Research Article

Development and Characterization of Fexofenadine-Loaded *Nigella sativa* Oil-based Nanoemulsion Nasal Spray for Allergic Rhinitis

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ABSTRACT

Allergic rhinitis is a common immune system disorder with a significant impact on quality of life. Traditional oral antihistamines such as fexofenadine have limited bioavailability due to first-pass metabolism and efflux mechanisms. The objective of this study was to develop and assess a nanoemulsion-based intranasal delivery system to improve drug absorption and therapeutic effectiveness. Black seed oil (Nigella sativa) was utilized as the oil phase, while Tween 80 and propylene glycol served as the surfactant and co-surfactant, respectively, in probe sonication to prepare fexofenadine-loaded nanoemulsions. The formulations were evaluated for physicochemical parameters, including pH, viscosity, droplet size, polydispersity index, osmolality, and in-vitro drug release. Among the formulations, F3 showed the most desirable properties, with a droplet size of 134.2 nm, PDI of 0.590, viscosity of 19.2 cP, and pH of 6.3, indicating the suitability for nasal administration. It was isotonic (289 ± 3 mOsm/kg) in nature and demonstrated the maximum in-vitro drug release over other formulations. The results showed that the nanoemulsion-based nasal delivery of fexofenadine in combination with Nigella sativa oil is a possible approach that may enhance the bioavailability and therapeutic outcomes in allergic rhinitis. This strategy may also provide rapid onset of action, improved patient compliance, and possible synergistic anti-inflammatory effects.

Keywords: Fexofenadine, Nanoemulsion, Intranasal drug delivery, Allergic rhinitis, Nigella sativa oil.

INTRODUCTION

Allergic diseases are among the most prevalent chronic diseases globally and are a major public health issue. These conditions arise from an overactive immune response to environmental substances that are otherwise harmless, known as allergens, such as pollen, house dust mites, animal dander and fungal spores.[1] Allergic rhinitis, or hay fever, characterised as four cardinal nasal symptoms: nasal itching, rhinorrhoea, congestion, and sneezing, after IgE-induced activation of mast cells and release of inflammatory mediators, including histamine.[2]

The nasal mucosa is a promising pathway for drug delivery because of its large surface area, high density of blood vessels, and thin epithelial barrier that allows rapid absorption and local and systemic therapeutic effects. The nasal cavity has three regions: vestibular, olfactory and respiratory. The vestibular area is the least involved in drug absorption due to its small surface area and vascularization. The olfactory area is found in the nasal roof, which contains specialized epithelial cells. It is a possible nose to brain transport route. Nasal medication distribution primarily occurs in the respiratory area. This has a large surface area, rich vascular supply and mucus secreting epithelium allowing rapid systemic absorption.[3]

Physiological barriers such as the nasal mucus layer and variable pH can affect drug diffusion and ionisation. Mucociliary clearance removes deposited drugs rapidly. These limitations can overcome with the use of mucoadhesive compounds to extend the nasal residence time and absorption.[3,4]

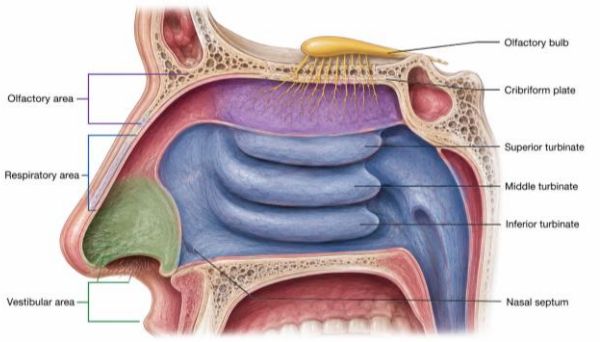

Figure 1: The Nasal cavity

The main routes of nasal absorption are the paracellular pathway, which entails the slow dispersion of tiny hydrophilic compounds through intercellular spaces, and the transcellular route, which enables transportation of lipophilic drugs throughout the epithelial cell membranes. Using absorption-enhancing agents like chitosan can transiently modulate tight intersections and enhance the drug permeation.[3,4]

