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FORMULATION AND CHARACTERIZATION OF RIVASTIGMINE NANOPARTICLES

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Abstract:

Nanoformulations have the potential to greatly improve our understanding of the causes and treatments for neurodegenerative and other disorders. Many factors were effectively tuned in developing novel nanoformulations for treating Alzheimer's disease using this approach. The coated nanoparticles were created using a set core-to-polymer ratio of 1:1, which controls the release pattern of the drug contained for an extended length of time. The coated nanoparticles that were produced had a size of less than 200 nm and slowly released the drug from the 66.83% drug-entrapped nanoparticles over 24 hours (98.46%). The best formula was selected because it was physically and chemically stable throughout three months at various temperatures. Thus, to get around the drug's low bioavailability problems, produced rivastigmine nanoparticles could be employed as an alternative delivery mechanism.

Keywords: *Nanoformulations, Alzheimer's disease, Rivastigmine, core-to-polymer ratio, drug release.*

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INTRODUCTION:

Alzheimer's disease (AD) is a neurological disorder that gradually impairs thinking, learning memory, and intellectual abilities as well as the capacity to do even the most basic tasks. Most individuals with late-onset symptoms often begin to show symptoms in their mid-60s [1]. The primary cause of the irreversible decline in cognitive function is the presence of plaques and tangles in the brain's hippocampus. The global prevalence of AD is estimated to be over 24 million, and as the world's population ages, the disease is predicted to rise every 20 years. Alzheimer's disease and head injuries have been linked in numerous studies; lifestyle, environmental, and genetic variables may also be involved. A head injury that leaves the victim unconscious may cause AD [2].

Additional environmental factors that raise concerns include age of the mother at delivery, occupational exposure to solvents and glues, gender, antacid use, and alcohol use, as well as smoking, aluminum absorption, zinc, and lower educational attainment [3]. The protein beta-amyloid, which is found outside neurons and is referred to as beta-amyloid plaques or neuritic plaques, and an aberrant version of the protein tau, which is found inside neurons and is referred to as tau tangles or neurofibrillary tangles, are said to have accumulated in cases of AD [4]. This beta-amyloid buildup affects several factors, including neuron-to-neuron communication, synapses' functionality, which results in information transfer failure at synapses, a reduction in the number of synapses, and neuron/cell death, which impairs memory and other functions. It also causes inflammation and oxidative stress [5]. Tau tangles create a microtubular malfunction, which results in blocked nutrition and other critical chemical supplies in the neuron, leading to cell death. The brain of an AD patient exhibits cell shrinkage and neuronal death. The brain of an AD patient exhibits cell shrinkage and neuronal death.

Rivastigmine is a carbamate-type cholinesterase inhibitor hypothesized to promote cholinergic neurotransmission by delaying the breakdown of acetylcholine produced by cholinergic neurons. One of the early pathophysiological symptoms of AD is memory loss caused by selective degradation of cholinergic neurons in the cerebral cortex, nucleus basalis, and hippocampus Rivastigmine enhances cholinergic function by reversibly inactivation of cholinesterase enzymes which is responsible for hydrolysis of acetylcholine at cholinergic synapses and hence, enhance concentration of acetylcholine at cholinergic synapses [6]. Therefore, rivastigmine may be able to improve the cognitive deficiencies caused by cholinergic mechanisms in dementia linked to Parkinson's and Alzheimer's diseases.

Despite the technical advancements and developments in the field of brain research, the issues of targeting drugs to the brain remains a very challenging domain and demands greater attention from formulation scientists [7]. The underdevelopment of these pharmacological categories is indicated by an examination of the global market trends for CNS pharmaceuticals. This is primarily because of the failure of most of the new drug molecules to permeate through the blood-brain barrier (BBB) for effective delivery. According to published research, nearly all large drug molecules were unable to pass the blood-brain barrier (BBB); only small drug molecules with exceptionally high lipid solubility and low molecular mass (<400–500 Daltons) succeeded [8]. Unfortunately, only a small number of brain disorders, including epilepsy, chronic pain, and depression, actually react well to small molecules. However, the traditional low lipid-soluble small molecular therapies do not work well for severe brain illnesses including AD, brain cancer, spinal cord injury, etc.

