Development and Evaluation of Rivastigmine tartrate drug-loaded microspheres

Authors: Dr.R.Anusha[1]*, Mrs.A.Madhu bindhu[2], Dr.Y.Kavya[3], T.Sindhu[4] K.Gayathri[5], Rubana Rahat Shahi[6]

1 Assistant Professor,Department of pharmaceutics, Pulla Reddy Institute of Pharmacy, Dundigal, Hyderabad, Telangana, India

2 Assistant Professor,Department of pharmacognosy, Pulla Reddy Institute of Pharmacy, Dundigal, Hyderabad, Telangana, India

3 Associate Professor,Department of pharmacognosy, Malla Reddy Institute of Pharmaceutical sciences, Malla reddy vishwavidyapeeth,Hyderabad, India

4,5,6 Students, Pulla Reddy Institute of Pharmacy, Dundigal, Hyderabad, Telangana, India

*Corresponding author:

Dr.R. Anusha

Department of Pharmaceutics,

Pulla Reddy Institute of Pharmacy,

Dundigal, Hyderabad, Telangana, India

E-mail address: anusha.rudroju1610@gmail.com

Tel: +91 8247867156; Fax: + 91 8247867156.

ABSTRACT:

This study focuses on the development and analysis of Rivastigmine tartrate microsphere's using the solvent evaporation method, aimed at enhancing therapeutic efficacy in Alzheimer'stherapy. Microspheres, as controlled drug delivery system, offer advantages such as sustained release, targeted delivery and improved patient compliance. Ethyl cellulose was employed as the polymer to encapsulate the drug. Three batches were prepared with varying polymer concentration. The microspheres were assessedfor drug entrapment effectiveness, particle size, drug loading, in-vitro release profile, along with surface morphology using SEM. FTIR studies confirmed drug-excipient compatibility. Among all formulations Third batch exhibited optimal properties, including Highest drug entrapment, drug loading, and sustained release. The release kinetics followed zero-order to Higuchi models. The findings suggest that Rivastigmine loaded microspheres offer a promising approach for the sustained and targeted delivery in Alzheimer's disease. By releasing the medication slowly over time, these microspheres could improve treatment outcomes and reduce side effects.

KEYWORDS:

Rivastigmine tartrate, Microspheres, Alzheimer's disease, Solvent evaporation, Controlled drug delivery, FTIR, SEM, Sustained release, in-vitro release.

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INTRODUCTION

Microspheres are free-flowing polymeric microparticles filled with physiologically active pharmaceuticals designed to provide a consistent and extended therapeutic impact, lowering dose frequency and enhancing patient compliance.[1] Microspheres are utilized to minimize adverse effects by targeting medication to a specific site in addition to provide sustained release. [2,3,4]. Microspheres are characterized as free-flowing powders composed of biodegradable synthetic polymers or proteins that are preferably have a particle size ranging between 1 to 1000 µm. [5]. Microspheres are also referred to as microparticles, it can be fabricated from wide range of materials such as glass, ceramics and polymers. The choice of material and particle size plays a crucial role in determining their application and their tiny particles are utilized in diverse fields such as drug delivery, diagnostics and material science due to their versatility. Microspheres can generally be categorized into two types: microcapsules and micro matrices. While microcapsules consist of a core substance enclosed within a distinct capsule wall or shell and micro matrices are solid matrix in which drug is uniformly dispersed.[5]. Microspheres are created using various natural and synthetic polymers and most often used microspheres are polyethylene and polystyrene [6]. Amicrosphere can be produced using a variety of ways,allowing for greatercontrol over drug

administration. This focus allows for accurate release of a component at the target site while reducing its presence at non target site. This factor protects compounds both before and after deliveryA recognition molecule can be used to control the vectorization of medical substances in microspheres. Exploiting variations in pharmacokinetic behaviorcan improve treatment outcomes. The goal of any pharmaceutical administration system is to deliver a therapeutic amount of the substance to the right location in the body, swiftly achieving an effective concentration and maintaining it for a set duration. A well-designedmodified release system for the chemical can improve therapeutic efficacy and improve patient quality of life addressing issues with conventional therapy [7]. Synthetic and natural polymers are the two primary forms of polymers utilized to create microspheres, which aid in the transportation of active substances. Ethyl cellulose and sodium alginate are naturally occurring polymers that come from sea brown algae. This is commonly utilized in topical and oral formulations due to its non-toxicity,biodegradability andbiocompatibility [8].

