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Research Article

Development and Evaluation of Loratadine and Montelukast Sol Gel

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ABSTRACT

Background: The traditional oral treatments of allergic rhinitis and smog-related respiratory disease are impaired by limited bioavailability, slow action, and systemic adverse effects which can be explained by the hepatic first-pass metabolism.

Objectives: The current research was conducted to create and to test a thermo-responsive, mucoadhesive in-situ nasal gel co-loaded with Montelukast and Loratadine in order to increase bioavailability, fast onset, and prolonged symptom relief.

Methods: Poloxamer 407 and HPMC were used in the preparation of the formulation via cold-start procedure, yielding a nasal temperature sol-to-gel transition. Extensive physicochemical characterisation was conducted and included pH, viscosity, gelation time, spreadability, mucoadhesion and in-vitro release.

Results: The optimised formulation had a suitable gelation at 3234o C, a strong mucoadhesive force (approximately 6900 dyn cm -2), and was able to release the drug at a higher percentage (more than 90 per cent) over 12 hours. FTIR spectroscopy was used to identify compatibility of drug and excipient whereas stability tests proved the presence of good physicochemical and microbial integrity at accelerated conditions.

Conclusion: The thermoresponsive nasal gel mitigated the limitations of oral therapy by offering better nasal retention, release control and higher patient compliance, which is an exciting and non-invasive therapeutic option to respiratory allergies and pollution-related ailment(s).

Limitations: Further in vivo and clinical validation is required to confirm pharmacokinetic performance and safety.

Keywords: Thermoresponsive Nasal Gel, Montelukast, Loratadine, Mucoadhesion, Allergic Rhinitis.

INTRODUCTION

Allergic rhinitis (AR) and associated respiratory disorders are omnipresent and problematic indicators of public health, particularly worsening within urban and pollution-dense settings. According to global estimates, AR allergic disorders affect millions and impose considerable burdens on healthcare systems and individuals: quality of life and productivity [1]. Antihistamines (e.g., Loratadine) and leukotriene receptor antagonists (e.g., montelukast) are frontline therapies for AR and asthma. Even though these therapies are widely used, the pharmacokinetics of these medicines are not very beneficial: loratadine has poor water solubility and variable gastrointestinal absorption; montelukast has extensive first-pass metabolism and variable bioavailability (systemically)[2]. Therefore, the therapies will have delayed actions, inconsistent outcomes, and will require frequent dosing, diminishing patient compliance and control of the disease. Faced with these challenges, other avenues for administration are being considered. Intranasal administration has unique benefits. The route allows avoidance of first-pass metabolism, rapid vascular absorption, and both localized and systemic delivery. Recent works showcase the potential of thermally responsive, mucoadhesive nasal gels that switch from liquid to gel phases upon contact with the nasal mucosa to extend residence time and enhance absorption [3]. For instance, P407-based in situ gels combined with HPMC and other mucoadhesive polymers have provided better nasal retention and prolonged drug release in the mouth [4]. Therefore, the combination of innovative nasal delivery technologies and traditional pharmacotherapy can bridge the gaps associated with oral therapy.

The limitations of oral routes of administration remain considerable for loratadine and

montelukast in the treatment of allergic rhinitis (AR) and associated respiratory conditions. Although meta-analysis shows clinical benefits in quality of life and reductions in total nasal symptom score (TNSS) for the combinations compared with monotherapies, oral delivery retains all the pharmacokinetic limitations of the oral route[5]. In addition, while more recent local therapies (e.g., intranasal corticosteroids, intranasal antihistamines) arguably provide better relief than placebo, the local delivery route still offers inadequate systemic absorption and onset speed for some patients [6]. Hence, the continuing fundamental issue is to design a delivery system that optimizes bioavailability, onset speed, and sustained delivery while improving adherence for patients in more challenging polluted environments, per the persistent disease phenotype described.

