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Research Paper

Formulation and Evaluation of Nasal Microspheres

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ABSTRACT

Montelukast, a leukotriene antagonist, anti-asthmatic drug, and anti-arrhythmia drug, was approved for clinical use by the US FDA in 1998 under the brand name Singulair. It is a conjugate acid of montelukast and belongs to the leukotriene receptor antagonist (LTRA) category. Although effective, it is typically used alongside inhaled corticosteroids in asthma step therapy. FDA-led investigations in 2008-2009 investigated the possibility of montelukast eliciting neuropsychiatric effects like agitation, hallucinations, and suicidal behavior in users. Although these effects are now included in the official prescribing information, the drug continues to be used worldwide through millions of prescriptions annually and is available as a generic and brand name product. The study aims to develop and evaluate nasal microspheres containing Montelukast for targeted drug delivery, improving bioavailability, patient compliance, reducing dosing frequency, minimizing side effects, and optimizing size and shape. It also evaluates drug release profiles, develops a stable manufacturing process, and compares with existing systems. The microspheres were found to be favorable for intranasal absorption, with particle sizes ranging from 7.90 ± 1.01 to 8.10 ± 0.93 µm. All batches showed good in vitro mucoadhesion (88-96%). The study also found no aggregation between drug and polymer in the microspheres, suggesting promising potential for delivering Montelukast intranasal.

INTRODUCTION

Montelukast was first approved for clinical use by the US FDA in 1998 as Merck's brand name Singulair. Montelukast is a member of quinolines, a monocarboxylic acid and an aliphatic sulfide (Figure 1). It has a role as a leukotriene antagonist, an anti-asthmatic drug and an anti-arrhythmia drug. It is a conjugate acid of a montelukast (1-). The medication is a member of the leukotriene receptor antagonist (LTRA) category of drugs (1). Although capable of demonstrating effectiveness, the use of such LTRAs like montelukast is typically in addition to or complementary with the use of inhaled corticosteroids or other agents in

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asthma step therapy. Regardless, in 2008-2009, there were FDA-led investigations into the possibility of montelukast to elicit neuropsychiatric effects like agitation, hallucinations, suicidal behaviour, and others in individuals who used the medication (2) And although these kinds of effects are currently included in the official prescribing information for montelukast, the drug still sees extensive use worldwide via millions of prescriptions annually and has since become available as a generic and as a brand name product (3).

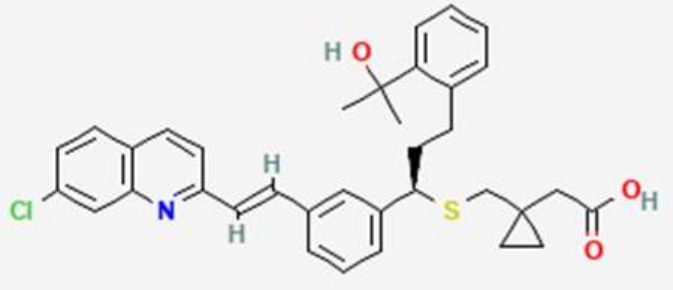

Figure 1: Chemical Structure of Montelukast

The study aims to develop and evaluate nasal microspheres containing Montelukast for targeted drug delivery, improving bioavailability, patient compliance, reducing dosing frequency, minimizing side effects, and optimizing size and shape. It also evaluates drug release profiles, develops a stable manufacturing process, and compares with existing systems.

MATERIALS AND METHODS

2.1. Preformulation Studies

The drug samples were examined for appearance, color, and odor. The melting point of drug was determined using the capillary method, where a fine powder of the drug was filled in a glass capillary tube and dipped in liquid paraffin. Solubility was also determined in various buffers of different pH values, with the drug being dissolved in different beakers containing solvents and shaken for 24 hours at regular intervals (6-10).

2.2. Preparation of Chitosan Nasal Microspheres

Chitosan microspheres were prepared using a simple w/o emulsification-cross linking process using liquid paraffin as an external phase. Chitosan was dissolved in a 2% aqueous acetic acid solution, then added to 100 mL of liquid paraffin containing 0.2% w/v of DOSS as a stabilizer. Montelukast was added to the chitosan solution, and the dispersion was added to the paraffin. A 25% solution of glutaraldehyde was added to the emulsion, and stirring was continued for 2 hours. The hardened microspheres were separated by vacuum filtration, washed with hexane to remove oil, and washed with distilled water to remove unreacted GA. The microspheres were air dried for 24 hours and stored in a vacuum desiccator until further use (11-13).

2.3. Characterization of Chitosan Nasal Microspheres

The prepared Chitosan Nasal Microspheres were evaluated for physical appearance, particle size, Entrapment Efficiency, swelling index, drug release and stability (14-16).