Rivastigmine is a para-sympathomimetic or cholinergic medication used to treat mild to moderate Alzheimer's dementia and to treat Parkinsons disease-related dementia. The drug roughly shows 36% bioavailability, metabolized by liver and has a biological half-life of 1.5hours, and apparent volume of distribution are the reasons for its selection [9]. Rivastigmine is absorbed in the stomach and intestine, with food slowing absorption by 30%, resulting in minimal drug interactions. However, high doses can cause gastrointestinal side effects like nausea and diarrhea. These adverse events are linked to rapid spikes in brain concentration and fluctuating plasma levels. Smoothing out these pharmacokinetics fluctuations may help to reduce side effects and improve tolerance for oral rivastigmine [10].

Rivastigmine chemical name is 3-[(1S)-1-(dimethylamine) ethyl] phenyl-ethyl-N-methylcarbamate, with a molecular formula of C14h22n2O2 and molecular weight is 250.33 g/mol. Rivastigmine id believed to inhibit cholinesterase (acetylcholinesterase and butyrylcholinesterase), preventing acetylcholine breakdown and boosting its levels in brain synapses. Rivastigmine action is more targeted towards brain acetylcholinesterase than peripheral tissues [11].

AD is the leading cause of major neurocognitive disorder and responsible to the 50-70% cases in older adults [12]. Dementia is the broad term for conditions that mental functions effects daily life [13]. Alzheimer's is the most common underlying cause of dementia [14].

From past three decades have seen a rapid surge in development of new therapeutic compounds. The advancements in drug delivery have enabled the effective use of these pharmaceuticals and paved the way for innovative treatments using existing approved medication. Microspheres represent a significant break-through in drug delivery enabling controlled release transdermal delivery and enhances patient compliances [15-18].

The goals of the therapeutic clinical treatment for AD are to improve diseasebehavioral, cognitive and non-cognitive symptoms. No new drugs have been approved in the past 20years to treat or prevent AD. To create a new anti-AD drug, is used to prevent the beginning of an illness or decrease its progression. The promising targets that alter the pathologic state of AD are cell oxidation, tau protein, and αβ [19].

Some possible benefits that are found in microspheres-based delivery for Alzheimer's disease include:

Controlled release: Microspheres can release therapeutics over an extended period, reducing the need for frequent dosing.

Targeted delivery: Microspheres can be designed for targeting specific areas of the brain, so this increases therapeutic efficacy and reduce side effects.

For patients, compliance is better: Delivery system that are microspheres based can simplify treatment regimens such that patients adhere better, and outcomes do improve overall.

COMPONENTS AND TECHNIQUES

Reagents and chemical compounds

Rivastigmine tartrate has been obtained as a trial sample taken from Merck limited and life science industry (Hyderabad). Ethyl cellulose was provided by BLD Pharm. Poly vinyl alcohol and Dichloromethane was given by SD. Fine chem. Ltd and Ethanol was offered by CSS. Fine Chemical. All the other chemicals, reagents, and solvents are of high analytical quality.

