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Selection of Excipients for Haloperidol Formulation for Nose-to-Brain Delivery: A Drug-Excipient Compatibility Study

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ABSTRACT

Objective: The current research was designed to assess the physical compatibility of short-listed pharmaceutical excipients with micronized haloperidol as a requirement for nasal formulation from nose-to-brain targeting point of view to the neonates. Physical and chemical stability of drug-excipient blends is principal in formulating safe and effective intranasal products.

Methods: Haloperidol-excipient binary combinations and some single excipients were kept in white and amber glass containers in a stable condition. Their physical state was monitored for the first time and at the end of 1, 3, and 6 months to test for any evidence of incompatibility like color change, precipitation, or phase separation. Poloxamer 407, benzalkonium chloride solution (50%), polysorbate 80, disodium edetate (dihydrate), microcrystalline cellulose and carboxymethyl cellulose (Avicel cl-611), and glycerol are some tested excipients.

Results: The entire excipients and their individual combinations with haloperidol were physically stable for the six months. No color, clarity, or consistency shift was detected in any of the mixtures or pure ingredients under either of the two storage conditions (amber or white glass vials). Combinations of haloperidol with disodium edetate (dihydrate), poloxamer 407, and Avicel CL-611 showed no change from their original white to off-white appearance, thus showing no detectable physical incompatibility.

Conclusion: Physical stability of the excipients investigated with micronized haloperidol was good and therefore were suitable candidates to be utilized for follow-up formulation development of a nasal formulation for nose-to-brain targeting. These results warrant the use of these excipients in preformulation screening and stability testing in preparation of an optimal intranasal delivery system for central nervous system targeting.

Keywords: *Neonates, Nose-to-brain delivery, Preformulation studies, Intranasal drug delivery, Poloxamer 407, CNS drug targeting*

1. INTRODUCTION

Neonatal inhalation therapy is a technique of giving medication directly into the lung for respiratory disease conditions such as respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), neonatal pneumonia, and airway inflammation. Medications used normally include bronchodilators such as salbutamol, corticosteroids such as budesonide, surfactants, and

sometimes hypertonic saline or antibiotics. Because of the distinct physiology of the neonate, such as low tidal volume and elevated respiratory rate, correct selection of delivery device is required. Jet nebulizers, ultrasonic nebulizers, and metered-dose inhalers (MDIs) with spacers and masks are among the most used devices, frequently with a face mask or endotracheal tube interface [1]. Optimal particle size of aerosols would be 1–5 micrometers for maximum deposition in the lower airways. Follow-up surveillance during treatment is required to monitor efficacy as well as identify possible side effects like bronchospasm or systemic absorption. Appropriate technique and equipment selection are important to ensure optimal drug delivery and prevent harm to this patient population [2].

Haloperidol, a first-generation antipsychotic, was synthesized by Bert Hermans in 1958 at Janssen Laboratories. It primarily works by blocking dopamine D2 receptors in the brain, with optimal efficacy achieved when about 72% of these receptors are occupied. The IUPAC name of haloperidol is 4-[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]-1-(4-fluorophenyl) butan-1-one with the molecular formula of $C_{21}H_{23}ClFNO_2$ (Fig. 1). Additionally, haloperidol interacts with noradrenergic, cholinergic, and histaminergic receptors, influencing both its therapeutic effects and side effects [3].

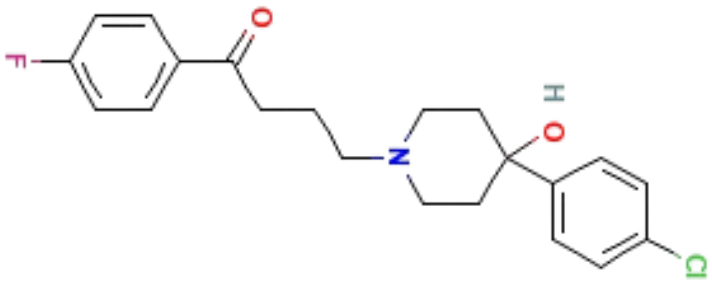

Fig 1. Chemical structure of Haloperidol

Pharmaceutical formulation is a complex process where the active pharmaceutical ingredient (API) is combined with excipients to create a stable, effective drug product. Key factors such as particle size, polymorphism, pH, and solubility are carefully considered for optimal drug performance. The success of the formulation depends on the API's properties, excipient compatibility, and the manufacturing process. The final product is a dosage form with a precise combination of active and inactive ingredients. This process also considers the drug's chemical characteristics, formulation strategy, and clinical use [4].