The intranasal dosage forms are most preferably used as nasal sprays because of its ease of use, accurate dosing and predictable drug delivery. They have a rapid therapeutic onset and are effective in acute conditions such as allergic rhinitis, sinus congestion and migraine. This can be achieved by direct deposition of sprays onto the nasal mucosa, thus bypassing the first pass metabolism and increasing

bioavailability. These are non-invasive, portable and patient friendly and can be used for all ages. Other recent innovations, such as mucoadhesive systems and nano emulsions increase the nasal residence time and absorption efficiency.[5]

The advantages of nasal medication administration include fast onset of action, avoid first pass metabolism, targeted local drug administration and enhanced patient compliance. Application of the nanoemulsion technology further improves these benefits by forming nano-sized oil droplets to improve medication solubility, stability and nasal mucosal absorption.[6]

Fexofenadine is a second-generation antagonist of the H_1 receptor, that is commonly used to treat idiopathic chronic urticaria. It is non-sedating, highly specific to peripheral H_1 receptors and has little CNS penetration. However, the oral bioavailability of fexofenadine is limited (~33%) by P-glycoprotein-mediated efflux, poor intestinal permeability, and first-pass hepatic metabolism.[7]

Nanoemulsions are kinetically stable optically transparent systems with droplet size, which typically ranges from 20 to 200 nm. It provides higher surface area, higher bioavailability and higher drug solubilisation for hydrophobic drugs. The oil phase used in this investigation which is black seed oil (*Nigella sativa*) also has anti-inflammatory and antioxidant action by its thymoquinone content.[8]

In this study, we present a new formulation strategy to combine a synthetic antihistamine with an herbal oil nanoemulsion system for intranasal delivery. Thymoquinone in *Nigella sativa* oil provides additional anti-inflammatory and antioxidant potential, unlike conventional formulations, where it only forms the oil phase. The dual-functional delivery system may not only improve the delivery of drugs, but also have supportive pharmacological effects, which would improve the therapeutic outcomes in allergic rhinitis.

MATERIALS AND METHODS

MATERIALS

Fexofenadine was procured as the gift sample from Morepen Laboratories Ltd., Maharashtra. Black seed oil was procured from Greenish Healthcare, Athirampattinam, Thanjavur. Chitosan and Tween 80 were obtained from Oxford Lab Fine Chem LLP, Maharashtra. Propylene glycol, NaCl and Citric acid were obtained from Nice Chemicals (P) Ltd., Edappally, Kochi. All other used ingredients were of analytical grade and were obtained locally.

METHODS

Preformulation Studies

The organoleptic properties of Fexofenadine were studied by observing its colour, appearance and odour. For solubility evaluation of the drug, 1-2 mg of drug was added to 5 mL of solvent, such as water, ethanol, black seed oil, methanol and hexane and was shaken gently. Accurately weigh 10 mg of Fexofenadine and dissolve it in 10 ml of ethanol. A stock solution with a concentration of 1 mg/ml was prepared to determine the λ_{max}. 1 ml of the stock solution was diluted with 10 mL of phosphate buffer (pH 5.5) to obtain a final concentration of 100µg/mL. The secondary stock solution was appropriately diluted with phosphate buffer (pH 5.5) to obtain a concentration of 2µg/mL. The absorption maximum (λ_{max}) of the solution was then determined by scanning in the range of 200-400 nm using a SYSTRONICS® UV-visible double beam spectrophotometer, with buffer 5.5 as the blank.[9] With absorbance measured at 245 nm, the calibration curve was constructed using concentrations of 5, 10, 15, 20, and 25 µg/mL in phosphate buffer (pH 5.5).

FT-IR Spectroscopy Compatibility Studies

FT-IR spectroscopy was used to assess the compatibility of fexofenadine, chitosan, and their physical mixture. Samples were prepared using potassium bromide discs. Approximately 2 mg of the sample was finely ground with dry KBr and compressed using a hydraulic press to form a transparent disc. Spectra were recorded on a SHIMADZU spectrophotometer at a resolution of 4000-400 cm^{-1}.