The principle cause of clinical failure of much therapeutically effective drug moiety not only goes to its potency but for too much extent it depends on the drug delivery methods to the brain. Therefore, the major challenges in the brain targeting of drugs are not only to overcome the resistance of BBB but also to develop suitable drug delivery systems with various innovative routes and drug delivery techniques [9]. Subsequently, numerous approaches have been designed and investigated for this purpose and have been described in recent reviews. The use of nanocarriers based on lipids, polymers, proteins, exosomes, nano-emulsions, nano-suspensions, viral vectors, etc. is new hopes on the horizon that are gaining much interest from researchers nowadays. Polymeric nanoparticles may be one of the solutions to overcome the problem associated with brain drug delivery [10].

MATERIALS AND METHODS:

Sigma Aldrich Bangalore, India was used to get rivastigmine tartrate (purity > 98%). Across Organics Ltd supplied the low molecular weight chitosan. From Evonik India in Mumbai, India, we were able to get some Eudragit NE 30D. We got our P 80 and glutaraldehyde from Industrial Grade in Indore, India. The liquid paraffin was purchased from Central Drug House in New Delhi, India, and came in two different

weights.

Preparation of Nanoparticles by Chitosan:
Ten millilitres of a 0.5% acetic acid solution containing 3 mg/ml of precisely measured medicine and chitosan were mixed, the pH was brought down to 4.6 using 10 N NaOH, and the mixture was filtered through a 0.45-micron filter. Chitosan nanoparticles loaded with rivastigmine tartrate were prepared using the specified approach. The emulsion crosslinking agent was used in their creation. The chitosan needed to be thoroughly dissolved, thus the sonication process was prolonged until a clear gel was created. Next, in a beaker, combine Polysorbate 80 with liquid paraffin [11]. And mixed well to get a consistent result. For the next ten to fifteen minutes, the drug-polymer solution was slowly introduced to the external oil phase while being continuously stirred at rpm. The emulsion is stirred for another three to five hours while the glutaraldehyde solution is slowly added to promote cross-linking. After 20 minutes, the nanoparticles had settled out of the solution thanks to gravity. We discarded the supernatant and used a vacuum filter to isolate the nanoparticles and trace quantities of oil that remained. After being freeze-dried at 60 ℃ for 24 hours, the nanoparticles were washed four to five times with petroleum ether to eliminate any remaining oil residue. After that, it was allowed to air-dry for 24 hours before being placed in a cold, dry location.

In Vitro Release:
Dialysis tube technique to investigate the in vitro release of rivastigmine. Accurately measure out 2 milliliters of a 6.4-pH nasal fluid solution containing 6 milligrams of the medication [12]. The temperature of the receiver fluid was kept constant at 37 0.5 ℃. Using the beer-Lambert's Law equation, we took 3 ml of sample solution from the receptor compartment at various times.

Entrapment Efficiency:
Weigh accurately 50mg of nanoparticles and dissolve them in 50 ml of acetonitrile and shake with a magnetic stirrer then keep aside for some time between 2-4 hours followed by filtration then the concentration of the drug in acetonitrile and quantified at 220 nm by using UV Spectrophotometer to know the amount of drug in the nanoparticles.

The Optimised Nanoparticles' Coating:
Nanoparticles are coated using the emulsion solvent evaporation method. Acetone may dissolve Eudragit NE 30D. To determine the impact of medication release, nanoparticles are made in a variety of ratios. The coating's exterior phase is liquid paraffin, and the emulsifier is Polysorbate 80. To coat the core, the optimized batch D6 was selected, and the required amount of polymer was dissolved in acetone before the previously prepared chitosan nanoparticles were gradually mixed in [13]. Following two hours of magnetic stirring at a constant speed, the blend was gradually added to a liquid paraffin and Polysorbate 80 solution to evaporate the acetone. Following recovery by centrifugation, the cured nanoparticles were sprayed three times with petroleum ether to remove the oil. Following their lyophilization, the nanoparticles were stored in a refrigerator. Several coating polymer-eudragit to nanoparticle mass ratios of 1:1 (batch C1), 1:3 (batch C2), and 1:5 (batch C3) was experimented with to create coated nanoparticles.

Polydispersity Index (PDI):
The size distribution of the nanocarriers and their degree of heterogeneity are described. The composition of the nanocarriers and the properties of the detergents utilized in them are only two of the many variables that affect this. Invariant size distribution is shown by a PDI of 0.0, whereas multiple size distribution is indicated by a PDI of 1.0. The most often accepted and respectable value for polymer-based nanocarriers is 0.2 PDI, whereas the most commonly accepted and respectable value for lipid-based nanocarriers is PDI [14].