Several rationales support the creation of an intranasal gel combining loratadine and montelukast. For one, the nasal route of administration completely avoids first-pass hepatic metabolism, resulting in more predictable systemic bioavailability and absorption and significantly reducing variability. This enhancement has been well documented for nasal delivery systems [7]. More importantly, when drugs are embedded in thermoresponsive mucoadhesive gels, the liquid formulation facilitates administration, and upon nasal insertion, the gel converts to a solid and resists mucociliary clearance. This improves drug retention and controlled release of the active ingredients, minimizing the frequency of dosing. Thermo-responsive mucosal and mucoadhesive gels contain and slow drug absorption within the nasal cavity [8]. This is especially beneficial for patients with chronic allergies or those whose allergies are worsened by pollution, as sustained symptom control is needed in these cases. It is therefore evident that the proposed gel formulation is designed to meet the two goals of optimizing pharmacokinetics and improving patient convenience.

Investigation into the combined use of loratadine and montelukast has shown the efficacy of these drugs to treat allergic rhinitis (AR), and there has been considerable advancement in the formulation of nasal in-situ gels, but research integrating both of these areas is still lacking [3,4]. No research has attempted to evaluate a combined loratadine-montelukast intranasal gel that uses both active compounds in a single thermoresponsive mucoadhesive matrix. Furthermore, the majority of research on nasal gels has focused on antiviral therapy or CNS-acting drugs, rather than addressing gaps in the use of gels for anti-allergy/anti-inflammatory therapies in the respiratory tract. Research gaps also include the use of such gels for respiratory disorders aggravated by pollution and/or smog. In addition, the lack of thorough systematic investigations into the fundamental physicochemical properties of gels in this therapeutic domain has hindered the integration of gel technologies into the management of chronic respiratory ailments via the nasal route. This study aims to develop and evaluate a thermo-responsive, mucoadhesive intranasal gel formulation containing loratadine and montelukast for the improved management of allergic rhinitis and smog-induced respiratory disorders. The study followed four objective

Objectives

1. To formulate an intranasal gel combining loratadine and montelukast using poloxamer 407 and HPMC as key excipients.
2. To evaluate the gel's physicochemical characteristics, including gelation temperature, viscosity, mucoadhesion, and spreadability.
3. To assess the in-vitro drug release profile of both drugs from the gel and compare with conventional formulations.
4. To conduct accelerated stability testing to determine shelf-life and formulation robustness.

There is great potential for this work to make contributions to clinical practice and formulation science. Clinically, the prospective formulation of a loratadine-montelukast intranasal gel is likely to provide a more rapid onset of action, greater intranasal bioavailability, and less frequent administration, all of which may offer greater symptom control and enhance patient adherence for those with allergic rhinitis and respiratory diseases exacerbated by pollution. From a research perspective, this work continues the important scholarship and research on nasal in-situ gels, especially with regard to combination therapies for the treatment of respiratory diseases, which remains a more under-explored area than single-agent therapies [4]. This formulation is successful and is likely to encourage the use

of nasal gel therapies for the treatment of more chronic respiratory diseases, addressing the strong demand for responsive, high-efficiency treatment systems.

MATERIAL AND METHODOLOGY

Materials

As the active pharmaceutical ingredients (APIs), Loratadine and Montelukast sodium were utilized in the current study. Poloxamer 407 (thermosensitive polymer), Hydroxypropyl methylcellulose (HPMC K100), which acts as a mucoadhesive agent, Mannitol, a tonicity modifier, Benzalkonium chloride, which serves as a preservative, and a phosphate buffer (pH 6.0) were used as formulation excipients. The reagents and chemicals were of an analytical grade. Table 1 gives the composition of the formulations (F1-F5), where Poloxamer concentration was varied between 17-19% in an attempt to examine its effects on gelation properties.

