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FORMULATION AND EVALUVATION OF NASAL DRUG DELIVERY SYSTEM FOR SELECTED MONTELUKAST SODIUM

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ABSTRACT

The main purpose of this study is to describe the formulation and evaluation of chitosan nanoparticles loaded with montelukast sodium. The prepared nanoparticles exhibited smaller particle size, acceptable polydispersity index, higher positive zeta potential, better trapping efficiency and loading capacity, and relatively improved release and permeation profiles of the prepared nanoparticles. Formulated montelukast sodium chitosan nanoparticles can exhibit higher drug concentration in the mucosa without animal mortality, hematologic changes, body weight fluctuations, and histopathological changes. Therefore, it was concluded that chitosan nanoparticles loaded with Montelukast sodium can facilitate direct delivery from the nose to the brain, thereby increasing drug concentration in the brain. The research could lead to the development of nanoparticle drug delivery systems that could help treat asthma and seasonal allergies such as sneezing, itching and rhinitis.

KEYWORDS

Montelukast sodium, Sneezing, Itchiness, Rhinitis, Chitosan and Nanoparticles.

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INTRODUCTION

In recent decades, there has been growing interest in intranasal drug delivery as a useful and reliable alternative to oral and parenteral routes of administration. The nose is a complex organ from a kinetic point of view because three distinct processes take place within the nose: drug deposition, clearance or translocation, and absorption. The first step in nasal absorption is the absorption of drugs from the nasal cavity through the mucus layer. Mucin, a major protein in mucus, can bind solutes and interfere with the diffusion

process. Proteins called mucins in the mucus are involved in drug absorption. In addition, the nasal absorption mechanism involves (i) aqueous paracells where slow passive absorption occurs; An inverse logarithmic relationship has been observed between intranasal absorption and molecular weight of poorly bioavailable water-soluble compounds for drugs with molecular weights greater than 1000 Daltons. (ii) Lipoid pathway. In the delivery of (transcellular) lipophilic drugs, active carrier-mediated transport has been observed through the opening of tight junctions, showing a rate dependence on their lipophilicity. Neural connections between the nasal mucosa and the brain provide a non-invasive pathway for centrally acting drugs (Illum 2000 and Colombo 2002)[1]. The olfactory neural pathway provides both intraneuronal and extraneuronal pathways to the brain (Kreuter 1995)[2]. (iii) transcytosis.

Advantages over the Nasal Drug Delivery, non-invasive course, pass the BBB and objectives the CNS, drug absorption thru effectively on hand massive floor area (180cm2), especially vascularized mucosa assisted speedy drug absorption, gives each neighborhood and systemic consequences with speedy absorption and brief onset of action, nasal gadgets gives ease, comfort and ease of self-management, Gastrointestinal tract's presystemic clearance and primary by skip hepatic metabolism may be averted which ends up in better bioavailability. Preferable course for sufferers with nausea, vomiting and swallowing difficulty.

From the literature review, Specific emphasis became laid at the biodegradable nanoparticles for drug and gene transport to cells and tissues. Shivakumar *et al*, (2005)[3], Tashi Chhojom Khom *et al*, (2014)[4] developeda mucoadhesive nanoparticulate gadget of ebastine through ionic gelation approach for nasal drug delivery, Bhavna *et al*, (2014)[5] defined the improvement of donepezil loaded nanosuspension the usage of the ionic go linking approach for direct olfactory management to the mind for remedy of Alzheimer`s disease.

In the existing have a look at traditional trial and error approach has been hired for the components and improvement of Montelukast sodium chitosan loaded nanoparticles to nasal drug delivery.

MATERIAL AND METHODS

Chemicals and Reagents

Montelukast sodium obtained from Dr. Reddy's Lab, Hyderabad, chitosan, 400 kD MW (Sigma Aldrich, Mumbai), sodium tripolyphosphate 85% deacetylated (Sigma Aldrich, Mumbai), acetic acid (S.D. Fine Chemicals).All other chemicals were of analytical grade. Pure water (Milli-Q plus system, Millipore, USA) was used to prepare all stock solutions.