Zeta potential:
The nanoparticles' surface charge is another crucial criterion for a roundabout assessment of their stability. Particles having a zeta potential of 30.20mV are less stable than those with a zeta potential of 5mV or below [15]. Particles having zeta potentials between -30mV and 30mV are said to be the most prone to aggregation. The opposite is true for particles with a zeta potential greater than 60 mV.

FTIR Analysis:
Similarities between the observed and reported FTIR spectra of the medication are noticeable. All of the necessary peaks of the pure medication were present in the spectra of the improved nanoparticles' formulation, although with a modest decrease in peak strength. In addition, no indication of a change in the drug's signature peaks was seen [16]. This means that the prepared formulation has no excipients that are incompatible with the medication.

In Vitro Mucoadhesion Testing:
In vitro muco-adhesion testing was undertaken to evaluate the ability of coated nanoparticles to remain

adhered to the nasal mucosa over a prolonged length of time [17].

Coated nanoparticles release rivastigmine in vitro:
Collective rivastigmine release patterns of coated nanoparticles and uncoated nanoparticles are provided [18]. Due to their ability to reduce mucociliary clearance, increase membrane permeability, and disrupt, chitosan and its derivatives have been widely used as mucoadhesive agents to increase the nasal absorption of hydrophilic drugs and macromolecules.

SEM Analysis:
Scanning electron microscopy was cast off to examine the nanoparticles after they were created. According to scanning electron micrographs, the size of the optimal uncoated nanoparticles.

Zeta potential, particle size, and particle size distribution:
Malvern Zeta Seizer (Nano ZS, Malvern & Worcestershire, UK) was used to assess the particle sizes of drug-free and drug-loaded NPs [19].

DSC Analysis of Nanoparticle Formulation:
An aluminum crucible cell was filled with a sample weighing between 2 and 5 mg, and the cell's lid was tightly crimped to create a tight seal. The samples were heated at a predetermined rate of 10 ℃/min from room temperature to 400 ℃.

Stability studies:
The optimized loaded formula's stability analysis during three months tested monthly at two distinct temperatures. At 25 ℃ and at 4 ℃ [20].

RESULTS AND DISCUSSION:

Preparation of Rivastigmine-Loaded Nanoparticle Design:

Table 1: Formulation of Rivastigmine Loaded Nanoparticles by Box Behnken design

Run	A-Drug: Polymer ratio	B- Stirrer speed (rpm)	C- Crosslinking time (hr)	Y1- Drug release (%)	Y2- % Entrapment Efficiency
F1	1	500	3	65.34	70.74
F2	3	1000	3	59.82	55.12
F3	3	1000	3	67.13	70.377
F4	3	1000	3	62.17	68.32
F5	3	500	4	68.12	61.572
F6	3	500	2	92.46	83.56
F7	3	1000	3	80.31	61.28
F8	3	1500	2	63.24	68.907
F9	3	1000	3	58.36	67.44
F10	3	1500	4	53.02	66.81
F11	5	1000	2	62.45	69.2

The Optimised Nanoparticles' Coating
To prolong the release of the nanoparticles, coating polymers were applied to the drug-loaded optimized chitosan nanoparticle [81]. Because Eudragit is frequently used as a coating material in the pharmaceutical industry.

Table 2: Zeta potential and particle size of coated nanoparticles

Batches	Particle size	Zeta potential
C1	165.3 ± 32.1	22 ± 4.6
C2	161.4 ± 33.3	21 ± 3.8
C3	154.2 ± 30.7	19 ± 2.1
C4	151.9 ± 28.5	18 ± 5.2
C5	148.9 ± 29.2	20 ± 5.8
C6	143.2 ± 28.4	21 ± 3.2
D1	173.4 ± 41.1	19 ± 3.6
D2	182.3 ± 40.9	18 ± 4.8
D3	191.1 ± 43.9	22 ± 5.2