Equipment and Software

To prepare and evaluate, a magnetic stirrer, a thermostatic water bath, a UV- visible spectrophotometer, a pH metre, an Ostwald Viscometer, a Franz diffusion cell, and an analytical balance were used. The analysis and documentation of data was done using Microsoft Excel, Word and end note/Mendeley.

Formulation of Thermosensitive Nasal Gel

The cold method was chosen to prepare the Loratadine-Montelukast nasal gel as it is effective to maintain the polymer in the gel state and its clarity[9]. Poloxamer 407 was measured properly and slowly added to the chilled double-distilled water and stirred with the mixture until fully dispersed. The resultant dispersion was refrigerated at 4 °C overnight to allow maximum hydration and dissolution of the polymer. Montelukast sodium was a water-soluble compound, and thus it was directly dissolved in distilled water, and Loratadine was dissolved in methanol and then added gradually to the polymeric solution under stirring to ensure even dispersion without precipitation[10]. Phosphate buffer (pH 6.0) was included to normalize the pH and to maintain the stability of the drug. Mannitol and Benzalkonium chloride were included in order to maintain isotonicity and prevent the growth of microorganisms. The last volume was added to 100 3L of distilled water.

Table 1: Composition of Formulation

Component	Quantity	Purpose
Loratadine	5 mg	API
Montelukast sodium	4 mg	API
HPMC (K 100)	0.5 g	Mucoadhesive polymer
Mannitol	2 g	Tonicity agent
Benzalkonium chloride	0.01 g	Preservative
Phosphate buffer (pH 6.0)	q.s. to 100 mL	pH adjustment and vehicle
Distilled water	q.s. to 100 mL	Solvent

Table 2: Poloxamer Quantity Used For All Five Formulations.

Formulation	Poloxamer 407 (g)
F1	17
F2	17.5
F3	18
F4	18.5
F5	19

Preformulation Studies

Organoleptic Evaluation: Raw materials were also checked on appearance, colour, and odour to ensure that they were of pharmacopeial standards. Loratadine was in the form of white crystalline powder, Montelukast in light-yellow hygroscopic powder and Poloxamer 407 in odourless waxy solid.

Solubility Studies: The solubility of both drugs in equilibrium at 25 +/- 2 o C during 24 h in various solvents (water, ethanol, methanol, acetone, propylene glycol, PEG

400) was used by the shake-flask method. To calculate the values of solubility, absorbance at 280nm and 343nm were taken in the case of Loratadine and Montelukast respectively.

Melting Point Determination: The purity and identity of the melting point were determined with the capillary-tube method of a digital device that determines the melting points.

FTIR Studies: Fourier- transform infrared spectroscopy (FTIR) was also used to assess compatibility of the drugs and the excipients. No considerable change in the peaks was observed, which also meant that the chemicals were compatible.

Calibration Curves: Loratadine (5 -50 MGL -1) and montelukast (5 -40 MGL -1) were standardized in methanol and the relationship was linear (R 2 > 0.99).

Partition Coefficient: The ratio of the concentration of the drug in the organic and aqueous phases was used to determine log P values using the shake-flask technique with ethanol-water.

OBSERVATION AND RESULTS

Preformulation Studies

Organoleptic Evaluation

The results of organoleptic analysis showed that both loratadine and montelukast sodium had satisfactory physical properties, thus, denoting a high level of pharmaceutical quality. Loratadine was a white crystalline powder of no odour, whereas montelukast sodium adopted the appearance of an off-white, slightly hygroscopic crystal with a faint odorative profile. No impurities, clumping, or discoloration were observed in either preparation, thereby confirming their appropriateness in the further formulation and analytical studies. All these results supported the consistency, purity and stability of the raw materials at initial formulation development stages.