Development of Fexofenadine Nanoemulsion

Table 1: Formulation Table of Fexofenadine Nanoemulsion

Formulation code	Drug (mg)	Tween 80 (mL)	Propylene glycol (mL)	Black seed oil (mL)	Distilled water
F1	5	15	7.5	2.25	q.s
F2	5	15	5	2.25	q.s
F3	5	15	2.5	2.25	q.s

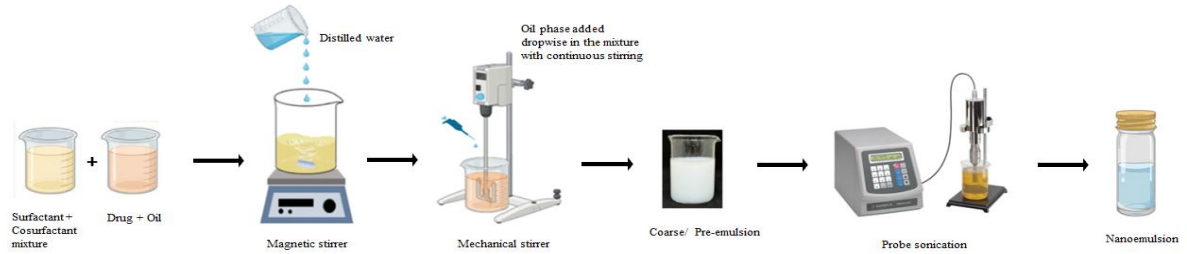

Figure 2: Formulation process of Nanoemulsion

The oil phase was prepared by precisely weighing fexofenadine and by dissolving it in black seed oil under gentle magnetic stirring at room temperature (if required, heat up to 30 °C). The aqueous phase was prepared by simultaneous dissolution of Tween 80 (surfactant) and propylene glycol (co-surfactant) in distilled water by using a magnetic stirrer. Thereafter, citric acid and NaCl were added to adjust the pH and tonicity. The oil phase was added to the aqueous phase dropwise at a rate of 0.4 mL/min and then stirred magnetically at 500 rpm continuously for 10-15 minutes to form a coarse pre-emulsion. The vessel was placed in ice bath to maintain the temperature below 30 to 35°C, and the coarse pre-emulsion was then probe sonicated at 20 to 40% amplitude for 10 minutes in pulse mode (10s on/10s off). The nasal tolerability was adjusted to an osmolality (~290-320 mOsm/kg) and pH (~5.5-6.5) after sonication. Three formulations were prepared by changing the concentration of propylene glycol.

EVALUATION OF NANOEMULSION

Physical appearance

Physical appearance was assessed by visual inspection for colour, clarity and phase separation.

Determination of pH

The pH of the nanoemulsion nasal spray was determined using a digital pH meter to ensure its compatibility with the nasal mucosa (around 5.5-6.5), to avoid irritation or discomfort during administration.

Determination of viscosity

The viscosity was measured by Brookfield viscometer to ensure suitable flow and spray ability. Optimum viscosity improves retention in the nasal cavity.

Determination of polydispersity index (PDI) and droplet size

The polydispersity index (PDI) and droplet size of the prepared nanoemulsion formulations were identified by a particle size analyser (Malvern Zetasizer). Nano-sized (<200 nm) droplets ensure uniform dispersion, enhanced absorption, improved physical stability and consistent therapeutic performance of the formulation.

Determination of osmolality

The osmolality was measured using an Osmometer. This is to ensure the formulation is isotonic with nasal fluids and therefore causes no nasal irritation and is comfortable for the patient.

Determination of in vitro drug release

The drug content was determined spectrophotometrically at a wavelength of 245 nm following appropriate dilution. For in vitro drug release, 5 mg of each formulation was loaded into a dialysis bag, which was sealed at both ends. The bag was agitated at 100 rpm in a buffer 5.5 at 37±0.5°C. At 5, 10, 15, 20 and 25 min, 5 mL of the media was eliminated and replaced with fresh media. Samples were analysed at 245 nm.