The term "excipient" comes from the Latin word excipere, meaning "to except" or "other than," and refers to inactive substances used alongside the active pharmaceutical ingredient (API) to enhance drug performance. Medicines are available in various dosage forms, such as tablets, capsules, nasal sprays, and injectables, with excipients playing crucial roles in bulk, stability, bioavailability, and patient acceptability. Though inactive therapeutically, excipients are rigorously evaluated for safety to ensure the efficacy and quality of the drug product. They are essential to the formulation process, supporting manufacturing and optimizing the drug's overall effectiveness [5].

Drug–excipient compatibility studies are essential in the preformulation phase, helping to identify suitable excipients and ensure a stable, effective dosage form [6]. These studies integrate physicochemical and biopharmaceutical principles to guide the development of optimal drug delivery systems [7, 8]. Analytical techniques are crucial for identifying potential incompatibilities, preventing material loss, and streamlining the development process to reduce time and cost.

Preformulation studies typically utilize three main categories of analytical techniques to evaluate drug–excipient compatibility and support the development of stable and effective formulations such as spectroscopic and specific detection methods contains these techniques help identify structural and molecular interactions between the active pharmaceutical ingredient (API) and excipients. Common methods include UV Spectroscopy, Infrared (IR) Spectroscopy, Nuclear Magnetic Resonance (NMR) Spectroscopy, and X-Ray Diffraction (XRD). Separation Methods such as used to isolate, identify, and quantify components within a formulation, particularly to detect degradation products or impurities. Key methods include Thin-Layer Chromatography (TLC), High-Performance Liquid Chromatography (HPLC), and Capillary Electrophoresis (CE). Thermal Analytical Methods such as techniques evaluate thermal behavior and detect potential incompatibilities based on changes in heat flow or decomposition patterns. They includes Thermal Analysis of calorimetric methods, such as Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA).

Nasal therapy, or Nasya Karma, is a traditional treatment in Ayurvedic medicine [9], and the nasal route gained prominence in the 1980s for systemic drug delivery [10]. Its highly vascularized mucosal membrane enables rapid absorption, bypassing hepatic first-pass metabolism, offering benefits like dose reduction, faster onset, and fewer side effects [11, 12]. Nasal administration also overcomes the limitations of oral delivery and mimics intravenous benefits while being non-invasive,

self-administered, and improving patient compliance. Lipophilic drugs are well absorbed, achieving nearly 100% bioavailability, and hydrophilic drugs can be enhanced with absorption promoters. Additionally, nasal delivery bypasses the blood-brain barrier, allowing direct CNS delivery, beneficial for peptides, hormones, vaccines, and CNS-targeted drugs [13]. A variety of formulation ingredients are used in nasal sprays to improve stability, solubility, and microbial control.

In nasal spray formulations, various excipients are incorporated to ensure stability, safety, efficacy, and patient well-being. Each component serves a specific function within the formulations includes Isotonicity Adjusters such as Sodium chloride and dextrose help match the osmotic pressure of the formulation to that of nasal fluids, preventing irritation or discomfort [14]. PH adjusters such as sodium chloride, hydrochloric acid, and sulfuric acid help to maintaining physiological pH (typically 4.5–6.5) is essential for drug stability and nasal mucosal tolerance [15].

Purging agent (nitrogen) used to displace oxygen and minimize oxidative degradation [16]. Buffering agents such as sodium citrate and sodium phosphate buffers help maintain a stable pH throughout the shelf life of product [16]. Humectants used to prevent the drying of the nasal mucosa and maintains moisture (glycerin) [16].

Antimicrobial preservatives are used to protect the formulation from microbial contamination, especially in multi-dose containers such as benzalkonium chloride, ethanol, propylene glycol, benzoyl alcohol, chlorobutanol, and methyl paraben [17]. Surfactants are included on the formulations to improve the solubility of poorly soluble drugs and help stabilize suspensions such as polysorbate 80, polysorbate 20, and poloxamer 407 [18]. Chelating agent (Disodium EDTA (EDTA-Na H_2)) enhances formulation stability by binding trace metal ions that may catalyze degradations [19]. Suspending agents (carboxymethyl cellulose and sodium carboxymethyl cellulose) usually added in the formulation to increase viscosity and help keep suspended particles evenly dispersed [20]. Co-solvents such as alcohol (ethanol), polyethylene glycol 400 (PEG 400), and propylene glycol improve the solubility of active ingredients and aid in formulation clarity [21]. Poloxamer 407 (P407) is a temperature-sensitive polymer generally used in nasal drug delivery because of its new sol-gel transition behavior. P407 at room temperature exists in salt like waxy granular powder and is easily administered.