RESULTS AND DISCUSSION

3.1. Preformulation Studies

3.1.1. Organoleptic Characteristics

The drug sample was analyzed for physical appearance and compared with the standard (Table 1).

Table 1: Observed organoleptic properties of drug sample

Organoleptic properties	
Parameter	**Observation**
Appearance	Powdered form
Colour	Light pink
Odour	Odourless
Taste	Tasteless

3.1.2. Melting Point Determination

The Indian pharmacopeia recommended the capillary method for melting point determination, and the standard melting point of drug was found to be 127.36 ± 0.384°C, within the reported range of 115–149°C, indicating the drug sample's purity.

3.1.3. Solubility

Solubility check is also a key parameter in drug development as it determines the ability of a drug to dissolve in various solvents. This information is crucial for designing dosage forms that ensure optimal absorption and bioavailability of the drug (Table 2).

Table 2: Solubility Study of Montelukast

Solvents	Solubility of montelukast (1mg/ml)
Acetone	Sparingly Soluble
Ethanol	Freely soluble
Methanol	Freely soluble
Water	Less soluble

3.1.4. Loss on Drying

The percentage loss on drying was found to be 0.16 %.

3.1.5. Partition Coefficient

The study showed that major portion of drug was partitioned towards organic phase. Partition Coefficient of montelukast was found to be 2.69. It indicated that drug is lipophilic in nature.

3.2. Evaluation Parameter of Optimized Formulation of Montelukast loaded Nasal Microspheres

The study focuses on the spherical particle size of chitosan microspheres, which are essential for the formation of niosomal vesicles. The hydrophilic hydrophobic segments of non-ionic surfactants play a crucial role in the formation of these vesicles, and the size distribution of microspheres is considered suitable for nasal administration. The study focuses on the spherical particle size of chitosan microspheres, which are essential for the formation of niosomal vesicles. The determination of drug content shows good uniformity, with drug contents close to theoretical values and good encapsulation efficiency between 88% and 96%. Encapsulation efficiencies are always high, increasing with increasing drug to polymer weight ratios. Swelling studies were conducted to determine the swelling ability of spray dried microspheres, with the maximum swelling

observed with microspheres containing the highest concentration of polymer. This study was important for studying clearance of drug from the nasal cavity, as it suggests that administration of microspheres lowers clearance due to the process of taking up water and swelling, leading to reduced mucocilliary clearance. Mucoadhesion studies were carried out to ensure the adhesion of the formulation to the mucosa for a prolonged period of time at the site of absorption. Percent mucoadhesion increased with increase in polymer concentration. Strong adhesive bonds are essential for the establishment of strong intimate molecular contact between the polymer and glycoprotein chain (Table 3).

Table 3: Characterization of Chitosan Based Microspheres

Formulations	Particle Size (mm)	Encapsulation efficiency (%)	Swelling studies (%)	In vitro mucoadhesion (%)
MN 1	7.99 ± 1.01	96.65 ± 0.92	0.98 ± 0.14	95.45 ± 0.15
MN 2	8.02 ± 0.95	90.15 ± 0.14	0.99 ± 0.74	89.45 ± 0.99
MN 3	7.98 ± 0.35	90.14 ± 0.45	1.01 ± 0.33	93.14 ± 0.54
MN 4	8.00 ± 0.64	93.45 ± 0.98	0.98 ± 0.47	95.14 ± 0.64
MN 5	7.99 ± 0.41	91.69 ± 0.14	1.03 ± 0.69	96.14 ± 0.37
MN 6	8.02 ± 0.34	90.54 ± 0.54	1.01 ± 0.99	88.59 ± 0.55
MN 7	8.00 ± 0.68	92.14 ± 0.66	0.99 ± 0.99	94.25 ± 0.54

CONCLUSIONS

In the present study chitosan microspheres were prepared by chemical-cross linking method. Various variables such as the drug: polymer ratio, glutaraldehyde concentration and the cross-linking time were optimized by the factorial design. An systematic experimental approach was employed to identify optimal formulation parameters for a microsphere preparation with the minimum value of particle size and maximum value of in vitro mucoadhesion. Particle size was in the range of 7.90 ± 1.01 to 8.10 ± 0.93 µm which is considered to be favorable for intranasal absorption. All batches showed good in vitro mucoadhesion (88- 96%). Results flow properties study indicated there is no aggregation between drug–polymer in the microspheres. Hence, the results of the present study clearly indicated promising potentials of chitosan microspheres for delivering Montelukast intranasal and could be viewed as a potential alternative to conventional dosage forms.

Conflict of Interest

None.

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