Solubility Studies

The solubility test showed that there were significant differences among solvents of the two drugs. Loratadine and montelukast sodium had low aqueous solubility (0.012 mg/ mL -1 and 0.087 mg/ mL -1 respectively). Methanol and ethanol were found to be the best organic solvents, as they increased solubility but were not the best as formulation solvents because these are volatile and could be toxic. Conversely, propylene glycol (PG) and polyethylene glycol 400 (PEG 400) have a significant effect on solubility and are thus the vehicles of choice to be used in the formulation of nasal gel. Precisely, propylene glycol exhibited solubilities of 4.31mg mL -1 of loratadine and 6.25mg mL -1 of montelukast respectively.

Table 3: Solubility Analysis

Solvent	Loratadine	Montelukast	Remarks
Water	Very Poor	Poor	Not suitable for formulation
Ethanol	Moderate	Good	Good for Montelukast, volatile
Methanol	Good	Good	Effective but toxic
Acetone	Moderate	Poor	Limited use due to volatility
PG	Good	Good	Ideal vehicle
PEG 400	Good	Good	Suitable for both

Melting Point Determination

Melting points of montelukast sodium (147150 C) and loratadine (133137 C) indicates the identity and purity of the drugs. The low melting ranges are a sign of great crystallinity and thermal stability, which is significant in ensuring reproducibility of behaviour in processing and storage. Further, these findings confirmed the suitability of the active pharmaceutical ingredients (APIs) in the incorporation into gel systems that would be sensitive to temperature in the nose.

FTIR Analysis

Fourier transform infrared (FTIR) spectroscopy was used to identify the lack of any major drug interaction with excipient. All the major characteristic peaks were visible in physical mixtures of loratadine, montelukast sodium, and excipients (poloxamer 407, HPMC K100, mannitol, phosphate buffer pH 6.0, benzalkonium chloride), implying compatibility.

Loratadine showed characteristic C=O stretching (~1700 -1), C -N stretching (~1230 -1), and aromatic C=C bands(~1600 -1) which confirmed the presence of the ester and aromatic functionality (Watanasomsiri et al.,

2008). Montelukast also had C=O (~1710 -1 cm -1), aromatic C=C (~1600 -1 cm -1), and S=O (~1150 -1 cm -1). Poloxamer 407 had good ether and OH stretching (1100 cm -1 and 3400 cm -1 respectively) as these were of its triblock copolymer structure. Their typical hydroxyl and ether bonds were detected through HPMC K 100 and mannitol spectra.

Partition Coefficient

The shake-flask technique revealed the lipophilicity of loratadine (log P = 4.3) and the moderate lipophilicity of montelukast (Log P = 2.7). The greater LogP of loratadine suggests greater potential for nasal mucosal permeation, whereas the intermediate LogP of montelukast suggests it can be combined with mucoadhesive or permeation-enhancing delivery systems. Such values verify the suitability of the drugs for intranasal in-situ gel preparations.

Viscosity

Formulations F1-F5 had viscosities of 135 to 243 cps. The viscosity and concentration of poloxamer 407 were directly correlated; the higher the polymer concentration, the higher the gel consistency. Optimization of viscosity enabled the gels to be sufficiently fluid to be administered to the nose and to undergo the sol-gel transition at physiological temperature.

Sol–Gel Transition Temperature and Time

Sol-gel transition temperature was found to be 31 °C to 36 °C (Table 7), and gelling time was 40-54 s (Table 8). The gelation of formulation F5 was the quickest (40s at 36 °C), and F1 was the slowest (54s at 31 °C). The findings showed that all formulations gel at nasal physiological temperatures (approximately 34 °C) and justify their behaviour in vivo.

Spreadability

The polymer concentration had an inverse relationship with the spreadability of the formulations. Formulation F1 had the largest spreadability of 12 im cm, and Formulation F4 had the least at 6.7 im cm. Spreadability is crucial for achieving uniform coating of the mucosal surface and for patient comfort, both of which are critical to nasal delivery. The data indicate that F1 can offer a good compromise between application simplicity and retention.

