Research Article

NOVEL, SUSTAINED-RELEASE, DRY-POWDER INHALABLE FORMULATION FOR MONTELUKAST SODIUM

K. Sathishkumar *, C. Kumaresan

Department of Chemical Engineering, Sri Sivasubramaniya Nadar College of Engineering, Kalavakkam, Kancheepuram, India

*Corresponding Author Email: sathishkumark@ssn.edu.in

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ABSTRACT

The objective of this research is to improve therapy for asthma patients by developing a drug delivery platform for inhalation of a sustained-release, dry-powder formulation for Montelukast Sodium (MS). Montelukast Sodium microparticles were prepared with solvent evaporation process. The microspheres were then blended with an inhalable lactose additive (Lactohale), which acts as a carrier molecule in the formulation. Total four formulations A, B, C and D were prepared with 1:1, 1:2, 1:3, 1:4 ratio of MS:Eudragit RS100. The developed formulations were studied for physicochemical properties, *in vitro* drug release and Anderson cascade impaction studies. Based on dissolution presentation, the 1:1 ratio of MS:Eudragit RS100 produces *in vitro* release 93.71% at 12 h and having particle size of microparticles ($D_{0.5}$ μm) 4.92 ± 0.7 and the pulmonary deposition of dry powder 38.4 ± 3.53 (respiratory fraction in percentage).

Key Words: Montelukast, sustained release, dry powder inhaler, microparticles

INTRODUCTION

Pulmonary diseases such as asthma and systemic diseases like diabetes are effectively treated through the pulmonary route. Bronchial asthma and allergic rhinitis are the most common chronic lung diseases and montelukast sodium is frequently used in the treatment of these conditions. The two forms of allergic rhinitis, seasonal and perennial, are caused by pollen exposure and various environmental allergens, respectively. Asthma causes airways to swell and narrow leading to wheezing, shortness of breath, chest tightness, coughing etc. It is often associated with increased numbers of eosinophils in the airways, lung tissue and peripheral blood, and this can correlate with asthma severity.

Treatment of asthma is done through inhalation formulation dry powder inhaler (DPI). The site and amount of aerosol deposition and the dissolution rate are significant factors for the speed of pulmonary drug absorption. The main objective of the work reported here is the development of a sustained-release, dry-powder inhaler formulation in hard empty gelatin capsules (Size 3) and a disposable, hand-held, breath-actuated, drug-delivery device. Breath-actuated aerosol drug particles exist in an amorphous state that produces an immediate local effect and reaches systemic circulation rapidly with the effective dose. This sustained-release formulation provides an effective, once-daily treatment with montelukast sodium. The drug used was montelukast sodium.

The empirical formula of montelukast sodium is $\text{C}_{35}\text{H}_{35}\text{ClNNaO}_3\text{S}$ and the molecular mass is 608.18. The melting point is 275.9°F (135.5°C), the water content (Karl Fischer method) is 1.33% (w/w) and the solubility in water is 100mg/ml. The cLogP value is 8.44, the logP value is 8.45 and the clearance is 45mL/min in healthy adults. According to the

Biopharmaceutical Classification System (BCS), montelukast sodium is a Class 1 drug (high solubility, high permeability). It is a white to off-white powder that is hygroscopic and optically active. It is stored at controlled room temperature in a tightly closed container under nitrogen atmosphere, protected from light and moisture. Montelukast sodium is a leukotriene receptor antagonist (LTRA)¹ used for maintenance treatment of asthma and to relieve seasonal allergy symptoms by inhibiting the physiological actions of cysteinyl leukotrienes (CysLT). It is mainly used to prevent the difficulty in breathing, chest tightness, wheezing and coughing caused by asthma, to prevent bronchospasm (breathing difficulties) during exercise, to treat the symptoms of seasonal (occurs only at certain times of the year) and perennial (occurs all year round) allergic rhinitis, a condition associated with sneezing and stuffy, runny or itchy nose.