Nasal sprays provide a targeted delivery method for medications like Haloperidol, a conventional antipsychotic used to treat psychotic disorders and behavioural conditions. Administering Haloperidol nasally offers benefits such as bypassing first-pass hepatic metabolism, enhancing bioavailability, and supporting dose reduction while promoting faster onset and fewer side effects. This study explores the feasibility of nasal delivery for Haloperidol, aiming for rapid drug release, quick therapeutic onset, and effective low-dose administration. Additionally, it focuses on selecting suitable excipients to develop a stable, efficient nasal spray formulation, improving clinical application and patient compliance.

2. MATERIALS AND METHODS

Haloperidol was obtained as a free sample by Shree Jee Pharmaceutical, Delhi, India. Benzalkonium chloride from Finar Ltd, India, polysorbate 80 from Spectrum Chemical, Disodium edetate (dihydrate) from Avantor, microcrystalline cellulose and carboxymethyl cellulose (Avicel CL - 611) from DuPont Nutrition, India. Glycerol from VM Chem. India. Hydrochloric acid and sodium hydroxide were procured from Merck, Mumbai. India. The Table 1 shows the list of selected excipients and their functions.

Table 1. The list of selected excipients and their functions

S. No	Ingredients	Function
1.	Haloperidol	Active ingredient
2.	Poloxamer 407	Surfactant/sol-gel agent
3.	Benzalkonium Chlorides Solution 50%	Preservative agent
4.	Polysorbate 80	Surfactant
5.	Disodium edetate (dihydrate)	Stabilizing agent
6.	Microcrystalline Cellulose and Carboxymethyl cellulose (Avicel CL - 611)	Viscosity agent
7.	Glycerol	Osmotic Agent
8.	Purified water	Diluent

Compatibility study

The compatibility studies were conducted by storing the drug haloperidol with excipients benzalkonium chlorides solution (50%), polysorbate 80, disodium edetate (dihydrate), Avicel CL - 611, and glycerol individually in white glass vials and amber glass vials. Additionally, the physical characteristics were evaluated while maintaining the temperature at 25 ± 2°C *and relative humidity at 75%* ± 5% *RH. Stability studies were performed over 1, 3, and 6 months.*

The haloperidol and selected individual excipient (disodium edetate) and haloperidol and Avicel CL – 611 were stored in a 1:1 ratio in both white glass vials and amber glass vials. The physical characteristics were evaluated while maintaining the temperature at 25°*C* ± 2°C *and relative humidity at 75* ± 5% *RH.*

3. RESULTS AND DISCUSSION

As per the method I of stability study, the individual API and excipients were stored in white glass vials and amber glass vials, maintained under controlled conditions at 25 ± 2°C and relative humidity at 75% ± 5% RH. Stability studies were conducted for 1, 3, and 6 months. The results from the initial and one month storage periods, along with those obtained after 3 months and 6 months, under these stability conditions are provided in Table 2.

Table 2. Appearance of Ingredients after 1, 3, and 6 months in white and amber glass vials

S. No	Ingredients	Physical appearance						
		Initial	After 1month		After 3 months		After 6 months	
			White glass Vials	Amber glass vials	White glass Vials	Amber glass vials	White glass Vials	Amber glass vials
1.	Haloperidol (micronized)	White to off white powder	White to off white powder	White to off white powder	White to off white powder	White to off white powder	White to off white powder	White to off white powder
2.	Poloxamer 407	White, waxy, free-flowing granules	White, waxy, free-flowing granules	White, waxy, free-flowing granules	White, waxy, free-flowing granules	White, waxy, free-flowing granules	White, waxy, free-flowing granules	White, waxy, free-flowing granules
3.	Benzalkonium Chlorides Solution 50%	Clear, colourless to faintly yellow solution	Clear, colourless to faintly yellow solution	Clear, colourless to faintly yellow solution	Clear, colourless to faintly yellow solution	Clear, colourless to faintly yellow solution	Clear, colourless to faintly yellow solution	Clear, colourless to faintly yellow solution
4.	Polysorbate 80	Yellow to amber-colored, viscous liquid	Yellow to amber-colored, viscous liquid	Yellow to amber-colored, viscous liquid	Yellow to amber-colored, viscous liquid	Yellow to amber-colored, viscous liquid	Yellow to amber-colored, viscous liquid	Yellow to amber-colored, viscous liquid
5.	Disodium edetate (dihydrate)	White crystalline powder	White crystalline powder	White crystalline powder	White crystalline powder	White crystalline powder	White crystalline powder	White crystalline powder
6.	Avicel CL - 611	White to off white powder	White to off white powder	White to off white powder	White to off white powder	White to off white powder	White to off white powder	White to off white powder
7.	Glycerol	Colourless Viscous liquid	Colourless Viscous liquid	Colourless Viscous liquid	Colourless Viscous liquid	Colourless Viscous liquid	Colourless Viscous liquid	Colourless Viscous liquid

