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Formulation and *In vitro* Characterization of Haloperidol Nanosuspension for Intranasal Brain Delivery

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Abstract
Background: *Intranasal delivery offers a non-invasive route to bypass the blood–brain barrier, enhancing CNS drug targeting while minimizing systemic side effects. Haloperidol, a poorly water-soluble antipsychotic, was selected for nanosuspension formulation to improve solubility and brain delivery.*
Objective: *To formulate and evaluate haloperidol nanosuspensions for potential nose-to-brain delivery in CNS therapy.*
Methods: *Nanosuspensions were prepared via high-speed and high-pressure homogenization using Poloxamer 407 and Avicel as stabilizers. Evaluations included clarity, pH, viscosity, particle size, PDI, zeta potential, in vitro release, TEM imaging, and 90-day accelerated stability.*
Results: *The optimized formulation (NSH 6) with Poloxamer 407 showed clear appearance, pH 6.5, and viscosity of 16 cP. TEM revealed particles within 10–100 nm, though DLS indicated aggregation (>1000 nm). PDI was 0.1956; zeta potential –0.15 mV. In vitro release reached 82.55 ± 2.14% in 8h and stability remained consistent over 30 days.*
Conclusion: *A stable haloperidol nanosuspension was successfully developed for intranasal delivery, showing enhanced drug release and brain-targeting potential. Further in vivo and toxicity studies are warranted.*
Keywords: *Haloperidol, Nanosuspension, Intranasal delivery, Brain targeting, Drug Carriers, Poloxamer 407, Blood–brain barrier*

INTRODUCTION

Neurodegenerative diseases (NDs), like Alzheimer's, Parkinson's, and migraine, are a growing global concern due to aging populations and unhealthy lifestyles. These conditions involve gradual nerve cell death, leading to nervous system dysfunction. Despite ongoing research, traditional treatments remain largely ineffective, mainly due to the challenge of crossing the blood–brain barrier (BBB) (Pandey *et al.*, 2025). The BBB is a tightly regulated structure that protects the central nervous system (CNS) by restricting molecule movement. Its tight junctions, efflux transporters, and metabolic enzymes prevent nearly all macromolecular drugs and about 98% of chemical drugs from entering the brain. This significantly hinders effective drug delivery to neural tissues. As a result, developing innovative drug delivery systems to bypass or overcome the BBB has become a critical focus of current research (Huang *et al.*, 2023).

Intranasal drug delivery offers a promising alternative for treating CNS disorders like Alzheimer's, Parkinson's, psychosis, epilepsy, and brain cancer. It provides advantages over traditional routes, including being non-invasive, easy to administer, fast-acting, and often requiring lower doses with fewer side effects. This route enhances patient comfort, improves compliance, and may enable quicker absorption than oral or injectable methods (Hogan *et al.*, 2020) Intranasal delivery has gained interest as a cost-effective, non-invasive alternative for brain drug delivery. Traditionally used for local treatments like rhinitis, it has also shown promise for systemic delivery due to its ease of use and high patient compliance. Its success in flu vaccines, pain relief, migraine management, and smoking

cessation has expanded its potential applications in the market (Bajpai *et al.*, 2023). Intranasal delivery is a promising, non-invasive method to bypass the BBB and deliver drugs directly to the CNS. Leveraging the natural nose-to-brain connection, it allows rapid drug transport without needing chemical modification or carrier systems, unlike traditional BBB-targeted methods (Talegaonkar and Mishra, 2004). After intranasal administration, the drug reaches the vestibular region, where mucus and cilia trigger mucociliary clearance, limiting its retention in the nasal cavity (Bonaccorso et al., 2024).