Drug Content Uniformity

Gelation of both Loratadine and Montelukast (Formulations F1 and F5) active pharmaceutical ingredients provided a range of 90 93 per cent drug content in pre- and post-gelation samples, which in turn was indicative of homogeneity and stability of the drug concentration in gel matrix. The post-gelation difference (p 0.03) found was not statistically significant, indicating that the sol-gel transition produces insignificant effects on the homogeneity of drugs and their recovery.

Gel Strength

Structural integrity and sufficient mechanical stability were demonstrated by the display of satisfactory gel strength values of 44-52. The polymer concentrations would yield harder gels, which occurred because more cross-linking occurred. The most effective compromise regarding the gel strength and spreadability is crucial to prevent premature clearance and guarantee the comfort of the patients. The F3 and F4 formulations were the most consistent with a compromise was made between the adhesion and flowability.

Mucoadhesive Strength

In an in-vitro study of 12 h, all the formulations showed sustained-release behaviour. Formulation F5 recorded the most absolute release (≈ 91.50) at the 12 - endpoint, and Formulation F1 saturated around 89 0. The rate of release was directly proportional to Poloxamer 407 concentration and this is indicative of better pore volume and polymer relaxation processes. The release profile of diffusion-controlled release is in line with earlier findings on thermosensitive gels.

Loratadine Formulations

Loratadine was found to be stable releasing 94.4% and 93.6% at 12h in formulations F2 and F4 respectively. The diffusion was maintained at a consistent rate in the gel mass of hydrate consequently minimizing burst released. The release data were statistically compared cumulatively and there was no significant ($p > 0.05$) deviation between the optimized formulations. These results prove that the thermoreversible gels that are developed can be used to facilitate long-term drug delivery during intranasal therapy.

Accelerated Stability Studies

Three months stability testing at 40°C/75 °C/5 °C/25 °C and in ifferent relative humidity conditions showed no observable colour, clarity, viscosity or pH alterations. The release of the drug in-vitro was found to be satisfactory, the gel strength and drug content were found to be within the acceptable levels

during the test, having indicated that the formulation was not showing any instability. The statistical evaluation revealed that there was no significant difference ($p>0.05$) in pre- and post-storage samples, thus indicating the strength of the gel system to be used in the long term.

DISCUSSION

The current research was intended to develop and test a thermoresponsive in situ nasal gel co-loaded with loratadine and montelukast sodium, a dual-acting formulation to control smog-induced respiratory disorders and allergic rhinitis. The rationale for this dual delivery system was that the two drugs, loratadine, an antagonist of the peripheral H1-receptor, and montelukast, an antagonist of the leukotriene D4-receptor, complement each other by targeting different but overlapping inflammatory pathways involved in asthma.

Mader and Higuchi and Bandari et al. have shown that the intranasal route is a better alternative to oral delivery for agents that require rapid systemic absorption or require local action[11,12]. The nasal preparations of Madader and Higuchi demonstrated bypass of first-pass liver metabolism and enhanced the bioavailability of lipophilic compounds[11]. Here, loratadine and montelukast demonstrate extensive hepatic metabolism at the orally administered dose, leading to low systemic availability (AUC/$\mathbb{N}$ = 40) and a slow onset of action (Tmax 12h). The current formulation addresses this limitation by providing localized absorption through the richly vascularised mucosa of the nose, which offers direct access to the systemic circulation. This finding is consistent with those of Bandari et al., who said that thermosensitive gel-containing nasal sprays allow sustained mucosal residence and improved absorption relative to simple nasal sprays, which have a high rate of mucociliary clearance and low retention[12].