From drug-excipient compatibility's point of view, it is preferable that haloperidol be stable in the formulation. Although there are not many direct studies of the compatibility between haloperidol and P407, the successful formulation of haloperidol in SLNs from GMS indicates compatible interaction. Besides this, it is also compatible with some other drugs and excipients

and therefore can be a good candidate for such formulations.

For haloperidol, a hydrophobic antipsychotic drug, it is difficult to prepare an effective nasal delivery system because of its low aqueous solubility. Nevertheless, research has shown that loading of haloperidol in solid lipid nanoparticles (SLNs) can improve its solubility and stability. For example, a study prepared haloperidol-loaded SLNs with glyceryl monostearate (GMS) as the lipid matrix, resulting in enhanced drug encapsulation and controlled release profiles.

As per the method II of stability study, the API and individual selected excipient were stored in both white glass vials and amber glass vials, maintained under controlled conditions at 25°C ± 2°C and relative humidity at 75% ± 5% RH. Stability studies were conducted for 1 month, 3 months and 6 months. The results from the initial and one month storage periods, along with those obtained after 3 months and 6 months, under these stability conditions are provided in Table 3.

Table 3. Appearance of haloperidol and selected excipients mixtures (1:1) after 1, 3, and 6 months

S. No	Ingredients	Physical appearance						
		Initial	After 1month		After 3 months		After 6 months	
			White glass Vials	Amber glass vials	White glass Vials	Amber glass vials	White glass Vials	Amber glass vials
1	Haloperidol + Disodium edetate (dihydrate)	A mixture of White to off white crystalline powder	A mixture of White to off white crystalline powder	A mixture of White to off white crystalline powder	A mixture of White to off white crystalline powder	A mixture of White to off white crystalline powder	A mixture of White to off white crystalline powder	A mixture of White to off white crystalline powder
2.	Haloperidol + poloxamer 407	White, waxy, free-flowing granules	White, waxy, free-flowing granules	White, waxy, free-flowing granules	White, waxy, free-flowing granules	White, waxy, free-flowing granules	White, waxy, free-flowing granules	White, waxy, free-flowing granules
3.	Haloperidol + Avicel CL - 611	White to off white powder	White to off white powder	White to off white powder	White to off white powder	White to off white powder	White to off white powder	White to off white powder

Poloxamer 407 (P407) is a temperature-sensitive polymer generally used in nasal drug delivery because of its new sol-gel transition behavior. P407 at room temperature exists in salt like waxy granular powder and is easily administered. As soon as the formulation in contact with the nasal mucosa, at body temperature it becomes gel, increasing residence time of the drug and its absorption.

4. CONCLUSION

In conclusion, the stability studies conducted under controlled conditions at 25°C ± 2°C and 75% ± 5% relative humidity, with such as Poloxamer 407, Disodium Edetate (Dihydrate), Avicel CL-611, and the rest are physically compatible with haloperidol during more than six months of storage. No visual or physical deterioration of any of the samples stored in white or amber glass vials was observed. No significant changes in the physical properties were noted during the study period, which further supports the suitability of these excipients for formulation development. Therefore, based on the positive outcomes of the compatibility studies, the selected excipients can be confidently used for preparing a nasal spray formulation with haloperidol as the active ingredient. This work provides a solid foundation for advancing to the next stages of drug formulation and optimization. These findings confirm that the excipients chosen are suitable for haloperidol nasal formulation intended for nose-to-brain delivery. These findings serve as a good starting point upon which to go further with more sophisticated formulation and stability experiments.

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