Haloperidol, a first-generation antipsychotic used for schizophrenia and Tourette syndrome, is a lipophilic BCS Class II drug (low solubility, high permeability). It acts by blocking dopamine and increasing its turnover. To enhance solubility, control release, and improve bioavailability, Haloperidol is a suitable candidate for mucoadhesive drug delivery systems. Several novel formulations of Haloperidol have been developed to enhance its solubility. Using citric acid as a pH modifier (1:5 ratio) improved dissolution under neutral conditions, which further increased to over 90% with the addition of propylene glycol in a 1:5:0.6 ratio (Ruby Ujawane, Vijay Mathur and Zim, 2015). Fast-dissolving strips of Haloperidol using swellable polymers like HPMC, sodium CMC, and PVA have been successfully developed via solvent casting to enhance dissolution. This approach also improves patient compliance for more effective hypertension therapy. Haloperidol fast-dissolving liquisolid tablets can be formulated using 80% Tween 20 (non-volatile solvent), Avicel PH102 (carrier), and Aerosil PH200 (coating agent). Liquisolid (LS) technology effectively enhances the dissolution and bioavailability of poorly water-soluble drugs like Haloperidol. The LS4 tablet showed significantly greater antipsychotic activity compared to the marketed resource tablet (M. Eisa, El-Megrab and El-Nahas, 2022). The formulated Haloperidol buccal film demonstrated over 75% drug release within 15 min, a quick disintegration time of 45 seconds, and suitable physico-mechanical properties for buccal application (Gidla, Sushmita, Lakshmi, J Maha KSS, Prathyusha, Rao, 2018). Melt-in-mouth tablets (MMTs) of Haloperidol were successfully developed using various superdisintegrants. MMTs offer multiple benefits, including improved patient compliance, rapid onset, low dosing, enhanced bioavailability, reduced side effects, and good stability. The prepared niosomal suspension of Haloperidol serves as an effective carrier to overcome issues like poor solubility, low bioavailability, and short half-life, ultimately prolonging the drug's action and enhancing its half-life (Nikita, Kumar and Sudha, 2024). Nanoformulation is a cutting-edge drug delivery strategy, yet no nanosuspension-based system for Haloperidol in CNS disorder treatment has been reported. This study aimed to develop an carrier-mediated nanosuspension to enhance Haloperidol's solubility and bioavailability for intra nasal brain delivery.

MATERIALS AND METHODS

Materials

The API, Haloperidol sample was provided as a kind gift sample by Shreejee Pharmaceuticals India. The remaining all the chemicals used here were analytical grade.

Drug Profile

Haloperidol is the first of the butyrophenone series of major antipsychotics. The chemical name is 4-[4-(p-chlorophenyl)-4-hydroxypiperidino]-4'-fluorobutyrophenone. The chemical structure is given in Figure 1. Haloperidol was one of the most frequently used antipsychotics around the world (McGrane *et al.*, 2022).

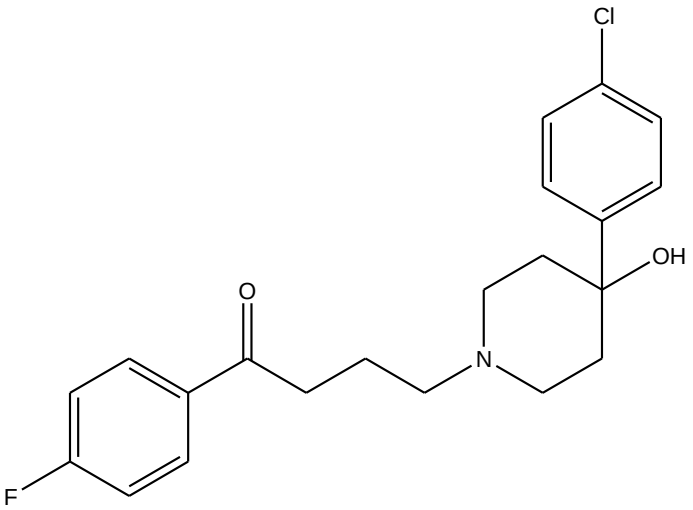

Fig. 1. Structure of Haloperidol

Haloperidol, a first-generation antipsychotic, mainly treats the positive symptoms of schizophrenia—like hallucinations and delusions—by blocking dopamine D2 receptors, with peak effectiveness achieved at approximately 72% receptor occupancy. It also interacts with noradrenergic, cholinergic, and histaminergic receptors, which may cause a range of side effects.