Montelukast sodium has rapid oral absorption and one disadvantage of the conventional oral formulation is that the drug undergoes hepatic first-pass metabolism. Its biological half-life is 2.5 to 5.5 hours (hrs)², thereby decreasing bioavailability up to 64%; therefore, it is a prime candidate for sustained-release dosage forms³. The dry-powder formulation for inhalation is especially useful for keeping the drug out of hepatic first-pass metabolism. Also, having sustained release reduces the frequency of administration and side effects, improves patient compliance, and reduces cost⁴ thereby improving asthma management. The aerodynamic particle size chosen for this DPI was in the range of 1-5 μm (micrometer), which is considered the optimal size range for the biological barriers of the lung⁵⁻⁹. The feature of the blend depends upon the mass of fines¹⁰ in the powder. Lactose was used as the carrier molecule and it will be directly blended with the montelukast microspheres¹¹.

MATERIALS AND METHODS

Inhalable hard empty gelatin capsules of size 3, montelukast sodium and inhalable lactose (Lactohale) of grade LH100. Eudragit RS100, Polyvinyl alcohol, dialysis membrane, dichloromethane were the kind gift of Orchid Pharmaceuticals, Chennai. Methanol and acetonitrile was obtained from Qualigens, Mumbai and potassium dihydrogen orthophosphate, sodium chloride and sodium hydroxide were obtained from SD fine chemicals, Mumbai, India.

Preparation of microparticles

The sustained-release dry powder microspheres were prepared with a polymer Eudragit RS100. The montelukast sodium and Eudragit RS 100 used in the ratio of 1:1, 1:2, 1:3 and 1:4. The solvent evaporation method involves preparation of o/w emulsion between organic phase consisting of Eudragit RS 100 in dichloromethane (DCM), to this mixture montelukast sodium solution was added and mixed by sonication using probe sonicator and injected this mixture drop wise into the aqueous phase containing 2% w/v polyvinyl alcohol. The organic phase was emulsified in aqueous phase by homogenization at 10 000 rpm for 10 min using a homogenizer (Viridis Cyclone IQ, USA). The emulsion was stirred for 12 h at $25 \pm 2^\circ\text{C}$ using magnetic stirrer to ensure complete evaporation of dichloromethane. The microparticles thus prepared were recovered by centrifugation (15 000 rpm, 20 min, 4°C). The precipitate was washed completely removed polyvinyl alcohol. The product dispersed in cold water and recovered by lyophilisation. Four formulations of montelukast sodium microparticles with varying proportion of the polymers were prepared by solvent evaporation techniques by keeping organic phase to aqueous phase ratio as (OP:AP::1:5) and varying drug:polymer ratios of Table 1.

Dry Powder inhaler Preparation

The preparation of DPI is a process of blending the inhalable lactose with sustained release montelukast microparticles¹² prepared. The diluent inhalable lactose (Lactohale LH100) of particle size of 63-90 μm fraction were used as carrier of montelukast microparticles in DPI formulation. Inhalable hard empty gelatin capsules (Size 3) were filled with the final blend and stored in airtight HDPE containers. The fill weight was 20mg per capsule. The drug content and particle size were evaluated.

Fourier Transform Infrared Spectroscopy (FTIR)

Infrared spectroscopy was used to determine various functional groups of the drug molecule. In general the functional groups can exhibit changes as a result of processing drug formulations¹³. The resulting FTIR spectra graphs of Montelukast sodium, and Trials A-D were given and discussed in figure 1-5

Scanning Electron Microscopy (SEM)

Scanning electron microscopy (SEM) was used to visualize the diameter, structural and surface morphology of the microparticles. The surface appearance and shape of the drug-polymer complex was investigated by SEM (VEGA3 LMU, TESCAN) with a maximum magnification of 1,000,000X and a resolution 3 nm at a maximum applied voltage of 30kV. The electronic images were recorded digitally at higher magnification. Particle surface was determined by examining the photomicrographs. The samples were plotted in the photomicrograph plates and examined the particle size and

structure. The SEM photos of trials A-D were given in figure 6-9.

Drug content of montelukast sodium

The standard calibration curve was prepared by using active, montelukast sodium. Montelukast sodium microparticles were dissolved in acetonitrile for the extraction to find drug content. Montelukast sodium was transferred into a 100ml volumetric flask and 10ml of sodium phosphate buffer saline (PBS; pH 7.4) was added to dissolve the capsules. A suitable volume of solvent was added and the suspension was sonicated for about 15 minutes with intermittent shaking for complete dispersion. The mixture was filtered through a $0.45\mu\text{m}$ membrane filter and the drug content was determined by measuring the absorbance at 351 nm using a UV/Vis spectrophotometer. PBS (pH 7.4) was used as blank.

$$\text{Amount of drug} = A_{\text{sam}} X C_{\text{std}} / A_{\text{std}}$$

Where A_{sam} =absorbance of sample solution, C_{std} =concentration of drug in standard solution, and A_{std} =absorbance of standard drug solution.