Devices used

1. **Magnetic stirrer (REMI 1 MLH)**
2. **Digital electronic balance (KEROY balance-FB360H)**
3. **Fourier transform infrared spectroscopy (FTIR) (BRUKER Alpha)**

4. **UV-visible spectrophotometer (UV 1800 Shimadzu)**
5. **JEOL JSM-6360 (JSM 6360 LV) is the SEM model**
6. **Sonicator (LOBO Life 3-5L Sonicator)**
7. **PH Meter (ELICO LI 120 pH Meter)**

Preparation of Rivastigmine tartrate microspheres

Rivastigmine tartrate microspheres arecreated through solvent evaporation process. The specific ingredients and different proportions of various microspheres preparation was listed

Table 1: Formulation details of Rivastigmine tartrate microspheres

S.NO	Ingredients	Batches of rivastigmine tartrate microspheres prepared		
		F_1	F_2	F_3
1	Rivastigmine tartrate	500mg	500mg	500mg
2	Ethyl cellulose	500mg	1000mg	1500mg
3	Dichloromethane	10ml	10ml	10ml
4	Ethanol	10ml	10ml	10ml
5	Poly vinyl alcohol (PVA)	750mg	750mg	750mg
6	Distilled Water	100ml	100ml	100ml

Rivastigmine tartrates were successfully fabricated using a solvent evaporation technique. The process involved the following steps:

Drug solution preparation: To create a uniform solution, Rivastigmine tartrate was dissolved in dichloromethane.

Preparing the Polymer solution: The drug polymer solution was thoroughly combined to create a homogenous mixture after the polymer was dissolved in ethanolic solution

Emulsification:Using a homogenizer, the drug polymer solution was added dropwise to polyvinyl alcohol (PVA) solution while being continuously stirred at 1500rpm.

Thermal treatment: The mixture was then heated to 80°C with continuous stirring for 1 hour to facilitate microspheres formation.

Solvent evaporation: The aqueous phase was removed completely through evaporation resulting in the formation of microspheres.

Microspheres collecting and washing: The microspheres were collected using Whatman filter paper and washed three times with distilled water to remove any residual impurities.

Drying: To obtain the final product, the microspheres were let too dry for 24 hours at room temperature.

EVALUTION OF MICROSPHERES:

FTIR (Fourier transform infrared spectroscopy):

The molecular structure ofmicrospheres and the drug was analyzed using FTIR. The Fourier transform infrared spectroscopy spectra was acquired by mixing a small amount of the sample with potassium bromide (KBr) and scanning it with a specific infrared range.

About 5mg of the sample and 50mg spectroscopic grade (KBr) were mixed throughout the sample preparation process. Then the samples were scanned at a resolution of4cm^-1 in the 500-3500cm^-1 infrared spectrum.

SEM (Scanning electron microscopy):

Particles that had been dried in air have beenexamined using scanning electron microscope (FEI-Quanta 200F) set to 51 kV to assess their exterior morphology.Double-sized adhesive tape was used to attach the specimens to metal substrate, and they were them sputter-coated with platinum in a vacuum environment.

Preparation of a calibration graph for Rivastigmine tartrate quantification:

Preparation of buffer solution (pH-6.8):

28.80gm of sodium dihydrogen phosphate and 11.45gm of potassium dihydrogen phosphate were dissolved in an adequate amount of distilled water to create phosphate buffer solution with a pH of 6.8. The solution was then diluted to a final volume of 1000ml with distilled water, thereby ensuring a precise buffer concentration.

Standard stock solution preparation:

A 100ml clean and dry volumetric flask was filled with 100mg of the working standard of the rivastigmine tartrate, which had been precisely weighed to create the standard stock solution. Approximately 100ml of a suitable solvent was added to the flask, and the mixture was agitated gently to facilitate dissolution of the Rivastigmine tartrate.

Preparation of working solution:

A series of working solutions were prepared by diluting the standard stock solution to achieve concentrations of 5, 10, 15, 20, and 25mg per ml. These working solutions were subsequently analyzed using a double-beam ultraviolet (UV) spectrophotometer, with absorbance measurements recorded at a wavelength of 217 nanometers.