Preformulation study

Compatibility studies were conducted to assess potential interactions between the active pharmaceutical ingredient (API) and excipients. Binary mixtures in defined ratios were prepared and stored in white and amber glass vials at room temperature (≤25°C, ≤75% RH) for 6 months. Physical characteristics were compared with placebos (API or excipients alone). Excipients were chosen based on the formulation's quality requirements. Solid mixtures used a gram-to-gram ratio, while liquid mixtures used a gram-to-milliliter ratio (Menaka and Pandey, 2014).

Preparation of Nanosuspension

Nanosuspension was performed with slight modifications to the previously established method. (Mehmood *et al.*, 2023)**.** Nanosuspensions were prepared using high-speed followed by high-pressure homogenization. The formulation of nasal nanosuspension for Haloperidol involved six formulation trials, each exploring different stabilizers and excipients to enhance solubility and stability. In all trials, purified water was first filtered using a 0.22 µm PVDF filter. For Trial 1, MCC & CMC Sodium (Avicel CL 591) was used as the primary stabilizer, while Trial 2 employed Avicel CL 611, whereas trial 3 and 4 were conducted to reduce the particle size at Homogenizer. In addition, Trial 5 and 6 used Poloxamer 407 at 10% w/w and 11% concentration respectively. In each trail, the stabilizer was dispersed in 60% of the total purified water volume and homogenized for one hour. No other ingredients were added until this mixing was completed. Buffer preparation was consistent across all trials. Benzalkonium chloride (50%) was dissolved in warm purified water (40 ± 5 °C) under stirring. In a separate step, disodium edetate dihydrate was dissolved in purified water at 60 ± 5 °C and added to the first solution. This was followed by the addition of either phenyl ethyl alcohol or glycerol, dissolved in purified water and incorporated under stirring. The complete buffer solution was filtered and checked for clarity. Polysorbate 80 was then dissolved in water at 45 ± 5 °C, after which the active pharmaceutical ingredient (API) was added and properly dispersed to form a uniform slurry, ensuring it was free of lumps or floating particles (Table 1). This slurry was then added to the corresponding polymer dispersion (from the earlier step), and the mixture was homogenized for 30 min using a probe sonicator, then homogenized at 800 bar to achieve an optimized particle size suitable for nose-to-brain delivery. The final volume was adjusted to 200 mL with purified water (Mulam, Kshirsagar and Kakad, 2021).

Filling and sealing

After final quality control testing and product approval, the nasal nanosuspension was filled into either 15 mL HDPE crimp-neck bottles sealed with a Bona pump or an Aptar classic pump, each delivering a 70 µL dose. The target fill volume was not less than 9.5 g, within a limit range of 9.5 g to 10.2 g. This process ensured the development of a stable, effective, and patient-friendly nasal formulation of Haloperidol.

Table 1. Formulation NSH nanosuspension Trials

S. No.	Ingredients	Function	Quantity for 100 mL / batch*			
			Trial 1 (NSH 1)	Trial 2 NSH 2	Trial 5 NSH 5	Trial 6 NSH 6
1	Haloperidol	Active	1	1	1	1
2	Phenyl Ethyl Alcohol	Preservative	0.25	-	-	-
	Benzalkonium chloride solution IP 50 %	Preservative	-	0.02	0.02	0.02
3	Polysorbate 80	Surfactant	0.01	0.01	0.01	0.01
4	Di sodium edetate (Dihydrate)	Stabilizer	0.05	0.05	0.05	0.05
5	Microcrystalline cellulose and Carboxy methyl cellulose (Avicel 591)	Viscosity Builder	2	2	-	-

	Poloxamer 407	Viscosity Builder	-	-	10	11
6	Glycerol	Osmotic Agent	-	2.3	2.3	2.3
	Anhydrous Glucose	Osmotic Agent	5	-	-	-
7	Purified Water	Diluent	q. s. to 100 ml	q. s. to 200 ml	q. s. to 200 ml	q. s. to 200 ml

*Trial 3 (NSH 3) and trial 4 (NSH 4) were conducted to reduce the particle size at homogenizer.

