Vol 13| Issue 2| 2023 | 52-55.

e-ISSN 2248 – 9142
print-ISSN 2248 – 9134

International Journal of
Current Pharmaceutical & Clinical Research

www.ijcpcr.com

FORMULATION, OPTIMIZATION AND EVALUATION OF NANO PARTICULATE SYSTEM OF RIVASTIGMINE FOR TREATMENT OF ALZHEIMER

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ABSTRACT

There are a number of restrictions to present therapies, and the intranasal methodology looks to be a possible way for medication delivery to the brain. "Neurotransmitter or enzyme modulation is the basis of the right now permitted medications for treating cognitive disorders associated with AD. Inhibitors of acetyl cholinesterase (AChE) have been associated with gastrointestinal side effects like nausea and vomiting, which frequently lead to the discontinuation of therapy. The formulation F-2 SLNs were studied for stability study as per ICH guidelines. The formulation was stable at room temperature with minor change in particle size in three months. The initial particle size at day 0 was 138.22+0.01 nm and the size after 3 months were 139±0.4 nm. This minor increase in particle size may be due to the weak Vander Waals force that holds the particles together which lead to the formation soft agglomerates. Thus, SLNs were stable at room temperature for 3 months.

Key words: Alzheimer, Rivastigmine, Solid Lipid Nanoparticles, Nanosuspension.

INTRODUCTION

Alzheimer's disease is a long-term neurological condition that begins gradually and gets progressively worse over time. The most frequent primary symptom is memory loss. As Alzheimer's disease progresses through its many phases, its symptoms, which include difficulties with language, confusion, changes in mood, loss of motivation, and behavioral disorders, get worse [1-2]. The loss of physical functioning progresses to death. Following diagnosis, the usual life expectancy ranges from three to nine years. There are several allopathic, homoeopathic, and ayurvedic Alzheimer therapies available [3-4].

According to the amyloid hypothesis, AChE encourages beta-amyloid (Ab) deposition, typically in the form of senile plaques or neurofibrillary tangles, on the disease-stricken individuals' brains. It was believed that the Ab deposition had a vital part in the beginning and development of AD. Inflammatory response is one of the acetylcholinesterase (AChE) diseases [5]. Acetylcholine (ACh) is a key neurotransmitter molecule that may be effectively degraded into choline across cholinergic synapses with the help of the enzyme AChE. ACh was closely associated with the production of amyloid fibrils, which is considered a key factor in the development of ADACh might rise as a result of inhibiting AChE activity, which is a successful way to treat AD symptoms. In order to create effective drugs for AD treatment, it was crucial to search for potential AChE inhibitors [6].

MATERIALS AND METHODS

Preformulation Study

Physical properties

The organoleptic features of Rivastigmine Tartrate drug, such as color, taste, and odor, were investigated [7]

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Determination of Wavelength Maxima (λ_{max})

In a 10 ml volumetric flask, 10 mg of rivastigmine tartrate drug were accurately and dissolved in 10 ml buffer solution, pH 6.8. Buffer solution was used to make up the volume in a 10 ml volumetric flask with 0.1 ml of this stock solution pipette in. A UV- Visible is double beam spectrophotometer was used to scan the resultant solution between 200 to 400 nm [8-9]

Preparation of calibration curve of rivastigmine tartrate

10 mg of drug are accurately measured and dissolve in 5 ml of buffer solution in a 10 ml volumetric flask, with the buffer solution utilized to make up the difference. The resultant solution has a concentration of 1000g/ml, so pipette out 1 ml and transfer to a 10 ml volumetric flask, then volume make up with buffer solution and perform a dilution to get it to a concentration range of 5-25g/ ml. the spectra of this solution was measured in the 200-400 nm range UV-Visible spectrophotometer. The absorbance of solution was compared to a control buffer solution, the calibration curve was created by plotting the absorbance versus the concentration. A straight line of greatest fit was created using a linear regression analysis [10].

