropsychiatric disorders.

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Conflict of interests

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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