Percentage Yield:

The percentage yield was calculated by using the following formula.

$$\text{Percentage yield} = \frac{\text{Actual wt. of microspheres}}{\text{Wt. of starting materials}} \times 100$$

Entrapment Efficiency

The drug content was determined from the microparticles. The MS was removed from microparticles with sodium hydroxide (0.1 M) after dissolving the microparticles in acetonitrile. After suitable dilutions, the montelukast sodium content was measured in a UV-VIS spectrophotometer (Jasco) at 351 nm. Entrapment efficiency was calculated using the following formula:

$$\text{Entrapment efficiency} = \frac{\text{Estimated \% drug content}}{\% \text{ drug content (theoretical)}} \times 100$$

Particle size determination

The laser diffraction method was used to estimate the particle size of microparticles. The HELOS particle size analyser VIBRO/RODOS drug dispersion system: Sympatec GmbH systems were used to measured particle size. 100 mg of the powder was used to achieve the required obscuration of 5%. The particle size data obtained were represented as $D_{0.5}$.

Anderson cascade impactor

The aerodynamic particle deposition¹⁴ of formulations were measured using an Anderson Cascade Impactor (ACI) (Copley Scientific, Nottingham, UK). The ACI consisted of initiation port (IP), pre-separator (PS), seven stages, and a final collection filter. The stages were coated with polypropylene glycol dissolved in hexane (2% w/w). The stages were left to dry under ambient room conditions for one hour. Experiments were conducted at an air flow rate of 60 L min^{-1} . The operating conditions and theoretical cut-off diameters are shown in Table 2. After actuation, the wash solutions from different parts were collected and quantitated for drug content by UV spectrophotometer. The respirable particle fraction (RF) and

emission dose (ED) were calculated to describe the inhalation properties of DPIs. Six replicates of the measurements were performed.

***In vitro* drug release study**

The *in vitro* release of montelukast microparticle was determined by a dialysis bag diffusion technique¹⁵. The *in vitro* release¹⁶⁻²⁰ was carried out with PBS of pH 7.4 as the diffusion medium and a dialysis membrane of 14kDa molecular weight cut-off (Himedia, Mumbai, India). An aqueous dispersion equivalent to 1mg of montelukast sodium was placed in a

dialysis bag and sealed at both ends. The dialysis bag was immersed in 250 ml of diffusion medium and stirred at 100 rpm. 1ml Sample was withdrawn at predetermined time intervals, and the receptor phase was replenished with an equal volume of blank after each sample was withdrawn. Drug content in aliquots were evaluated using UV method and the graph was plotted with the percent drug released versus time. Absorbance of the samples at 351nm was determined by UV/Vis spectrophotometer with pH 7.4 PBS as blank. The cumulative percent drug at various time intervals was calculated and plotted against time. All experiments were done in triplicate.

RESULTS AND DISCUSSION

Table 1: Formulation of Montelukast sodium, Eudragit RS 100 microparticles

Formulation Code	MS: Eudragit RS100	Weight of MS (mg)	Weight of Eudragit RS100 (mg)	Vol. of DCM (ml)- OP	AP Vol. (2% PVA) (ml)- AP	% yield
A	1:1	50	50	5	25	73.57±1.81
B	1:2	50	100	5	25	71.22±2.12
C	1:3	50	150	5	25	70.35±1.97
D	1:4	50	200	5	25	69.92±2.06

Table 2: Operating conditions and theoretical cut-off diameters of ACI

ACI Parameters	ACI Results
Flow rate (L/min)	60
Time per actuation (s)	4
Volume per actuation (L)	4
Cut off diameter (µm)	
Stage 0	5.7
Stage 1	4.6
Stage 2	3.2
Stage 3	2.1
Stage 4	1.3
Stage 5	0.7
Stage 6	0.39
Stage 7	0.15
Stage 8	Filter

