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Original Article

CHITOSAN NANOPARTICLES AS A NASAL DRUG DELIVERY FOR MEMANTINE HYDROCHLORIDE

J. JOYSA RUBY*, V. P. PANDEY

Department of Pharmacy, Annamalai University, Chidambaram 608002 Tamil Nadu.
Email: Joysaruby2010@gmail.com

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ABSTRACT

Objective: The aim of the present study is to prepare crosslinked chitosan nanoparticles of memantine hydrochloride by using ionic gelation for nasal drug delivery system.

Methods: The Memantine Hydrochloride loaded chitosan nanoparticles were prepared by ionic gelation of chitosan with tripolyphosphate anions (TPP). Various trials have been carried out to optimize the particle size, polydispersiblity index and zeta potential. The different concentration of chitosan to TPP of 2:1,3:1,4:1,5:1with varying the stirring time 2 hrs,4 hrs,6 hrs,8 hrs and stirring speed 500 rpm, 1000 rpm, 1500 rpm, 2000 rpm were used to prepare the memantine loaded chitosan nanoparticle was prepared.

Results: The effects, including chitosan concentration, stirring speed and stirring time on the physicochemical properties of the nanoparticle, such as particle size, polydispersibility index was studied

Conclusion: The formulation was optimized for the particle size and polydispersibility index and the particle size of nanoparticle was found to be 129 nm at 4 hrs of stirring times, 1000 rpm of stirring speed and 2:1concentration ratio of chitosan and TPP. Memantine loaded chitosan nanoparticle is a potential new delivery system for treatment of Alzheimer's disease, when transported via olfactory nasal pathway to the brain.

Keywords: Chitosan, Memantine hydrochloride, Nanoparticles, Tripolyphosphate.

INTRODUCTION

Chitosan contains abundant amino and hydroxyl groups, which enable nanoparticle formulation via both physical and chemical cross-linking [1]. Ionic cross-linking of Chitosan is a typical non-covalent interaction, which can be realized by association with negatively charged multivalent ions such as tripolyphosphate (TPP) [2,3]. For pharmaceutical applications, physical cross-linking is more promising since the cross-linking is reversible and may largely avoid the potential toxicity of the reagents. Although diverse efforts have been made to obtain the chitosan nanoparticles via TPP cross-linking following the pioneering work of Calvo et al [4].

The nasal route of administration has gained substantial interest for obtaining brain uptake of polar or hydrophilic drugs [5,6]. The olfactory region connected to nasal cavity is the only site of the body where the CNS is in direct contact with the external environment. Consequently, a drug able to deposit on the olfactory regions should have more chances to reach the cerebro-spinal fluid (CSF), upon diffusion across the mucosa. Afterwards, the drug diffuses into the interstitial fluid from where it can penetrate the brain parenchyma [7,8].

The memantine is a psychoanaleptic anti-dementia drug for the treatment of moderate to severe Alzheimers disease. Memantine is an Amantadine derivative and the antagonist of N-methyl-D-aspartate (NMDA) receptors.

The principal mechanism of action of memantine is believed to be the blockade of current flow through channels of N-methyl-d-aspartate (NMDA) receptors — a glutamate receptor subfamily broadly involved in brain function [9].

Currently marketed NMDA receptor antagonists are found entirely in oral dosage form. However, alternative routes, in particular intranasal administration, may provide benefits relative to oral dosing. [10]. In addition, these NMDA inhibitors also showed the gastrointestinal side effects such as diarrhoea, nausea, anorexia and muscle convulsions etc. As a result, it is very important to develop a long term, non- gastrointestinal delivery system of these NMDA inhibitors for the treatment of AD [11].

The aim of this work was to develop a new formulation of memantine hydrochloride loaded chitosan nanoparticles for possible targeted delivery to the brain.

MATERIALS AND METHODS

Memantine hydrochloride is a gift sample obtained from Hetero Drug, Hyderabad, Chitosan (Sigma Aldrich, Mumbai), Sodium Tripolyphosphate (Sigma Aldrich, Mumbai), Acetic Acid (S. D. Fine Chemicals). All other chemicals were of analytical grade.