Preparation of Chitosan Nanoparticles

Chitosan was dissolved in 1.0% (v/v) aqueous acetic acid and pH was adjusted to 4.6-5.0 with 10N NaOH. Sodium tripolyphosphate (STPP) was dissolved in distilled water to give a clear solution (0.5mg/ml). Montelukast sodium was added to the chitosan solution (20ml) at different drug-polymer concentration ratios from 1:1 to 1:5.5. Nanoparticles were obtained by adding the STPP aqueous solution to the chitosan solution mixture under magnetic stirring at room temperature. The STPP solution was added drop wise to the chitosan drug solution using a 1ml microsyringe and stirred using a magnetic stirrer (Remi, Mumbai, India) at 1000rpm for 1 hour. The nanoparticles obtained were concentrated by centrifugation at 15,000rpm for 20 minutes at 4°C. (Remi Cooling Centrifuge C-24, Mumbai, India). The supernatant was removed and the free drug present in the supernatant was measured at 248nm using a UV-visible spectrophotometer (UV-1601, Shimadzu, Japan). The nanosuspension was lyophilized using sucrose as a cryoprotectant to form a dry powder of chitosan nanoparticles loaded with montelukast sodium.

RESULTS AND DISCUSSION

Calibration Curve

Working standard stock solutions of Montelukast sodium was prepared (1mg/ml). The calibration curve was determined UV Spectroscopy at 286 nm.

Calibration curve **(**Figure No.1) was plotted by using recorded absorbance values vs. corresponding drug concentrations with least squares linear regression analysis. The obtained correlation coefficient (R2) of Montelukast sodium was > 0.999 that indicated linearity over selected concentration range. The Beer's Lambert's law was obeyed in the specified concentration range of 10 to 50µg/mL.

Particle size, Polydispersibility index and Zeta potential

Particle size and surface charge are the major criteria to be focused in order to have an effective drug delivery. The particle size, polydispersibility index and zeta potential of the formulated nanoparticles was determined by Malvern Zetasizer as described and the results were summarized in Table No.1. The particle size, polydispersibility index and zeta potential of the formulated nanoparticles was determined and ranges were found to be 142.06±7.62nm to 303.23±10.49, 0.233±0.14 to 0.534±0.02 and 24.53±2.4 to 44.10±0.3mV respectively.

Entrapment efficiency and loading capacity of Montelukast sodium loaded

The entrapment efficiency and loading capacity of nanoparticles was determined by ultracentrifugation at 16000 x g for 30 min at 15°C on a glucose bed, the amount of free Montelukast sodium in the supernatant was measured spectrophotometrically at 284 nm using pre-constructed calibration curve method. The results of entrapment efficiency of prepared nanoparticles were summarized in Table No.2.

DSC Analysis of Montelukast Nanoparticles

The DSC thermogram of MON was shown in Figure No.2. The DSC curve recorded between 8-10min. of its operation referring temperature 80°C to 280°Capproximately. No peaks of MON and Polymer was visible in the MON loaded NP. This finding suggests that MON was molecularly dispersed within the polymer NP showing the amorphous nature that further authenticates the entrapment of MON.

Scanning electron microscopic analysis

The shape and surface texture of the nanoparticles were detected by using scanning electron microscopic (SEM) analysis. The SEM photographs showing that the prepared MON were spherical in shape with smooth surface texture and the fig showed in Figure No.3.

***Ex Vivo* Permeation Study of Montelukast Nanoparticles**

In the present study, the ex vivo nasal permeation study was carried out in isolated porcine nasal mucosa as it's histological and biochemical aspects are closely resembles to human. Ex vivo permeation of MON from plain solution and MON across sheep nasal mucosa using a Franz diffusion cell using phosphate buffer solution (pH 6.4) The values represent mean ± SD (n=3) of three batches. The significant difference in permeation profile ($P<0.05$) of the optimized formulation MONF8 might be due to the permeation –enhancing effect of CHI. The maximum permeation in 284 min was found to be 71.72% whereas MONS was only 35.36% (Table No.3). The increase in permeation of MON could be attributed to an interaction of a positively charged amino group CHI with negatively charged sites on the mucosal membranes. Finally, on the basis of smaller particle size, higher entrapment efficiency and better loading capacity with relatively enhanced permeation profile, MONF8 was selected as suitable optimized formulation for further study.

