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Selection of Excipients for Memantine Hydrochloride Nanoparticles Through Drug Excipient Compatibility Testing

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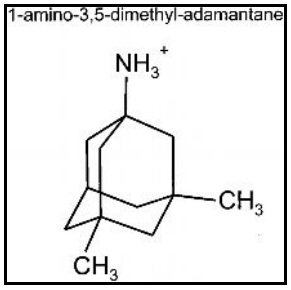
Abstract: Memantine is a clinically useful drug in many neurological disorders, including Alzheimer's disease. The mechanism of memantine is believed to be the blockade of current flow through channels of N-methyl-D-aspartate (NMDA) receptors, a glutamate receptor subfamily broadly involved in brain function. Preformulation is the first step in the rational formulation of an active pharmaceutical ingredient (API). For any formulation interactions studies are very important. When there was no interaction between the choosen drug- excipient or excipient-excipient then the formulation will be a appropriate one. The selection of suitable study method to evaluate the interaction between the drug and the excipients is a prime most achievement in the pre-formulation study. Recently the thermal analytical techniques is applied to study the interaction study. The objective of the study was to study the compatibility of memantine drug substance with the excipients employed in the formulation of nanoparticle for nasal drug delivery system by adopting Differential Scanning Calorimetric (DSC) study and Fourier transform Infra red spectrophotometric study (FTIR). Based on the DSC and FTIR results memantine was found to be compatible with excipients chitosan and Sodium Tripolyphosphate.
Keywords: Memantine, FTIR, DSC, Excipients.

Introduction

Memantine Hydrochloride (I-amino-3,%dimethyladamantane hydrochloride) a psychoanaleptic anti-dementia drug for the treatment of moderate to severe Alzheimers disease. Memantine is an amantadine derivative and antagonist of *N*-methyl-*D*-aspartate (NMDA) receptors. Memantine also has antagonistic activity at the type 3 serotonergic (5-HT_3) receptor with a potency that is similar to that at the NMDA receptor, and lower antagonistic activity at the nicotinic acetylcholine receptor.



Preformulation is an investigation on the physical-chemical properties of the drug substance alone and in combination with excipients. Assessment of the possible incompatibilities between the drug and various excipients is an important part of the preformulation[1] . Study of drug –excipient compatibility is an important process in the early development stage of stable dosage forms. The successful formulation of a stable and effective dosage form depends on a careful selection of the excipients. However, no universally accepted protocol is available for evaluating the drug compatibility with different excipients[2].

A formulation is considered appropriate when no interaction drug excipient or excipient- excipient occur. In this sense, devising a quick and accurate method to test and select the best excipients for stable dosage forms constitute, a real achievement in the preformulation stage[3]. Thermal analysis is one of the most frequently used instrumental techniques on pharmaceutical researchers to solve technological problems in the preformulation stages of solid dosage forms, In particular, differential scanning calorimetry (DSC) has been proposed as a rapid method for evaluating physico-chemical interactions[4] between the formulation components and therefore selecting excipients with suitable compatibility[5].

The aim of this work was to evaluate the compatibility between memantine and some pharmaceutical excipients, using thermo analytical techniques (DSC) and Fourier Transform Infrared Spectroscopy (FTIR).

Materials and Methods

Memantine as a gift sample was Procured from Hetro Drugs Pvt. Ltd. The excipients examined were: Chitosan (Sigma Aldrich, Mumbai), Sodium Tripolyphosphate (Sigma Aldrich, Mumbai), Acetic acid (S.D Fine Chemicals, Mumbai).Physical binary mixture Memantine with each excipient alone 1:1 w/w ratio obtained by grinding in the mortar were also studied.

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 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^{o} C to 400^{o} C temperature range under static air, with heating rate of 10^{o} C/min, using Shimadzu DSC-60 equipment.

Fourier Transform Infrared spectroscopy (FTIR)

The FTIR spectra of memantine were recorded on a FTIR multiscope spectrophotometer (Perkin Elmer, UK) equipped with spectrum 11.0.0.0449 software using KBr pellet method. The spectrum for each sample was recorded over than 450 -4000 cm^{-1}.

Results and Discussion

DSC Analysis

The DSC analysis allowed the quantitative evaluation of thermal properties of drug and polymer such as melting point thermogram[6] of memantine showed 341^{o}C (Figure 1). In majority of the cases, melting endotherm[7] of drug was well preserved with slight changes in terms of broadening or shifting towards the lower temperature[8]. It has been reported that the quantitiy of material used, especially in drug excipient mixture[9] affects the thermogram of the drug. Thus, these minor changes in the melting endotherm of drug could be due to the mixing of drug and excipients[10] which lowers the purity of each component in the mixture and may not necessarily indicates potential incompatibility[11].However, in the physical mixture of the memantine hydrochloride and chitosan no chemical instabilities were found.