Methods

Chitosan loaded nanoparticles were prepared by the ionic crosslinking method according to the procedure first reported by Calvo et al., (1997 b) based on the technique of gelation between the chitosan and STPP anions. Chitosan was dissolved in acetic acid solution at the concentration of 1% w/v. Under magnetic stirring at room temperature the TPP aqueous solution (5 ml) was added to 10 ml chitosan solution of various concentrations such as the ratio of Chitosan to TPP concentrations are 2:1, 3:1, 4:1, 5:1, 6:1 with various stirring speeds (500 rpm, 1000rpm,1500rpm,2000rpm) and Stirring time (2 hrs,4 hrs, 6 hrs, 8 hrs).

The Drug memantine hydrochloride loaded nanoparticles were formed upon incorporation of 5 ml TPP solution (1mg/ml) into 10 ml chitosan solutions (1mg/ml, 1.5mg/ml, 2mg/ml, 2.5mg/ml, 3mg/ml). Memantine hydrochloride concentration was 0.66 mg/ml for the preparation of nanoparticles loading memantine hydrochloride.

Preformulation Study (Drug Excipients Compatibility study)

Sample Preparation

Each material was sieved and the respective 75 - 150µm granulometric fraction was selected. Physical mixture of memantine and each selected excipients were prepared in the 1:1 w/w ratio gently blending with a spatula at room temperature. The blends were considered homogeneous mixture when the mixture is used for further analysis.

Differential Scanning Calorimetry (DSC)

Samples of Individual components as well as each drug excipient were weighed (Mettler Electronic balance), directly in pierced aluminium crucible pans (5-10 mg) and scanned in the 50° C to 400°C temperature range under static air, with a heating rate of 10°C/min, using Shimadzu DSC-60 equipment and recorded. The DSC analysis allowed the quantitative evaluation of thermal properties of the drug and polymer such as melting point thermogram [12] of memantine showed 341°C. In majority of the cases, melting endotherm [13] of the drug was well preserved with slight changes in terms of broadening or shifting towards the lower temperature [14]. It has been reported that the quantity of material used, especially in drug excipient mixture [15] affects the thermogram of the drug. Thus, these minor changes in the melting endotherm of the drug could be due to the mixing of drug and excipients [16] which lowers the purity of each component in the mixture and may not necessarily indicate potential incompatibility [17].

Table 1: Effects of the Stirring speed on particle size and Polydispersibility Index

S. No.	B. No	Conc CS: TPP	Speed (rpm)	Time (hrs)	Particle Size (nm)	PDI
1	MCS 500	4:1	500	4	204.90±14.09	0.359±0.03
2	MCS 1000	4:1	1000	4	158.96±8.63	0.534±0.02
3	MCS 1500	4:1	1500	4	310.23±10.49	0.437±0.06
4	MCS 2000	4:1	2000	4	211.76±6.10	0.336±0.05

All values represent mean ± SD, n=3

Abbreviations: CS-Chitosan; TPP, tripolyphosphate: PDI – Polydispersibility Index

Table 2: Effect of Chitosan concentration on Particle Size

S. No.	B. No	Conc CS: TPP	Speed (rpm)	Time (hrs)	Particle Size (nm)	PDI
1	MCS21	2:1	1000	4	127.46±14.99	0.293±0.06
2	MCS31	3:1	1000	4	203.33±7.52	0.541±0.18
3	MCS41	4:1	1000	4	158.96±8.63	0.534±0.02
4	MCS51	5:1	1000	4	314.30±14.29	0.426±0.07

All values represent mean ± SD, n=3

Abbreviations: CS-Chitosan; TPP, tripolyphosphate: PDI – Polydispersibility Index

Table 3: Effect of Stirring time on Particle Size

S. No.	B. No	Conc CS: TPP	Speed (rpm)	Time (hrs)	Particle Size (nm)	PDI
1	MCS2	4:1	1000	2	278.46±16.77	0.370±0.17
2	MCS4	4:1	1000	4	152.63±12.95	0.437±0.14
3	MCS6	4:1	1000	6	212.90±4.78	0.342±0.05
4	MCS8	4:1	1000	8	290.70±7.60	0.474±0.18

All values represent mean ± SD, n=3

Abbreviations: CS-Chitosan; TPP, tripolyphosphate: PDI – Polydispersibility Index

Fourier Transform Infrared spectroscopy (FTIR)

The FTIR spectra of memantine were recorded on an FTIR multiscope spectrophotometer (Perkin Elmer, UK) equipped with spectrum 11.0.0.0449 software using KBr pellet methods.