Table No.1: Physicochemical parameters of Montelukast sodium

S.No	Formulation code	Particle Size (nm)	PDI	Zeta Potential (mV)
1	F1	152.96±8.31	0.534±0.02	24.53±2.4
2	F2	157.09±11.32	0.233±0.14	38.65±2.8
3	F3	166.08±14.09	0.518±0.03	26.34±1.4
4	F4	211.76±6.10	0.336±0.05	25.33±2.2
5	F5	303.23±10.49	0.437±0.06	29.25±2.1
6	F6	301.30±14.29	0.284±0.21	30.02±1.2
7	F7	281.42±8.46	0.258±0.34	29.42±3.2
8	F8	142.06±7.62	0.260±0.12	44.10±0.3
9	F9	225.84±16.07	0.254±0.52	32.26±2.0
10	F10	177.24±12.06	0.288±0.33	24.56±0.6

Table No.2: Evaluation of entrapment efficiency for Montelukast sodium chitosan nano-formulation

S.No	Formulation code	Drug: polymer	Entrapment efficiency Ratio (%)	Loading capacity (%)
1	MON-F1	1:1	33.45	28.17
2	MON-F2	1:1.5	42.68	42.68
3	MON-F3	1:2	56.52	29.45
4	MON-F4	1:2.5	61.47	33.68
5	MON-F5	1:3	68.74	30.42
6	MON-F6	1:3.5	70.36	27.14
7	MON-F7	1:4	74.49	28.63
8	MON-F8	1:45	67.45	22.78
9	MON-F9	1:5	60.24	32.14
10	MON-F10	1:5.5	63.87	35.36

All values were triplicate, expressed in average ± SD (n=3)

Table No.3: *Ex vivo* permeation of Montelukast nanoparticles (MONNP) and Montelukast solution (MONS)

S.No	Time in min	MONNP (%)	MONS (%)
1	0	0	0
2	30	22.82±3.26	6.24±1.45
3	60	28.34±6.42	9.36±4.62
4	90	36.26±3.87	13.84±6.38
5	120	44.52±4.18	18.52±3.41
6	150	49.67±2.52	23.45±5.12
7	180	56.78±7.10	27.28±4.84
8	210	63.61±6.06	30.14±3.12
9	240	71.72±5.78	35.36±5.63

All values were triplicate, expressed in average ± SD (n=3)

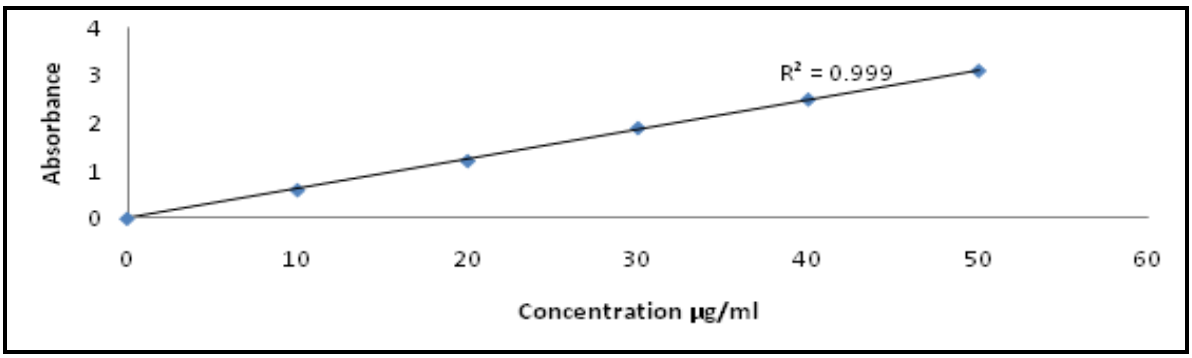

Figure No.1: Calibration curve Montelukast sodium drug concentration Vs absorbance