Calculating the practical yield:

The microspheres, after drying at ambient temperature, were weighed, and microspheres yield was determined using a formula

$$percentage\ yield = practical\ yield \div theoretical\ yield \times 100$$

Determination of drug content:

Drug entrapment efficiency = quantity of drug present÷ theoretical drug load expected×100

Drug loading in microspheres is determined by:

Drug loading efficiency in microspheres was calculated with an equation

$$L = Qm \div Wm \times 100$$

Where

L = Drug loading percentage in microspheres

Wm = The weight of microspheres in grams

Qm = The amount of rivastigmine tartrate in microspheres(in Wm grams)

Determining the mean particle size of microspheres:

The particle size distribution of microspheres was determined using optical microscopy. A little amountof dried microspheres was suspended in glycerin and the particle size of 100 microspheres was measured in each batch, with the mean particle size estimated.

In vitro release studies:

The in vitro drug release tests were conducted for 8 hours in pH 6.8 buffer using a USP type II dissolution device. Microspheres samples that had been precisely weighed were added to the 37°C dissolution medium. Aliquots were taken out at regular intervals and replaced with an equal volume of the dissolution medium to keep the volume constant. After dilution, samples were analyzedspectrophotometrically at 217nm.

Kinetics analysis of dissolution the data

Severalmodels including Zero order, first order, Higuchi, and Kosmeyer-Peppas plot were utilized to match the profiles of different batches of microspheres.

RESULTS AND DISCUSSION:

Pre-formulation studies:

Properties of drug were tested as part of pre-formulation studies, and the results were combined with pharmacopeial values. The results were illustrated in table.

Table 2: RIVASTIGMINE TARTRATE PRE-FORMULATION STUDIES

S.NO	PARAMETER	RESULT
1	Physical appearance	Off white fine crystalline powder
2	Solubility	Freely soluble in water, ethanol and acetonitrile slightly soluble in n-acetonol and ethyl acetate
3	Melting point	123-125°C

Studies on drug and Excipients Compatibility:

FTIR:

FTIR spectroscopy was used to ensure that there were no chemical interactions between the drug and the polymer. All Rivastigmine characteristic peaksare present in the physical mixture (NPs), indicating compatibility between the drug and excipients, confirmingthere is no chemical modification of the drug and that its chemistry remained unchanged.

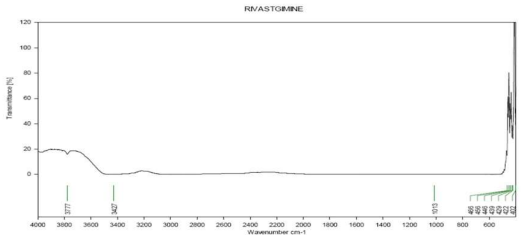

Figure 1: FTIR of Rivastigmine Tartrate

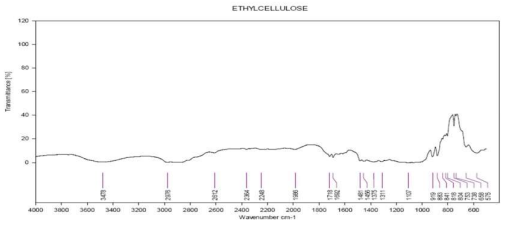

Figure 2: FTIR of Ethyl Cellulose

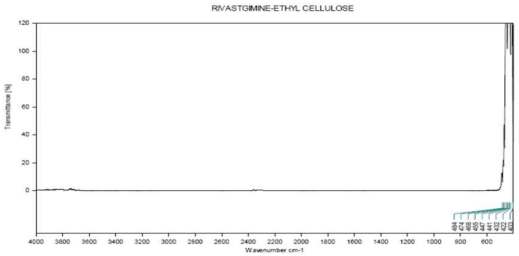

Figure 3: FTIR of Rivastigmine tartrate and Ethyl cellulose

Evaluation of Microspheres:

Linearity plot of Rivastigmine tartrate (phosphate buffer pH-6.8):

A UV spectrophotometer was used to detect the absorbance of the resultant solution at 217nm after rivastigmine tartrate solution was made. The table displays the absorbance which has been noted

Table 3: Linearity plot of Rivastigmine tartrate in pH 6.8 phosphate buffer

Concentrations	Absorbance
5	0.1584
10	0.3212
15	0.4731
20	0.6089
25	0.7834

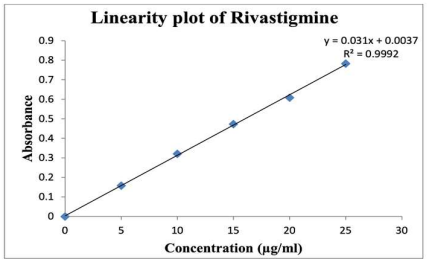

Figure 4: Linearity plot (Rivastigmine tartrate)

Percentage of drug loading and entrapment efficiency:

Table Provides the % of drug loading and entrapment for three batches.