FTIR Study

The infrared (FT-IR) spectra were obtained in a KBr pellets using a Perkinelmer FT=IR spectrometer spectrum one at resolution 4cm^{-1} from 4000 to 400 cm^{-1} . A typical FT-IR spectra 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.

FTIR spectroscopy has been successfully used for exploring the differences in molecular conformations, crystal packing and hydrogen bonding arrangements for different solid state forms of an organic compound. Spectral variations originates due to alteration in bonds that exhibit characteristic vibrational

frequencies, leading to frequency shifts and splitting in absorption peaks.The FTIR spectrum of samples (Figure 3 to Figure 7) showed characteristic absorption bands[12] which were comparable with absorption bands of individual sample. The results illustrated that, there were no chemical instabilities in drug – excipient combinations[13] .

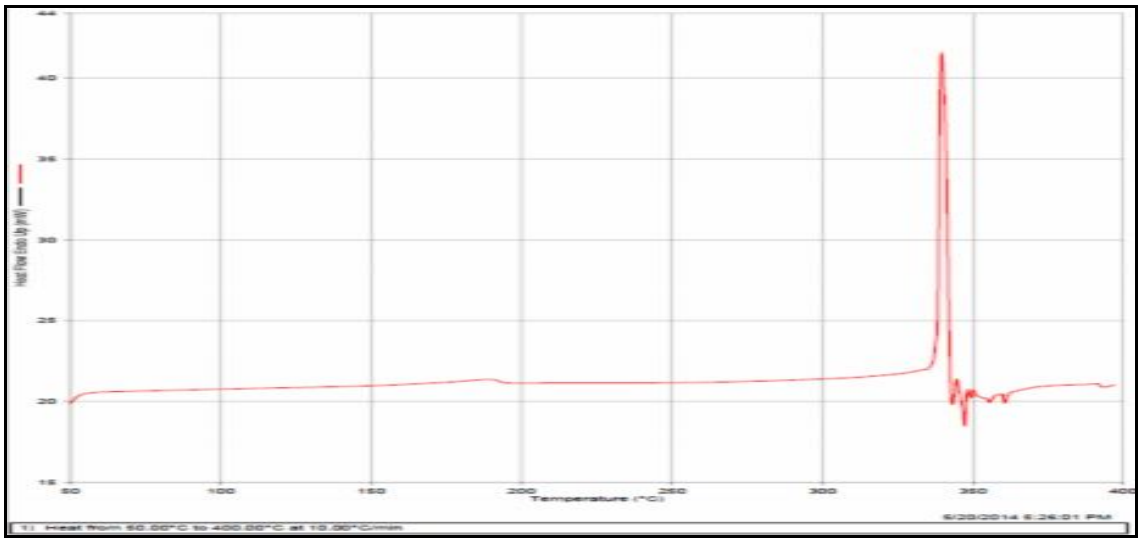


Figure 1: DSC of Drug Memantine Hcl

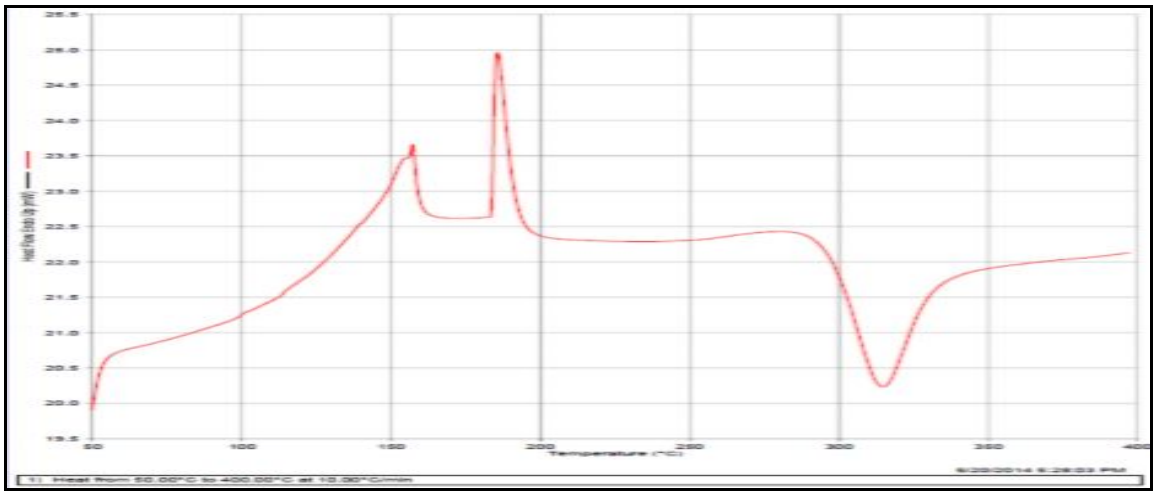


Figure 2: DSC of Polymer Chitosan

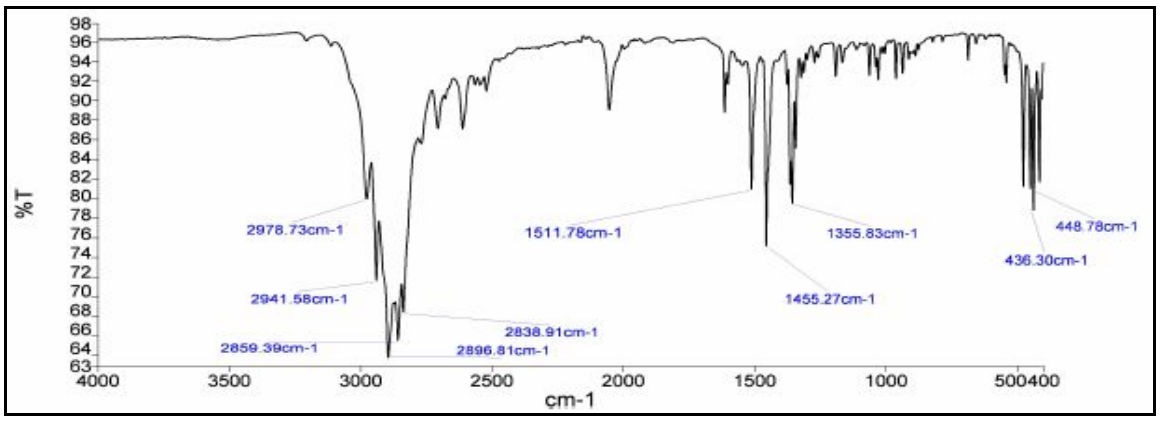


Figure 3: FTIR of Memantine Hcl

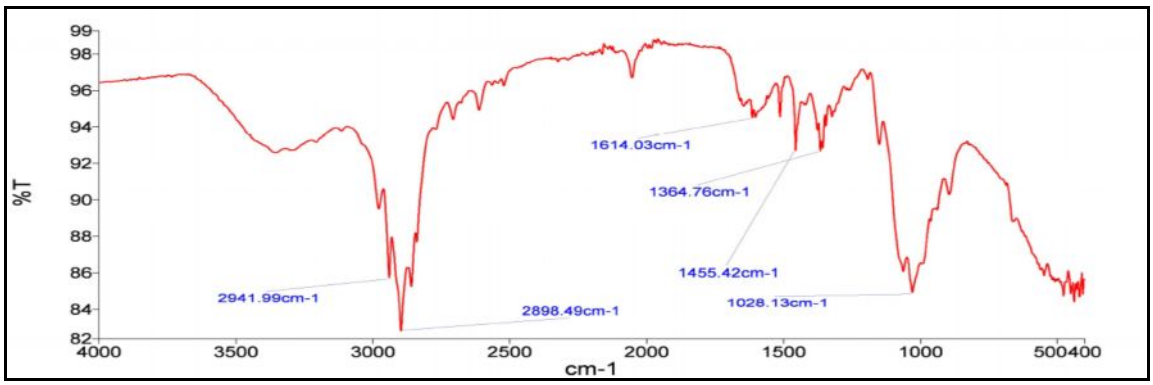


Figure 4: FTIR of Chitosan

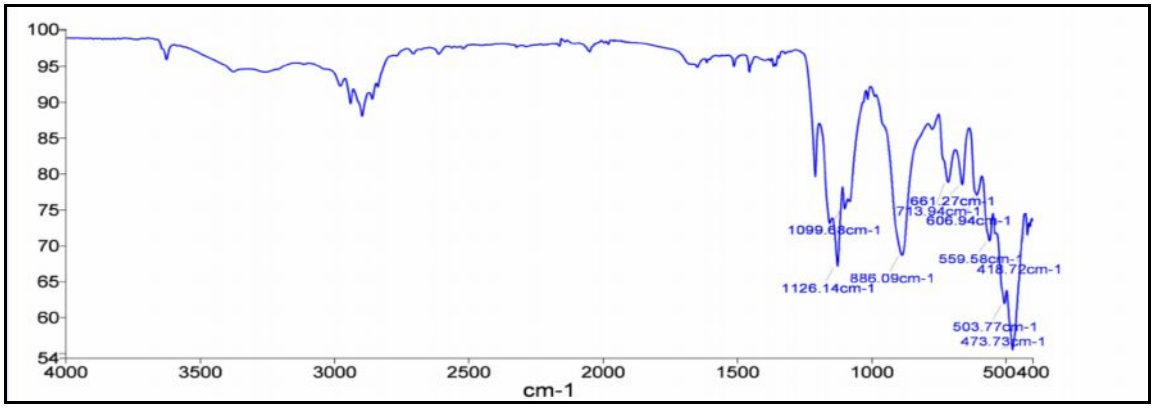


Figure 5: FTIR of STPP