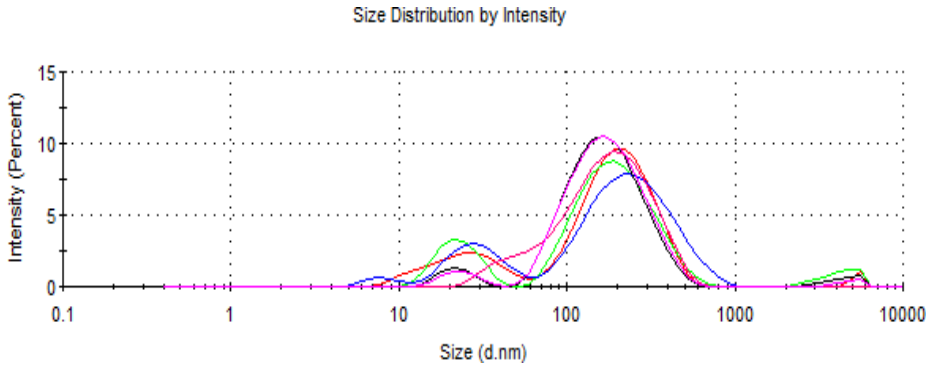

Figure 1: Spectrum of polydispersity of particles

FT-IR Spectroscopy:

The major peaks, which represent the main functional groups in pure rivastigmine, are located at 3318 cm-1 for N-H stretching, 1715 cm-1 for C=O stretching (the carbamate band), 1401 cm-1 for C-N stretching in tertiary amines, and 954 cm-1 for =C-H bending. Additional vibrational bands are visible as a result of the stretched vibrational bands of the structural aromatic ring's C=C, the tartrate's O-H band, and the produced N-H between the tartrate and the drug [82,83,84].

Additionally, there was no indication that the drug's typical peaks had shifted. Therefore, it can be said with certainty that the medication and other excipients utilized in the improved formulation did not have any compatibility problems.