Table 4: Percentage loading and percent entrapment of Rivastigmine tartrate microspheres (RTM)

Formulation	Yield %	Drug Loading	Entrapments
F1	45.0	17.80	35.80
F2	56.6	20.68	62.04
F3	62.5	22.30	89.30

Mean Particle Size

Optical microscopy was used to determine the mean and average particle size. The final results are shown in table

Table 5: Mean particle size of RTM

S.No	Mixtures	Mean particle (µm)
1	F1	9.82
2	F2	22.07
3	F3	50.41

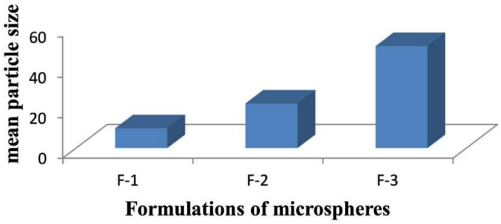

Figure 5: Mean particle size of microspheres

SEM

The microspheres created using the solvent evaporation process displayed smooth surface,

good sphericity, and evenly distributed particles free of lumps. The below figure contains the scanning electron micrographs.

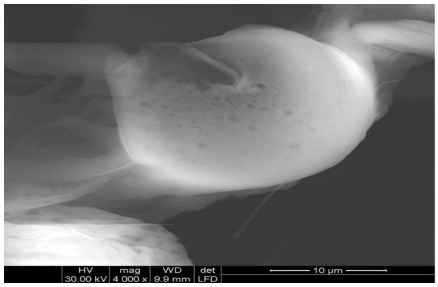

Figure 6: SEM photograph of Rivastigmine tartrate microspheres

In-vitro release studies

Rivastigmine tartrate microspheres were released in vitro for eight hours in a pH 6.8 phosphate buffer.

Table 6: Dissolution conditions

Medium	PH6.8 Phosphate Buffer
Apparatus	Paddle (USP apparatus II)
RPM	50
Temperature	37.0±0.5°C
Time	8hrs
Capacity	0.9l
Sampling period	1hr,2hr,3hr,4hr,5hr,6hr,7hr, and 8hr

Table 7: Cumulative drug release of rivastigmine tartrate microspheres

Time (hour)	**% Cumulative drug release**		
	F1	**F2**	**F3**
0	0	0	0
1	15.97	12.64	9.66
2	17.44	19.01	21.04
3	23.29	25.40	25.93
4	26.24	33.38	32.46
5	45.23	54.09	40.62
6	65.70	66.87	50.41
7	75.98	71.72	58.58
8	81.90	78.16	73.27

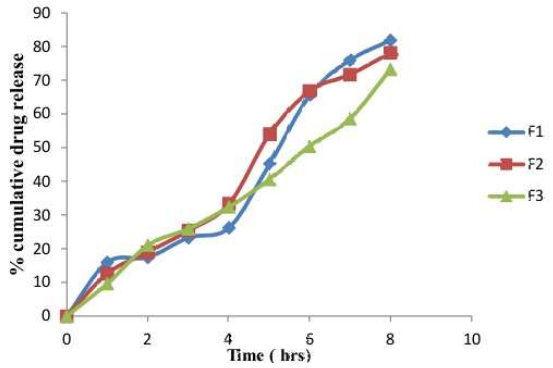

Figure 7: In-vitro drug release Rivastigmine tartrate microsphere

Rivastigmine tartrate containingethyl cellulose microspheres release kinetic graphs