RESULTS AND DISCUSSION

Preformulation Studies

The organoleptic properties of Fexofenadine were evaluated and confirmed to be a white crystalline odourless powder. Solubility tests revealed that the drug was insoluble in hexane, sparingly soluble in water and black seed oil, soluble in ethanol and methanol. The poor aqueous solubility of Fexofenadine is the reason for the need of a nanoemulsion system to enhance solubility and drug delivery via nasal route. The λ_{max} of absorption (λ_{max}) of Fexofenadine was found by scanning a suitable working solution of the drug in buffer 5.5 in the range of 200-400 nm by using UV spectrophotometer. The maximum absorption was found to be at 245 nm. This wavelength was chosen for further quantitative analysis of the drug. The standard calibration curve of Fexofenadine was prepared in concentration range of 5–25 µg/mL using buffer 5.5. The absorbance values were recorded on UV spectrophotometer at 245 nm. A linear relation was observed between absorbance and concentration, and it confirms that, the drug obeys the Beer-Lambert's law. The calibration curve's slope was 0.0325 and R^2 = 0.9999.

Compatibility Studies (FT-IR)

The compatibility of fexofenadine hydrochloride with chitosan and any potential interactions were investigated using infrared spectroscopy. FTIR studies revealed the characteristic peaks of Fexofenadine at 3302.03cm^{-1}, 2938.33cm^{-1} and 1704.92cm^{-1} for O–H stretching, C–H (aliphatic) stretching and C=O (carboxyl) functional groups respectively. The peaks at 1460.54 cm^{-1} and 1160.09 cm^{-1} were assigned to C=C (aromatic) and C–O stretching vibrations. The FTIR spectra of chitosan showed the peaks at 3583.78 cm^{-1} and 3293.40 cm^{-1} could be attributed to the stretching vibration of O–H and N–H, respectively. The primary peaks of Fexofenadine were present in spectrum of the physical mixture indicating no significant interaction between the drug and polymer.

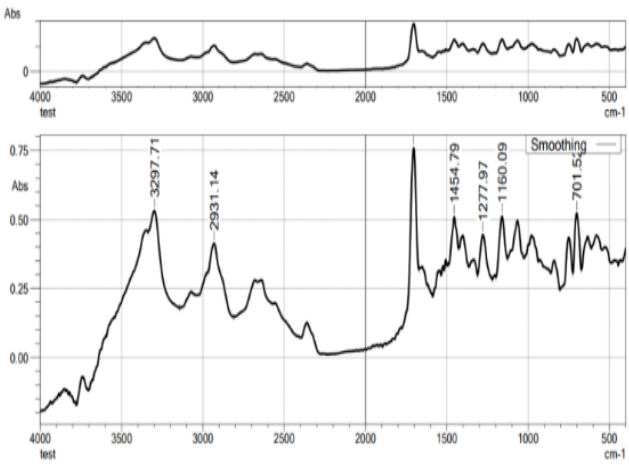

Figure 3: FT-IR spectra of Physical Mixture

EVALUATION OF NANOEMULSION

Physical Appearance

All the nanoemulsion formulations were observed as clear to slightly translucent, yellow to golden yellow liquids with characteristic odour and no phase separation or creaming were observed. The transparent appearance and absence of turbidity or creaming shows that a kinetically stable nanoemulsion system has formed. The golden yellow colour is inherent to the black seed oil ingredient, which forms the oil phase of the formulation.

Determination of pH

The pH of prepared nanoemulsion formulations were found to be 6.0, 6.2 and 6.3 for F1, F2 and F3 respectively. All the three formulations are in the range of 5.5-6.5 which is the physiological pH of the nasal cavity and is critical for intranasal dosage forms. The pH values found for F1–F3 suggest that these formulations are unlikely to cause discomfort to the nose upon administration and are compatible with the delicate nasal epithelium.

Determination of Viscosity

The viscosity of nanoemulsion formulations were 28.5 cP, 23.8 cP and 19.2 cP for F1, F2 and F3 respectively. The results of F1 to F3 showed a gradual decrease in viscosity which may be associated with the differences in the composition of the formulations and the reduction in droplet size in F3. In intranasal delivery, viscosity plays a dual role, it should be high enough to enhance the residence time of the formulation in the nasal cavity, but low enough for ease of administration and to avoid blockage of nasal passages. The viscosity of F3 (19.2 cP) is a relatively low value but it is practically acceptable for a nanoemulsion for nasal use; it is easy to spray or instill but it has a better retention compared with aqueous solutions.