Characterization of formulated Nanosuspension

Clarity

The clarity of the formulated nanosuspensions was determined by visual inspection under a black and white background.

pH measurement

The pH of nasal formulations is crucial to prevent bacterial growth, avoid mucosal irritation, and preserve ciliary function. The pH of all NSH formulations was measured at room temperature and tabulated (Table 2).

Rheology and Viscosity

Viscosity was measured using a Brookfield digital viscometer (DV3TLVKJ0) with spindle no. 61 and RheocalcT 1.2.19 software. Readings were taken both before (at neutral pH) and after formulation (pH 5.5–6.5) (Amkar, Rane and Jain, 2023). Samples were tested for viscosity without dilution. The rheological behaviour of NSH formulations was evaluated by placing 40 mL of each sample in a graduated cylinder and measuring viscosity at spindle speeds of 100 rpm and the viscosity were tabulated (Table 2). Tests were conducted in triplicate, and the results are expressed as mean ± standard deviation (Fadhel and Rajab, 2022; Chen *et al.*, 2020)

Particle Size Distribution and Zeta Potential

Mean particle size, PDI, and zeta potential were assessed using a Zetasizer (Malvern Instruments, UK) via photon correlation spectroscopy. Measurements were taken immediately after preparing the nanosuspension in filtered water and tabulated (Table 2). (Mehmood *et al.*, 2023)

TEM Analysis

Transmission electron microscopy (TEM) was used to analyze particle size and optimize nanosuspension morphology. Samples were placed on a carbon-coated grid, stained with phosphotungstate for 20 seconds, dried under an IR lamp, and examined using a Tecnai G2 Spirit BioTWIN TEM. Images were captured at various magnifications using Gatan Microscopy Suite (GMS3) (Amkar, Rane and Jain, 2023).

***In vitro* release study**

In vitro drug release of pure haloperidol and nanosuspensions was evaluated using the dialysis membrane method (MWCO 12,000–14,000 Da). A dialysis bag containing 1 mg of drug in 5 mL distilled water was sealed and immersed in 500 mL of release media (0.1 N HCl pH 1.2 and phosphate buffer pH 7.4) at 37 ± 0.5 °C with stirring at 50 rpm. At intervals over 8 h, 2 mL samples were withdrawn and replaced with fresh media. Samples were filtered (0.45 µm), diluted with mobile phase, and analyzed by HPLC to calculate drug concentration and percentage release using a validated calibration curve (Mehmood *et al.*, 2023)

Stability Study

Stability studies for the formulated nanosuspensions were conducted over 90 days under accelerated and intermediate storage conditions, adjusted to 30 ± 2°C and 60 ± 5% RH for 30 days. The optimized batches (NSH 1–3) were evaluated for key parameters including particle size, drug content, and *in vitro* dissolution, which are critical for assessing their activity and physical stability (Ramesh and Chandana, 2021).

Statistical analytical

The outcomes of each trail were determined in triplicate and displayed as mean standard deviation (SD). The statistics were analysed using one-way analysis of variance (ANOVA; $p < 0.05$.), with an appropriate significance level.

RESULTS AND DISCUSSION

Compatibility Studies

A compatibility study was conducted to evaluate the physical interactions between the active pharmaceutical ingredient (API) and selected excipients over a 6-month period. Binary mixtures were prepared in a 1:1 ratio and stored in both white and amber glass vials at controlled room temperature conditions (≤25°C and ≤75% RH). Throughout the 6-month duration, no changes in physical appearance were observed for any of the API-excipient mixtures. All combinations maintained a white to off-white crystalline powder form initially, and at 1, 3, and 6 months. This consistency indicates good physical compatibility of the API with excipients such as Benzalkonium chloride, Disodium edetate, MCC & CMC sodium (Avicel 611 and 591), Anhydrous glucose, Poloxamer 407, Polysorbate 80, Glycerol, and Phenyl ethyl alcohol. The drug excipients compatibility studies demonstrate no significant change in physical appearance of mixture of liquid samples till 3 months.

The formulated nanosuspensions using poloxamer is clear and transparent in nature by visual inspection under a black and white background. The pH of the formulated nano suspensions ranged from 5.94 – 6.5. The viscosity of formulated nanosuspensions (NSH 1 - 6) was tabulated in Table 2. and found to be 13 to 23 cps. They show the result within satisfactory limits.