FTIR Spectra of rivastigmine tartrate

Using a Fourier Transform Infrared Spectrophotometer, the KBr method was utilizes to record the FTIR spectra of medicine. A baseline correction was accomplished using dried potassium bromide in a pressure compression apparatus to from a potassium bromide drug pellet with a diameter of roughly 1 mm. The sample pellet was scanned at wavelengths raining from 4000 cm-1 in an IR compartment [11]

Melting point determination by DSC

One of the factors for determining the purity of drug is this. The melting point of pure substance is extremely precise and consistent. Because the medication contains a verity of ingredients, they have a melting point range given to them [12].

DSC was used to determine the melting point (DSC). The sample (2mg) was heated at a rate of 5oC/ min in a non-hermetically crimped aluminum pan across a temperature range of 50 to 200oC. A DSC thermo gram was used to determine yhe melting points of rivastigmine tartrate [13].

Solubility study

At room temperature (25.94+ 0.06), solubility tests were prepared using lipid carriers i.e. Apifil, Compritol, GMS, Precirol ATO 5 (PA) and Stearic acid. An excess volume of medication was administered to 5 ml of solvent in screw-capped glass vial and mechanically shaken for 48 hours at 25oC before equilibrium was reached. Solubility was evaluated after aliquots were collected and filtered using a membrane filter [14].

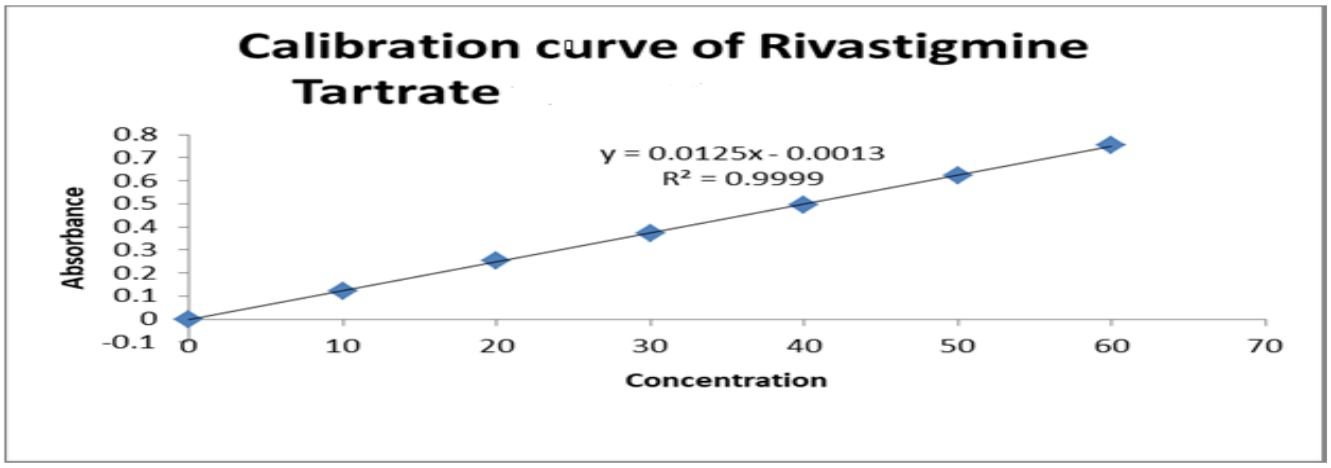
Partition coefficient

The partition coefficient of a drug may be determined by shaking it with equal parts of two immiscible solvents (the organic layer, which is saturated with water, and the aqueous drug solution) until equilibrium is attained. The content of the drug in one of the layers is determined and the value is calculated [15].

Drug – Excipient Compatibility

The thermo grams were monitored using a differential scanning calorimeter. Weighed samples (5-10mg) were placed in metal pans with flat bottoms and hermetically sealed. These samples were heated at a continuous rate of 10oC per minute in an environment of nitrogen (200ml/min) over a temperature range of 50-400oc, with alumina as the reference standard[1]

Calibration curve of rivastigmine tartrate



RESULTS AND DISCUSSION

Between concentration and absorbance, a calibration curve was produced. In buffer solution, rivastigmine tartrate a linear connection with correlation coefficient of 0.999 in the concentration range of 2-14g/ml (6.8). Absorbance of rivastigmine tartrate in buffer solution pH 6.8. Calibration curve was prepared by plotting the absorbance against concentration of RT[16-17].