The spectrum for each sample was recorded over than 450 -4000 cm^{-1}.

Physicochemical characterization of nanoparticles

Dynamic light scattering (DLS) (Malvern, Autosizer 4700) was used to measure the hydrodynamic diameter and size distribution (polydispersibilty index, PDI = (μ_2) / τ^2) (Chu et al., 1991). All DLS measurements were done with a wavelength of 532 nm at25° c with an angle detection of 90° C. The Zeta potential of nanoparticles was measured on a zeta potential analyzer (Malvern Zetasizer, USA). For zeta potential measurements, samples were measured in the automatic mode. All measurements were performed in triplicate.

RESULTS AND DISCUSSION

Preformulation studies

DSC analysis

DSC is a helpful technique for investigating the thermal properties of a formulation., providing information about the physicochemical state of the drug in the system. There is no detectable endotherm if the drug is present in the dispersion state [18]. If no interactions, the thermogram of a formulation will show patterns corresponding to those of the individual components. If interaction occurs, there may be appearance of one or more new peaks, disappearance of one or more peaks corresponding to those of the individual components. [19] or a shift in peaks[20]. The DSC thermogram of pure MEM, polymer CS and physical mixture of MEM, CS and TPP. The drug shows melting endotherm was well preserved with slight changes in terms of broadening or shifting towards the lower temperature. It has been reported that the quantitiy of material used, especially in drug excipient mixtureaffects the thermogram of the drug. Thus, these minor changes in the melting endotherm of the drug could be due to the mixing of drug and excipients which lowers the purity of each component in the mixture and may not necessarily indicates potential incompatibility. However, in the physical mixture of the memantine hydrochloride and chitosan no chemical instabilities were found.

FTIR analysis

The infrared (FT-IR) spectra were obtained in a KBr pellets using a Perkinelmer FT=IR spectrometer spectrum one at a resolution 4 cm^{-1} from 4000 to 400 cm^{-1}. A typical FT-IR spectrum of novel memantine showed absorption at the following wave number in cm^{-1} 2978.73, 2941.58, 2859.39, 2896.81, 2838.91, 1511.78, 1455.27,

1355.83, 436.30 and 448.78. The FTIR spectrum of samples showed characteristic absorption bands [21] which were comparable with absorption bands of an individual sample. The results illustrated that. There were no chemical instabilities in drug – excipient combinations [22].

Particle Size Analysis

The different trial has been carried out by varying the speed, the concentration, time and the effect of particle size have been determined. The stirring speed of 500 rpm, 1000 rpm, 1500 rpm, 2000rpm with the concentration ratio of chitosan and TPP 4:1 the particle size was found to be 190 nm, 149 nm, 298 nm, 210 nm and the polydispersibility index was found to be 0.351,0.523,0.411, 0.283 (Figure1,2,3&4). The formulations of varying the concentration of chitosan to TPP such as 2:1,3:1,4:1, 5:1 was carried and particle size was found to be 129 nm,194 nm, 149 nm, and 318 nm and the polydispersibility index were found to be 0.364,0.664,0.523,0.509 (Figure 5, 6, 7 & 8). The formulations by varying the time from 2 hrs, 4 hrs, 6 hrs, 8 hrs were carried out and the particle size was found to be 259 nm, 149 nm, 218 nm, 283 nm and the polydispersibility index was found to be 0.561, 0.523,0.394, 0.686 (Figure9,10,11&12). Variations in particle size to increase the stirring time is due to agglomeration of the particles. The zeta potential of the trial MES 41 with a concentration of chitosan 4:1 was found to be -54 and it implies that having good stability (Fig. 13).