Table 2. pH, PS, PDI, viscosity of formulated nanosuspensions from NSH1 to NSH6

Trial No.	NSH1	NSH2	NSH3	NSH4	NSH5	NSH6
pH	5.94±0.08	6.01±0.04	6.1±0.07	6.05±0.08	6.4±0.13	6.5±0.11
API particle size (Avg, nm)	1315±121.03	1260±135.45	1224±157.07	1150±121.01	1160±127.91	1035±102.22
Polydispersity Index	1±0.002	1±0.082	0.02742±0.085	1±0.089	0.3875±0.071	0.1956 ±0.054
Viscosity (cP)	23±2.224	16±2.17	16±2.71	17±2.11	13±2.71	16±2.98

Particle size, poly dispersivity index and zeta potential

The polydispersity of the formulated nanosuspensions (NSH 1 - 6) ranged from 0.02742 PDI to 1.0 PDI and zeta potential ranged from -0.1501 mV to -4.79 mV. The particulate distribution ranges from 1035 nm to 1260 nm as shown in Table 2. Zetapotential for the trail 6 is found to -0.1501 (Fig. 2)

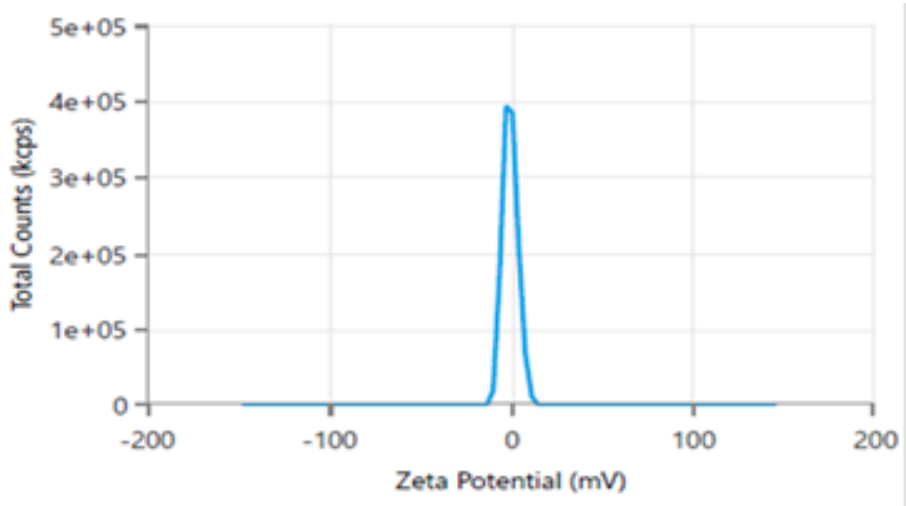

Fig. 2. Zeta potential of formulated NSH 6

TEM Analysis

In the TEM image, it is clearly observed that the prepared nanoparticles are in the range of 10–100 nm (Fig. 3) of optimized nanosuspension (NSH 1 - 6). Thus, the particle size studied by Zeta and TEM states that the desired particle size is achieved. According to performed studies, poloxamer 407 batch (NSH) exhibits optimum results. Hence, NSH 6 is considering for the preparation of nanosuspension loaded haloperidol.

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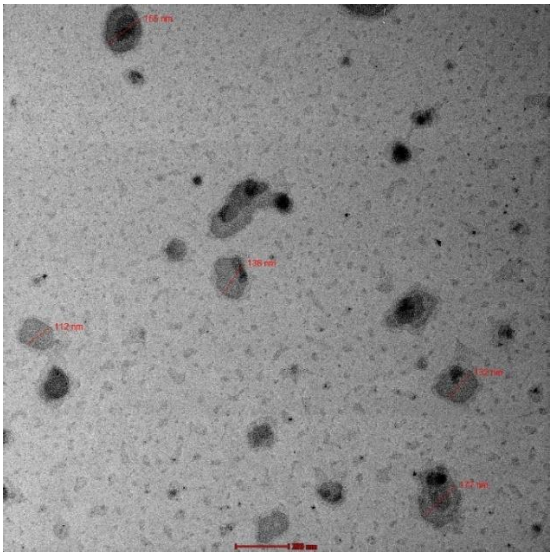