In- vitro drug release study for SLNs

Percentage of drug diffused over duration (in hours) during *in-vitro* diffusion between rivastigmine tartrate solid lipid nanoparticles and rivastigmine tartrate aqueous solution With RT-SLNs, the percentage of RT diffused up to 24 hours was 97.11+0.44%, while with rivastigmine tartrate, it was 28.36+0.22%. Because of rivastigmine tartrate increased aqueous solubility in aqueous medium, there is a modest increase in drug diffusion when using drug solution at the beginning time points.

In contrast, the initial time needed for the drug to leach out of the lipid core in RT-SLNs was longer than it was for the drug solution. The composition of the lipid matrix and the quantity of surfactants may have an impact on how quickly drugs are released from SLNs. The amphiphilic nature of GMS, which gives RT good solubility and leads to homogeneous distribution of RT within the lipid matrix, could explain why SLNs release more RT. Lowering of enthalpy and intensity, respectively, with lipid in RT-SLNs verified a flaw in the crystal structure of GMS, as demonstrated in DSC. As is common knowledge, melting less perfect crystal material needs less energy than melting a less ordered and/or flawed crystal lattice. Since the drug diffused out through defective crystal lattices on the lipid surface of RT-SLNs, this may be one of the causes of greater diffusion in the case of SLNs.

The Rivastigmine tartrate SLNs particle size was inversely proportional to the drug release i.e. as the size of the nanoparticles decreases; there was increase in the drug release. Lower concentration of lipid and lower concentration of surfactant retarded the drug release whereas higher concentration of surfactant showed faster drug release.

Evaluation of Nanosuspension

Drug content:

The percentage drug content of nanosuspension of optimized formulation of Rivastigmine tartrate [SLNs –F-2] was estimated by UV-spectroscopic method and was found to be 95.20%.

Entrapment Efficiency

The percentage entrapment efficiency of nanosuspension of optimized formulation of Rivastigmine tartrate [SLNs –F-2] was found to be 77.82%. Results show that maximum drug was entrapped in the formulation.

Particle size and Zeta potential

The particle size of nanosuspension of optimized formulation of Rivastigmine tartrate [SLNs –F- 2] was found to be 138.22+0.01nm with PDI 69.27+0.23%. There was a slight increase in particle size when formulated into nanosuspension. The zeta potential of nanosuspension of SLNs was found to be -24.8+0.01 mV showing excellent stability.

In-vitro release study

In-vitro drug release study of nanosuspension of optimized formulation of Rivastigmine tartrate [SLNs –F-2] and pure drug (Rivastigmine tartrate) suspension is represented graphically as percentage cumulative drug release v/s time profile. The cumulative percent drug release is shown in figure 5.25. Data is shown in table 5.15. From the graph, it is clear that the suspension of pure Rivastigmine tartrate released almost 99.51±0.024% of the drug at the end of 8 hrs, while the nanosuspension of SLNs released 84.19±0.52 % of drug after 24 hours. The drug release pattern of nanosuspension was bi-phasic in nature; with an initial burst release followed by sustained drug release. Initial burst release of about 25% was observed at the initial 30 minutes followed by slow sustained release. This burst release may be due to the presence of the free drug Rivastigmine tartrate in the external phase and on the surface of the SLNs. This bi-phase release pattern could be used to provide sustained release of drug for prolonged time period.

Conclusion

One of the best ways to examine the bio-distribution of a medicine is to do whole-body gamma imaging to quantify radioactivity in various tissues following drug delivery. Depicts the labelling stability and efficacy of free drug and 99mTc-labeled nanoparticles. Both the free drug and the rivastigmine tartrate SLNs had a radiochemical purity of more than 90%. The development of a stable 99m Tc rivastigmine SLNs complex and the successful adhesion of the free drug to 99mTc are thought to be the causes of the high labelling efficiency. The initial material for technetium nucleus is pertechnetate ions. Typically, acidic stannous chloride or other stannous salts decrease these ions. The same procedure was used in the current work on the bio-distribution of 99mTc rivastigmine tartrate SLNs administered to Balb/c mice both orally and intravenously. The radioactivity in several organs was estimated 1 and 4 hours after injection and the findings.

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