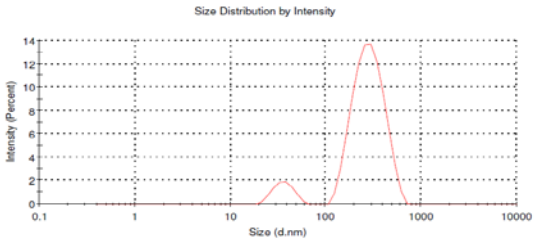

Fig. 1: Particle size of MCS 500 (particle size 190 nm)

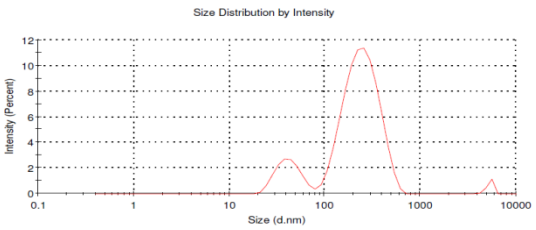

Fig. 2: Particle size of MCS 1000 (particle size 149 nm)

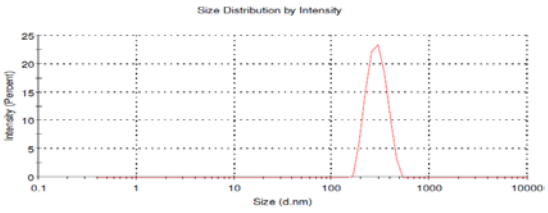

Fig. 3: Particle size of MCS 1500 (particle size 298 nm)

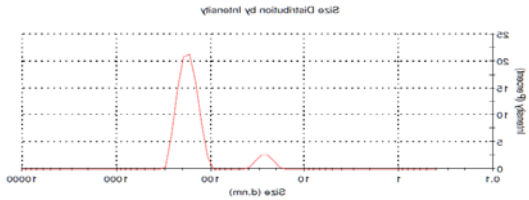

Fig. 4: Particle size of MCS 2000 (particle size 210 nm)

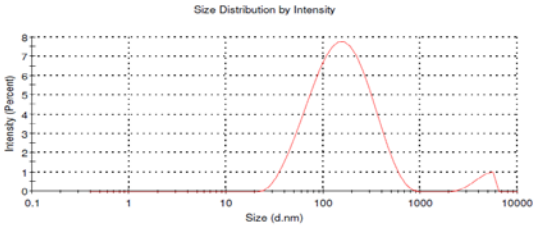

Fig. 5: Particle size of MCS 21 (particle size 129 nm)

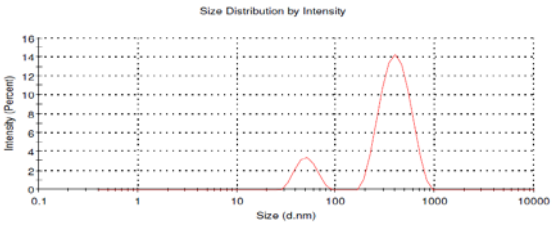

Fig. 6: Particle size of MCS 31 (particle size 194 nm)

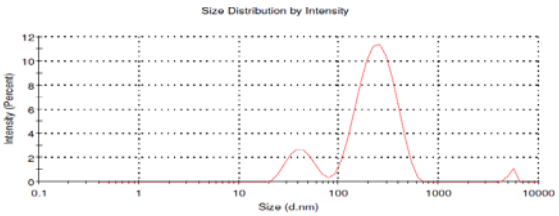

Fig. 7: Particle size of MCS41 (particle size 149 nm)

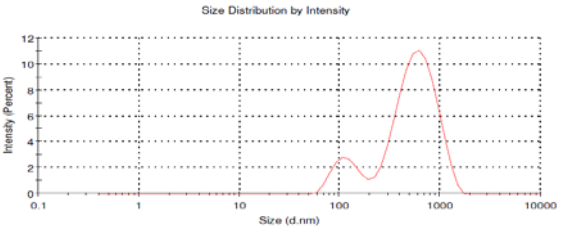

Fig. 8: Particle size of MCS 51 (particle size 318 nm)