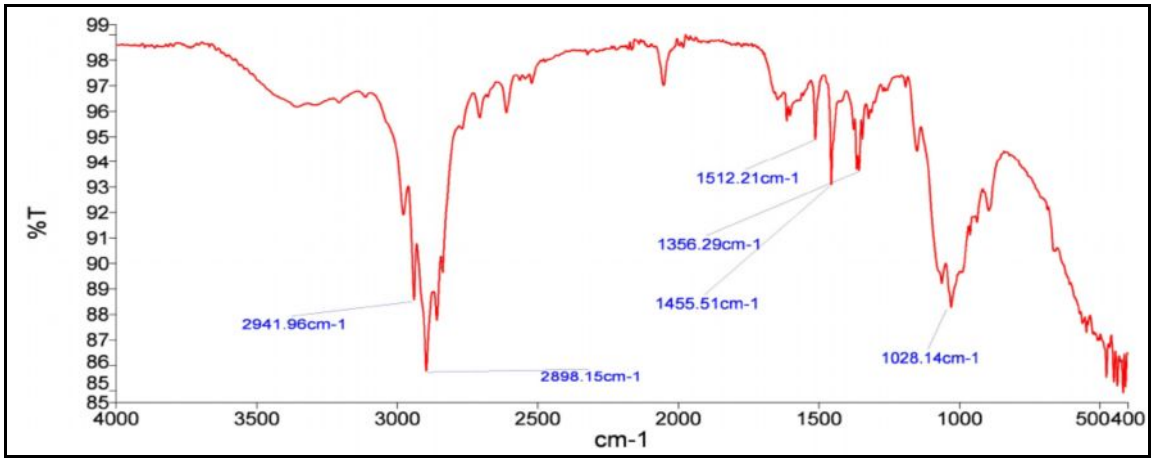


Figure 6: FTIR of Memantine + Chitosan

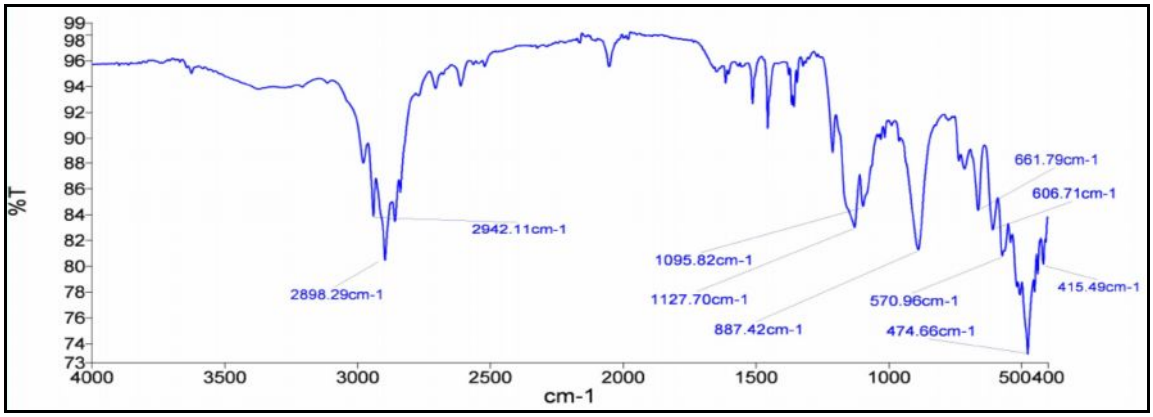


Figure 7: FTIR of Memantine+ chitosan + STPP

Conclusions

From the results of FTIR and DSC methods, it is proven that FTIR and DSC as fast screening tools to check compatibility in early stages of a preformulation process. Based on our results, all mentioned excipients were found to be fully compatible with memantine. It is conclude that the selected excipients can be further used for formulating memantine chitosan coated nanoparticle.

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