Table 3: Physical Characteristics of Microparticles

Formulation Code	Drug:Polymer	Particle size (D _{0.5} µm) Mean±SD	Entrapment efficiency (%) Mean±SD
A	1:1	4.92±0.7	72.60±0.06
B	1:2	4.72±0.8	70.50±0.04
C	1:3	4.69±0.5	68.30±1.20
D	1:4	4.59±0.2	62.60±1.84

Table 4: Physicochemical characterization of DPI capsules

Formulation Code	Weight Variation (mg ± SD)	Drug Content (%)
A	19.95±0.17	98.2-102.3
B	20.03±0.19	99.5-103.5
C	20.15±0.36	98.5-102.1
D	19.99±0.13	99.9-101.8

*The values are represented as Mean ± SD for n=20

Table 5: Anderson Cascade Impactor (ACI) results for the Trial A-D measured using an air-flow rate of 60 L min⁻¹ (n = 6).

Particle size Attributes	ACI (inhalation indices) Mean ± SD			
	A	B	C	D
Emitted dose (%)	91.6 ± 2.96	90.2 ± 3.12	87.1 ± 3.54	85.7 ± 2.67
Respiratory fraction ^a (%)	38.4 ± 3.53	35.7 ± 3.11	34.1 ± 3.15	34.5 ± 3.24
Total recovery	98.5 ± 0.92	97.7 ± 3.23	95.1 ± 2.54	96.9 ± 2.92
Mean median aerodynamic diameter (µm)	2.22 ± 0.01	2.72 ± 0.01	2.67 ± 0.01	2.92 ± 0.01

^a Respiratory fraction calculated as ratio of total drug deposited in the lower stages of the ACI (stages 2–8) to total theoretical dose.

Figure 1: Fourier Transform Infrared Spectra graph of Montelukast sodium

Figure 2: Fourier Transform Infrared Spectra graph of Trial A

Figure 3: Fourier Transform Infrared Spectra graph of Trial B

Figure 4: Fourier Transform Infrared Spectra graph of Trial C

Figure 5: Fourier Transform Infrared Spectra graph of Trial D

Figure 6: Scanning electron microscope photograph of Trial A

Figure 7: Scanning electron microscope photograph of Trial B

Figure 8: Scanning electron microscope photograph of Trial C

Figure 9: Scanning electron microscope photograph of Trial D

Figure 10: ACI for % deposition profiles in each stage for Trial A showing mean (SD) percent emitted dose deposited on each stage of the ACI using Rotahaler at 60 L min^{-1} (n = 6)

Figure 11: ACI for % deposition profiles in each stage for Trial B showing mean (SD) percent emitted dose deposited on each stage of the ACI using Rotahaler at 60 L min^{-1} (n = 6)

Figure 12: ACI for % deposition profiles in each stage for Trial C showing mean (SD) percent emitted dose deposited on each stage of the ACI using Rotahaler at 60 L min^{-1} (n = 6)

Figure 13: ACI for % deposition profiles in each stage for Trial D showing mean (SD) percent emitted dose deposited on each stage of the ACI using Rotahaler at 60 L min^{-1} (n = 6)

Figure 14: Cumulative Percent drug release versus time (h) for Trials A- D (n=3)

DISCUSSION

Dry-powder, lactose carrier formulations prepared for inhalation can deliver drug-loaded polymeric microspheres of 1-5 μ m to the lungs. The development of an effective inhaler must take into consideration the formulation composition of the DPI particle, the type of inhaler, particle size of carrier and capsule used in formulation and all parameters must be considered²¹. During the formulation studies several challenges were overcome in the development of a successful platform for DPI. The dry-powder formulation for sustained release of montelukast was prepared by solvent evaporation and then freeze dried. SEM micrographs showed that most of the microsphere were spherical type in appearance and had a firm, smooth surface, which was given in figure 1.

Physicochemical characterization of DPI

The drug content, sustained release of montelukast, particle size, and moisture content were evaluated²². The Table 4 described on the content weight variation and assay of Trials A-D. The drug content was not less than 96% in all the trials. The average weight of all capsules was 20 mg. In all formulations, the values for drug content were found to be uniform among different batches of DPI and ranged from 90 to 110% of the theoretical value. This assessment confirms the uniformity of drug content in the capsules²³. These results demonstrated that the right calculated quantity of montelukast sodium available in DPI trials A-D.