Fig. 3. TEM image of formulated NSH 6

***In-vitro* Drug Release Studies**

The dissolution profiles of nanosuspension formulations (NSH 6), shows better controlled released compared to other formulations (Fig. 4). The release of drug solution was found to be 65.04 ± 2.11% and the release of nanosuspension was found to be more about 82.55 ± 2.14% at 8h. This comparison of the drug release states that the permeation of the drug increases with a decrease in the particle size of the drug by preparing a nanoformulation.

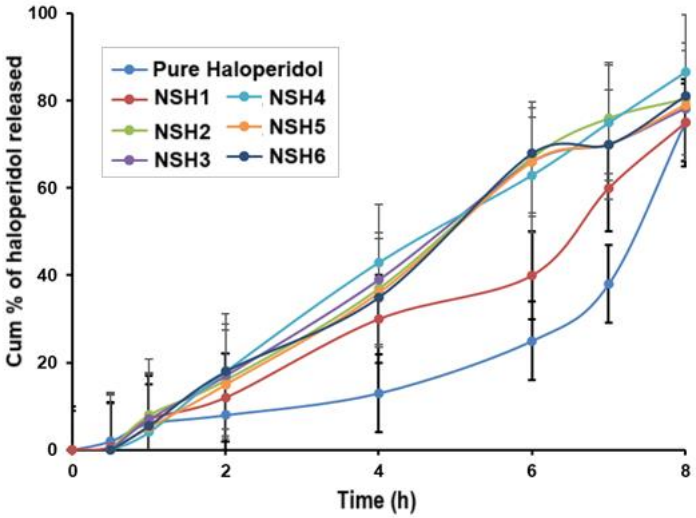

Fig. 4. *In vitro* drug release studies of formulated nanosuspensions NSH1- 6

Stability studies

Stability studies are done for formulated nanosuspension (NSH 1 - 6) as per ICH guideline as follows Acceleration stability studies intermediate storage condition has been changed from 30 ºC ± 2 ºC and 60% RH ± 5% RH. It focuses that there was no change in Drug content, *In vitro* drug release, and particle size (Table 3). The best nanosuspension formulation (NSH 6) was then tested for 30-day accelerated stability. The pH was 6.5 ± 0.11, and it became ever so slightly acidic at 6.2 ± 0.19 on day 30, which is still within acceptable limits for intranasal delivery. The particle size grew from a mean of 1035 ± 102.22 nm initially to 1243 ± 135.90 nm on day 30, indicating some degree of aggregation over the time frame. Polydispersity index (PDI) increased from 0.1956 ± 0.054 to 0.291 ± 0.043, indicating a rise in variation of size distribution to a moderate level.

Table 3. Various stability studies of optimised preparation of NSH6, mean ± SD, n = 3.

Evaluation parameters	Initial	7 days	14 days	30 days
pH	6.5±0.11	6.3±0.21	6.2±0.42	6.2±0.19
API particle size (Avg, nm)	1035±102.22	1087±111.34	1112±136.41	1243±135.90
Polydispersity Index	0.1956 ±0.054	0.256 ±0.088	0.268±0.084	0.291 ±0.043
Viscosity (cP)	16±2.98	18±2.66	21±3.09	24±2.65
Drug content	91.51 ± 0.43	88.71 ± 0.79	85.34 ± 055	84.07 ± 0.12
***In vitro* drug release (after 30 min)**	82.55 ± 2.14	81.56 ± 5.43	78.56 ± 7.15	75.01 ± 6.33

Viscosity increased slowly from 16 ± 2.98 cP to 24 ± 2.65 cP, and this represented a minimal change in dispersion properties. Drug content decreased from 91.51 ± 0.43% to 84.07 ± 0.12% from the start to the end of the research, while 30-minute *in vitro* drug release decreased from 82.55 ± 2.14% to 75.01 ± 6.33%, indicating minimal loss in release efficiency over time. Overall, the formulation exhibited good physicochemical stability with no significant changes that detracted from its performance through the 30-day study.