Determination of polydispersity index (PDI) and droplet size

The polydispersity index (PDI) and droplet size of all formulations were identified by Malvern Zetasizer. Formulation F1 revealed a particle size of 229 nm with a PDI of 0.761 whereas F2 showed a higher particle size of 388 nm with a polydispersity index of 0.964. The relatively high PDI values of F1 and F2 suggest significant heterogeneity in droplet size distribution, which is indicative of formation of less uniform nanoemulsions. Whereas formulation F3 resulted into the least droplet size of 134.2 nm with least PDI of 0.590 in all the three batches which confirmed the formation of acceptable nanoemulsion with moderate size distribution. PDI of 0.590 indicates moderate polydispersity and is relatively more uniform in size distribution as compared to F1 and F2.

Determination of Osmolality

The osmolality of the optimised formulation F3 was determined to be 289 ± 3 mOsm/kg, which is within the physiological isotonic range (280–320 mOsm/kg). This value suggests that F3 is close to isotonic with nasal secretions; hence the formulation is safe for intranasal delivery and is not likely to cause any adverse local effects at the site of application.

Determination of In-vitro Drug Release

In vitro drug release from all the three nanoemulsion formulations were studied for 25 min diffusion-based method. The maximum cumulative release was observed in F3 at the end of the study period (2.13%). The values for F1 and F2 were 1.86% and 1.68%, respectively. The primary mechanism that governs the drug release from these nanoemulsions is the diffusion of Fexofenadine from the oil droplets across the interfacial film into the surrounding aqueous medium. This process is inherently size dependent, i.e., smaller droplets reduce the diffusion path length and increase the rate of drug transfer. The reduced and more uniform PDI of F3 also contributes to the consistency and reproducibility of its release profile, as opposed to the polydisperse behaviour observed in F1 and F2.

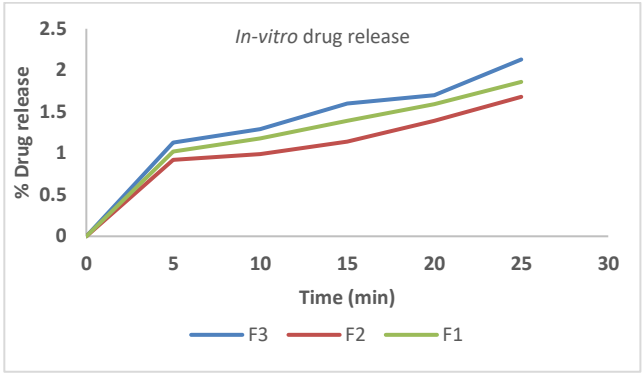

Figure 4: In-vitro release of nanoemulsion formulations

CONCLUSION

The present study successfully demonstrated the development of a fexofenadine-loaded nanoemulsion nasal spray using black seed oil (Nigella sativa) as an oil phase. The formulation strategy effectively overcomes the limitations of low oral bioavailability of fexofenadine by using the advantages of intranasal drug delivery. Among all the prepared formulations, F3 was found to be the optimized formulation with desirable physicochemical properties such as appropriate pH, low viscosity for efficient sprayability, acceptable droplet size in nano range and near isotonic osmolality. Nigella sativa oil was used as a suitable oil phase and can also provide further therapeutic benefits because of its inherent anti-inflammatory and antioxidant properties, which can enhance the management of allergic rhinitis. In conclusion, the developed nanoemulsion nasal spray is a promising alternative to conventional oral therapy, characterized by rapid onset of action, improved drug absorption, and enhanced patient compliance. Further studies should include long-term stability studies, ex-vivo permeation analysis, and in-vivo evaluation to understand the pharmacokinetic and pharmacodynamic behavior. Clinical studies may further validate its safety, efficacy and patient acceptability thereby endorsing its potential

translation to an intranasal drug delivery system of commercial value.

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