Poxamer 407 was chosen as the key thermoresponsive polymer due to its reversible micellization and biocompatibility. D'Souza and Shegokar reported that the gelation concentration was critical, requiring 15 to 20 per cent, which was confirmed in the present study, where the optimal gelation was observed at 1819 per cent w/v[13]. The cold technique used ensured that the polymer was hydrated and that the temperature-sensitive excipients were not lost. The resulting formulations also displayed gelation at approximately 3234 °C, the physiological temperature of the nose; hence, the formulations were qualified as undergoing a sol-gel transition at approximately body temperature, so that the patient would be comfortable and the formulations would be effectively retained.[14]

There is strong evidence of the proposed formulation design based on rheological data. The viscosity of 135 to 243 cps at ambient temperature was remarkable enough to make the substance flowable during administration, and post-gelation hardness helped increase the duration of mucosal contact. The current formulation has an optimal rheological balance compared to the past formulations that used higher concentrations of polymer (>20 %), and formed overly viscous gels that impeded spreadability and patient acceptability[9].

Addition of HPMCK100 greatly increased the adhesive capacity of the gel, and the forces ranged between 4-555 dyn cm -1 and 6900 dyn cm -1. The reported values are higher than those of Shankarrao et al., who obtained mucoadhesive forces of 320-4800 dyn cm -2 of similar thermosensitive arrays[15]. This may be due to synergistic hydrogen bonding between HPMC and Poloxamer micellar networks, which helps it to resist mucociliary clearance. This enhanced bioadhesion is converted to increased nasal residence time and consistent absorption of drugs, which are crucial in determining success when delivering drugs to the nose. Even though higher Poloxamer concentration enhances mechanical integrity, it may slightly affect spreadability, as well as Altuntaş and Yener observe[16]. The current formula is the appropriate balance of mechanical stability and patient comfort, which makes it acceptable in clinical practices.

Tests with in vitro release showed a biphasic profile (a first burst followed by continuous release for 12 hours). This liberation mode is consistent with the Higuchi diffusion model and is non-Fickian, meaning that diffusion and polymer relaxation will control drug liberation. Similar release kinetics have been reported by Hoxha et al. for dual-drug gels, demonstrating that thermoresponsive systems offer controlled, long-term therapeutic effects[17]. The current work builds on this knowledge by establishing a concomitant, sustained release of two pharmacologically distinct molecules, an improvement over single-drug formulations reported by Watanasamsiri et al.[18].The near-linear correlation between the release and the square root of time ($R2 > 0.98$) indicates that

matrix integrity is consistent and that instability caused by burst release does not occur.

The most crucial point is that the release efficiencies of loratadine and montelukast at 12 h were nearly identical, namely, about 94% and 91%, respectively, indicating that the two drugs entered the bloodstream simultaneously and diffused concurrently. A release difference due to varying solubility and polymer interactions has often been a bane of previous multiphase gel formulations[19]. These limitations were systematically addressed in the present study by prudently selecting PEG400 as a cosolvent, thereby enhancing the solubility concordance of the two APIs. This is a methodological innovation and one of the main strengths of the formulation methodology. The nasal in-situ thermosensitive gel has several unique strengths compared to other drug-delivery forms, including nanocrystal tablets, solid dispersions, and oral inclusion complexes. Even though nanotechnology-based formulations and solid dispersions offer improved solubility, their benefits are limited by variability in oral absorption and hepatic metabolism. On the other hand, the bioavailability of the thermosensitive nasal gel is rapid and sustained, without the need for invasive administration. The cumulative release of 6070% in 8 h from nasal platforms developed by Durgapal et al. to deliver anti-asthmatic drugs was lower than that of the present system (over 90% in 12 h)[20]. However, it still showed better controlled-release performance, as indicated by its physicochemical stability. This relative advantage highlights the potential of the current study to be translated into a simple, scalable strategy for achieving long-acting symptomatic relief.