Zero Order

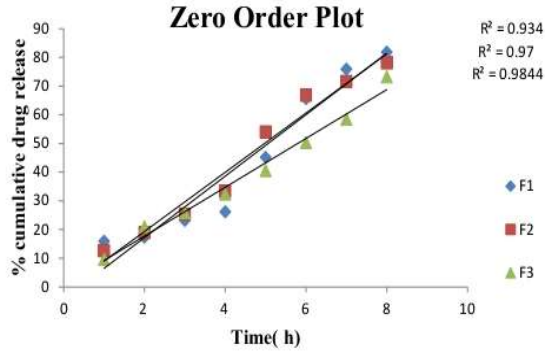

Figure 8: Zero order release of Rivastigmine tartrate microspheres

First Order

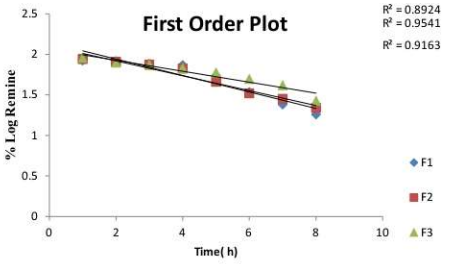

Figure 9: First order of Rivastigmine tartrate microspheres

Higuchi Plot

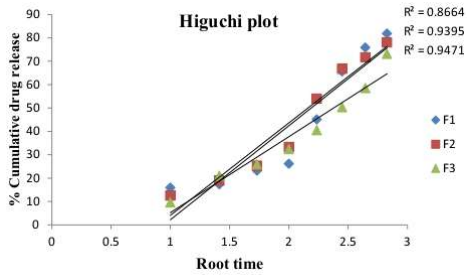

Figure 10: Higuchi plot of Rivastigmine tartrate microspheres

Peppas Plot

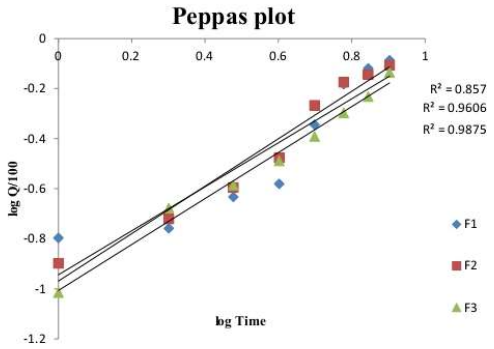

Figure 11: Peppas plot of Rivastigmine tartrate microparticles

Table: Drug release Kinetics of Rivastigmine tartrate microparticles

Formulation	Zero-order R^2	First-order R^2	Higuchi-plot R^2	Peppas-plot		
				R^2	K	N
F1	0.934	0.829	0.866	0.857	11.387	0.878
F2	0.970	0.954	0.939	0.960	10.754	0.947
F3	0.987	0.916	0.947	0.984	9.853	0.918

SUMMARY AND CONCLUSION

Rivastigmine tartrate is an acetyl butylcholinesterease inhibitor of the carbamate type. Though to Facilitecholinergic neurotransmission by slowing the degradation of Ach released by cholinergic neurons.

The current study used ethyl cellulose polymer to create Rivastigmine tartrate microspheres. For bulk drugs, preformulation studies were conducted. Rivastigmine tartrate microspheres were prepared and tested. All the microsphere formulations entrapment efficiencies were determined to be F1 35.80, F2 62.04, and F3 22.30. All the microsphere formulations percentage drug loading was found to beF1 17.80, F2 20.68, and F3 22.30. All the microsphere formulations had a yieldpercentage of F1 45.0, F2 56.6, and F3 62.5. Dissolution tests on formulations revealed that the drugs released in 8 hours werebF1 81.9, F2 78.16, and F3 73.27.

The percentage of the drug release versus time dissolution profile graph was plotted for each formulation. The F3 displays the trustworthy results after all parameters mentioned above were taken into consideration.

Therefore, the F3 formulation can be used for additional researchprojects like stability studies, preclinical and clinical research.

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