Montelukast sodium in Trials A-D compatibility by FTIR spectra

FTIR spectroscopy was used in compatibility studies to evaluate pre-formulation characteristics including formulation composition and poor interaction between carrier molecules²⁴. FTIR graph given as Wavenumber (cm⁻¹) vs. Transmittance (%). Figure 1 was montelukast sodium and figure 2-5 were the trials of A, B, C, and D. The characteristic peaks of montelukast sodium described as the tertiary hydroxyl group which exhibits a very broad peak around 3300cm⁻¹ and the most intense carboxylic acid peak in the form of salt obtained at 1700cm⁻¹. Also present are many aromatic CH peaks observed from 2900cm⁻¹ to 3000cm⁻¹. The trial A exhibited the hydroxyl peak at 3341cm⁻¹. The conjugated amide peak obtained at 1661cm⁻¹ and CH peaks were like those of the pure drug. The trial B exhibited the hydroxyl peak at 3379cm⁻¹. The conjugated amide peak obtained at 1661cm⁻¹ and CH peaks were like those of the pure drug. The trial C exhibited the hydroxyl peak at 3343cm⁻¹ and the conjugated amide peak obtained at 1659cm⁻¹ and CH peaks were like those of the pure drug. The trial D exhibited hydroxyl peak at 3379cm⁻¹. The conjugated amide peak obtained at 1659cm⁻¹ and CH peaks were like those of the pure drug. This study proves that the montelukast sodium was compatible in Trials A-D.

The *In vitro* dissolution of DPI

The dissolution was carried out in PBS at pH 7.4 with 0.5% SDS at 37°C $\pm$ 0.5°C. The drug released at 12 hours was as follows: Trial A, 93.71%; Trial B, 86.60%; Trial C, 81.27%; and Trial D, 74.30%. The drug releases were found to be not less than 79% at 12 hours in all trials. The figure 14 represents, Percent drug release versus Time in hours for Trials A-D. By the figure 14, it was understood that the drug release versus time was the linear curve and showed sustained release of drug montelukast sodium in all formulation trials of A to D. Among

the four trials, formulation A exhibit better drug release over other trials B, C and D.

ACI Deposition Studies for Trials A-D

DPI formulations are becoming increasingly popular for delivering medication to lungs²⁵⁻²⁷, because two-thirds of inhaled particles usually end up in the gastrointestinal tract (or the IP & PS in the ACI) after adhesion to the lactose diluent. Aerosolization of dry-powder formulations depends on bulk flow and the carrier must be selected with consideration of the desired particle size and its compatibility with the drug and the polymer. The common critical factor in DPI drug development is the particle size range. In the formulation tested here, the particle size tended to increase due to solid-phase interaction after blending with lactose. The smaller particles give remarkably superior²⁸ bronchodilation. There is also connection between mass-median aerodynamic diameter (MMAD) and lung deposition²⁹⁻³¹. A multistage cascade impactor was used to determine the mass weighted aerodynamic particle size distribution and the data was used to calculate the mass-median aerodynamic diameter of the samples³². The flow rates through the DPI device were measured for the period of inhalation³³. The efficiency of drug deposition mainly depends upon the particle size³⁴. The pattern of drug deposition by ACI of sustained-release montelukast sodium microspheres of mean particle size³⁵, mean percent (SD) of total recovery for formulation and the emitted dose was shown in Table 5. Trial D exposed the better deposition among the 2-8 stages of ACI than other trials A-C.

CONCLUSION

Respiratory drug delivery is one of the greatest pharmaceutical objectives in formulation research. The pulmonary route is a convenient and painless alternative to invasive parenteral administration. The advanced technology inherent in DPI leads to ease of use, efficient administration and economy. In general, sustained-release DPIs exhibit better patient compliance in the treatment of asthma and infectious diseases than the immediate-release dosage forms. The sustained-release montelukast microspheres and the use of lactohale produced a formulation with low density and good flowability. The particle size distribution and *in vitro* dissolution study data prove that the dry-powder inhaler formulation developed here provides excellent sustained-release characteristics for montelukast.

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