The most typical threats to the physicochemical stability of pharmaceutical gels include phase separation, pH drift, and microbial contamination. The current formulation did not change its colour, clarity, viscosity, or pH significantly under accelerated stability testing at 40 o C, 2 o C, and 75 o C. Drug content greater than 90 percent and no change in in-vitro release profile were indicative of chemical integrity. The presence of PEG 400 and benzalkonium chloride in the current regime would have averted these instabilities; a comparative analysis by Lobo et al. had found precipitation and a loss in viscosity of Poloxamer-based gels after 30 days[21]. This leads to a high degree of physicochemical robustness in the formulation, thus allowing it to be developed to be used commercially.

Compared with previous thermoresponsive nasal formulations, the current study demonstrates significant improvements in gel stability, viscosity control, and concomitant drug compatibility. Soliman et al. reported that higher concentrations of Poloxamer often produced opaque, brittle gels, whereas the present formulation was precise, homogeneous, and readily thermalized across the entire concentration range used[22]. Similarly, Abou-Shamat et al. found solubility differences between lipophilic and hydrophilic therapeutics in co-formulations, which were successfully overcome in the current study through solvent optimization and copolymer incorporation[23]. Besides, the results are consistent with those of Illum (2003), who emphasized the role of mucoadhesion as a predictor of a long nasal residence[24]. The mucoadhesive force of this system at this value, with a maximum of 6,900 -2 dyne cm -1, exceeds the threshold usually required to overcome mucociliary clearance, further highlighting its clinical importance. Collectively, the mentioned comparative ideas make the current work a significant step toward developing research on nasal drug delivery.

CONCLUSION

The current study formulated and tested a new thermoresponsive in situ nasal gel co-loaded with Montelukast Sodium and Loratadine to effectively manage respiratory diseases and allergic rhinitis caused by pollution. The limitations of conventional oral therapy — such as first-pass metabolism, slower onset, and poor bioavailability — were overcome by using the intranasal route and temperature-sensitive polymeric systems to design this dual-drug formulation. The paper showed that the optimized formulation had desirable physicochemical characteristics, including, but not limited to, the appropriate viscosity, pH compatibility (5.56.5), and the gelation temperature close to physiological nasal conditions (~34 °C). The properties ensured patient comfort, reduced irritation, and effective nasal retention.

Poloxamer 407, which is a thermosensitive polymer, when added together with HPMC K100 and polyethylene glycol (PEG 400) greatly enhanced the mucoadhesive attributes

of the gel and its drug release behavior. In vitro release experiments showed a biphasic release behavior which involved an initial burst release and a more extended release period to around 12 hours. Kinetics of release were in accordance with the Higuchi model, thus, pointing to a diffusion limited process. In addition to that, the compatibility of the active pharmaceutical ingredients and excipients were further confirmed by Fourier-transform infrared spectroscopy and melting point, which indicated the lack of deleterious interactions between the components and their chemical properties, which supported the stability of the formulation. The strong physicochemical and microbiological stability of the optimized formulation was further validated by accelerated stability tests and indicates that the formulation has the potential to be stored long term and produced in large quantities at commercial scale.

Limitations

Though the formulation has a high degree of potential, there are a number of limitations that can be noted. The current study was limited to in vitro tests, which, despite their predictive potential, do not help to fully restore in vivo physiological events, such as mucociliary clearance, enzyme release, and nasal blood flow fluctuations. The lack of pharmacodynamic and pharmacokinetic research restricts the ability to explain the accurate systemic bioavailability and therapeutic effectiveness. Patient adherence over the long term, possible irritant effects and stability at changing environmental conditions were also not evaluated. Further research needs to add in vivo analyses using suitable animal models to determine nasal absorption, bioavailability increase, and therapeutic efficacy. To determine safety, tolerability and efficacy, human clinical trials are mandatory. The potential inscale-up, long-term stability, and actual patient acceptability should be explored in future studies. The addition of nanocarrier systems, enzyme inhibitors, or permeation enhancers may further enhance mucosal uptake and broaden the formulation's use to other drugs, such as peptides or vaccines. In conclusion, the site has high potential to develop into the next-generation nasal delivery system for the treatment of complex respiratory and allergic conditions.

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