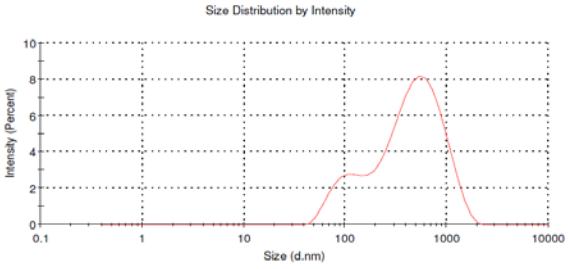

Fig. 9: Particle size of MCS 2 (particle size 259 nm)

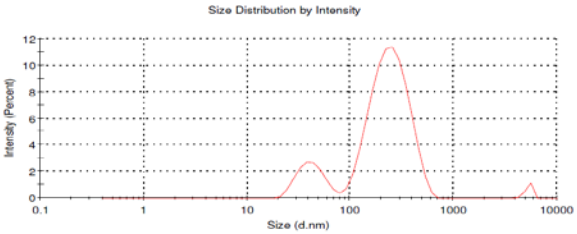

Fig. 10: Particle size of MCS 4 (particle size 149 nm).

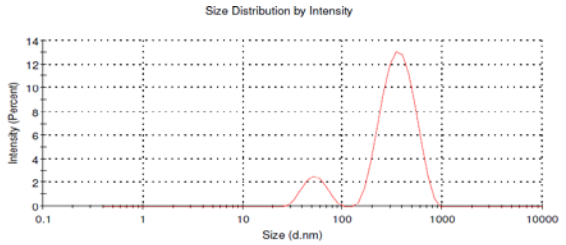

Fig. 11: Particle size of MCS 6 (particle size 218 nm)

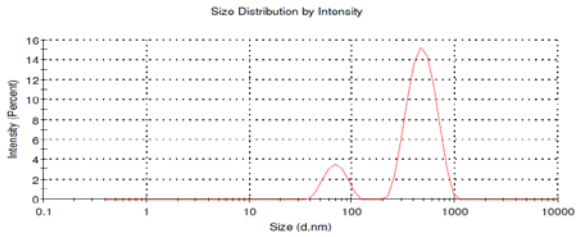

Fig. 12: Particle size of MCS 8 (particle size 283 nm)

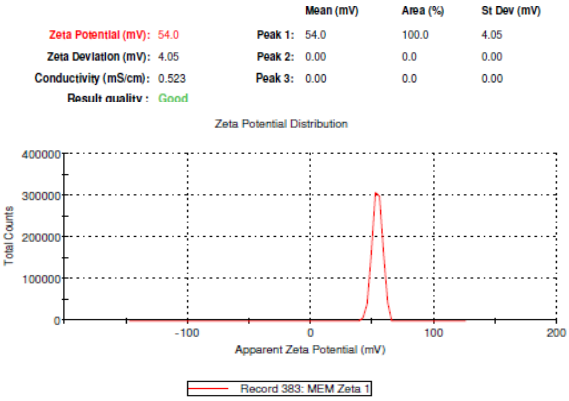

Fig. 13: Zeta potential of MCS21

CONCLUSION

From the DSC and FTIR study, it is concluded the drug memantine and polymer chitosan and other excipients used for the formulation of nanoparticles for nasal drug delivery were found to be compatible and suitable for formulations without any interactions. The various trials with changing the RPM, concentration ratio and time, it is proven that the best suitable speed for the formulation of chitosan nanoparticle for effective particle size of 129 nm is 100 rpm and suitable concentration of chitosan and TPP is 2:1 and the time is found to be 4 hrs based on the particle size and polydispersibility index values. The zeta potential of optimized formulation was found to be 54 and it implies the formulation having good stability.

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CONFLICT OF INTERESTS

Declared None

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