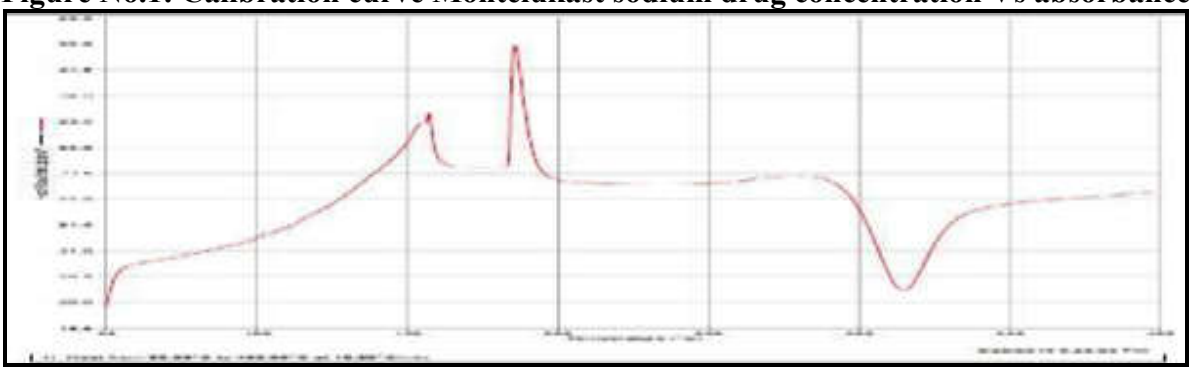

Figure No.2: DSC analysis of Montelukast nanoparticles and polymer

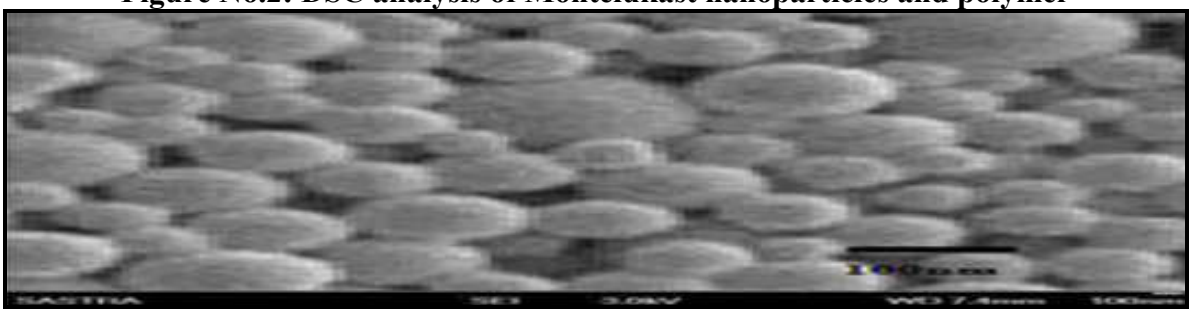

Figure No.3: SEM photographs of Montelukast nanoparticles

SUMMARY AND CONCLUSION

The present study describes formulation and evaluation of Montelukast nanoparticles loaded chitosan nanoparticles. The prepared nanoparticles showed smaller particle size, acceptable polydispersibility index, higher positive zeta potential, better entrapment efficiency as well as loading capacity, and relatively enhanced release and permeation profile of prepared nanoparticles. The formulated Montelukast loaded chitosan nanoparticles were able to show higher drug concentration in *Ex-vivo* permeation of Montelukast nanoparticles. From the DSC there is no interaction between drug and polymer, S providing direct nose-to-brain delivery, thereby enhancing drug concentration in the brain. The implication of the study could be the development of nanoparticulate drug delivery system which has the potential utility for treatment of neurodegenerative disorder by reducing the dose, avoiding the first pass effect and side effects.

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CONFLICT OF INTEREST

The entire author's declared as no conflict of interests.

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