DISCUSSION

The present study focused on the development of a nanosuspension-based nasal formulation of Haloperidol to enhance brain-targeted delivery for the treatment of CNS disorders. The intranasal route was chosen to bypass the blood-brain barrier (BBB), improving drug bioavailability and reducing systemic side effects (Gidla, Sushmita, Lakshmi, J Maha KSS, Prathyusha, Rao, 2018). Compatibility studies demonstrated excellent physical and chemical stability between Haloperidol and all selected excipients, including MCC/CMC, Poloxamer 407, and preservatives. Among all formulations, NSH 6, (with 11% w/w Poloxamer 407) exhibited superior clarity, optimal pH (6.5), suitable viscosity (16 cP), and satisfactory physical appearance (Bhenki and Dhage, 2022).

Particle size analysis showed a gradual reduction in average particle size across trials, with NSH 6, achieving the lowest size of 1035 nm, which, while still within the submicron range, does not meet the ideal nanoscale size (<200 nm) for efficient nose-to-brain delivery. Interestingly, TEM analysis indicated particles in the 10–100 nm range, suggesting that DLS (Zetasizer) results may have been affected by particle aggregation or polydispersity (Jha et al., 2008). The PDI for NSH 6 was 0.1956, indicating a narrow size distribution and uniformity, while the zeta potential was –0.15 mV, which is too low to ensure strong electrostatic stabilization. Typically, a zeta potential above ±20 mV is preferred for physical stability; thus, NSH 6 may require optimization to prevent aggregation over time (Nikita, Kumar and Sudha, 2024).

The *in vitro* release profile of the optimized formulation (NSH 6) demonstrated enhanced drug release (~90% at 8h) compared to pure Haloperidol, confirming that nanosizing significantly improves drug dissolution and permeation (S. Vadje, K. Surawase and S. Surana, 2020). Furthermore, the stability studies over 90 days under accelerated conditions showed consistent particle size, drug content, and drug release, indicating good formulation stability. There are no prior nanosuspension-based Haloperidol formulations reported for nose-to-brain delivery, making this study novel. However, there's a lack of standardized data on in vivo nose-to-brain pharmacokinetics, especially for nanosuspensions. The influence of formulation excipients on mucosal permeation and enzymatic degradation remains unexplored Amkar, Rane and Jain, 2023). The correlation between *in vitro* release and brain bioavailability needs to be established with further preclinical studies.

Limitations

Despite the promising results, several limitations must be noted. A major concern is the low zeta potential across all formulations, with NSH 6 showing only –0.15 mV, far below the ±20 mV threshold needed for colloidal stability, suggesting a higher risk of aggregation. While TEM confirmed nanoscale particles (10–100 nm), DLS showed sizes >1000 nm, indicating possible aggregation or broad distribution in solution. The study also lacks in vivo pharmacokinetic and brain-targeting data, which are essential to validate CNS delivery (Amkar, Rane and Jain, 2023). Additionally, nasal residence time, mucociliary clearance, and mucoadhesive properties were not assessed. The absence of toxicity or histopathological studies further limits understanding of safety. Lastly, no *in vitro–in vivo* correlation (IVIVC) was established. These limitations should be addressed in future work for clinical translation (Fadhel and Rajab, 2022).

CONCLUSION

This study successfully formulated and evaluated a Haloperidol nanosuspension for intranasal delivery targeting CNS disorders. The optimized formulation (NSH 6) demonstrated acceptable clarity, pH, viscosity, narrow PDI, and improved *in vitro* drug release. TEM confirmed that the particle size was within the nanoscale, although DLS

results suggested possible aggregation. Despite limitations in zeta potential and absence of in vivo studies, the results support the potential of nanosuspension-based intranasal delivery as a promising approach to enhance the bioavailability of poorly soluble CNS drugs like Haloperidol. Future studies should focus on improving formulation stability, validating in vivo brain targeting, and evaluating safety and tolerability for clinical translation.

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