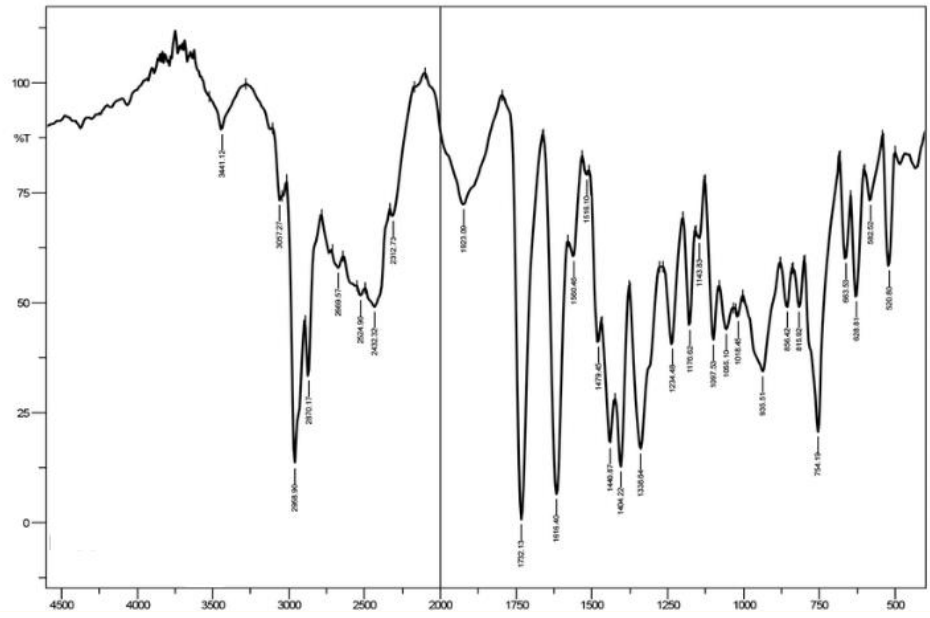

Figure 2: FTIR spectra of Rivastigmine tartrate

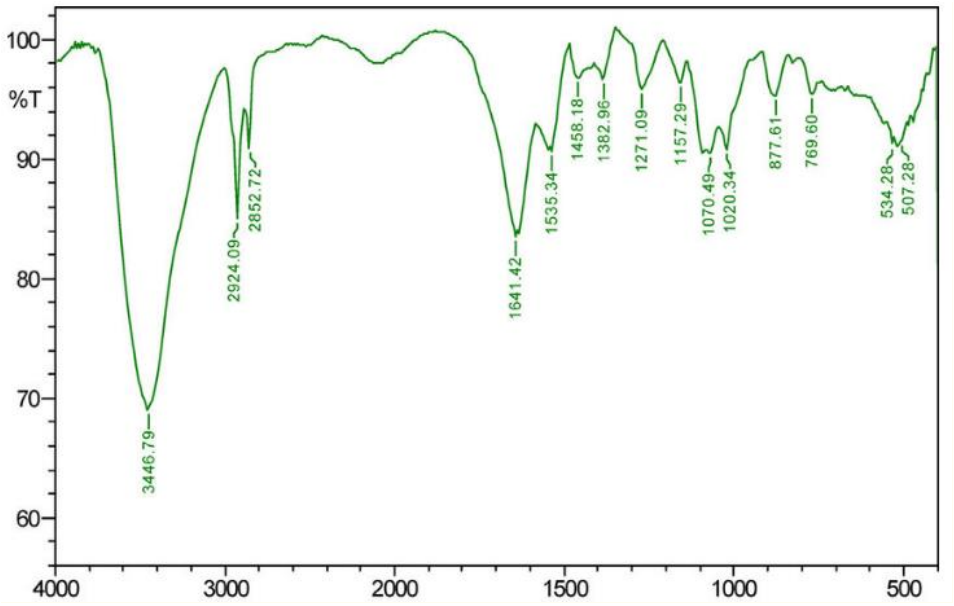

Figure 3: FTIR spectra of chitosan

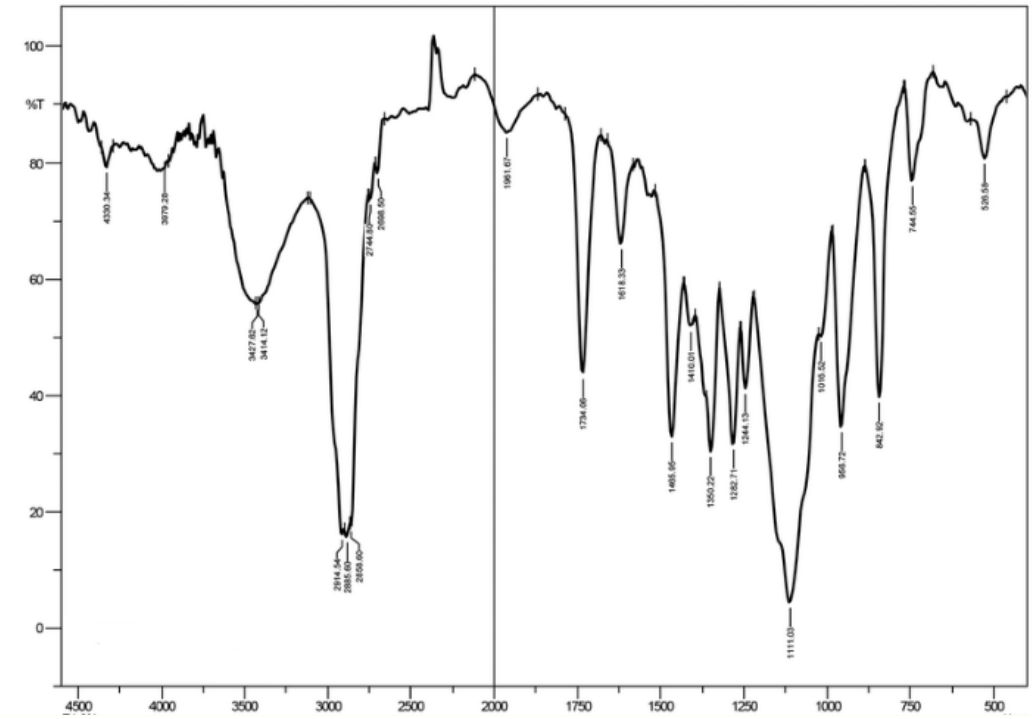

Figure 4: FTIR Rivastigmine-loaded nanoparticles (batch C6)

In vitro release study of Rivastigmine from the Coated Nanoparticles

The three batches of eudragit-coated nanoparticles (batches D1, D2, and D3) as well as the uncoated batch C8's cumulative rivastigmine release profiles are shown in Figure 18.Chitosan and its derivatives have been examined extensively as mucoadhesive agents to improve the nasal absorption of hydrophilic drugs and macromolecules because of their capacity to decrease mucociliary clearance, increase membrane permeability, and disrupt the formation of tight junctions in naso-respiratory epithelial cells. Using the dialysis sac method, rivastigmine loaded in uncoated chitosan nanoparticles released just 85% of its full

dose during 24 hours, according to statistics.

Eudragit coating decreased the release rate of the entrapped medication, possibly as a result of covering the chitosan nanoparticles with an extra barrier. Over 24 hours, the coated formulations' cumulative release of rivastigmine was 98.46%, 91.53%, and 74.13%, with core-to-coat ratios of 1:1, 1:3, and 1:5, respectively.

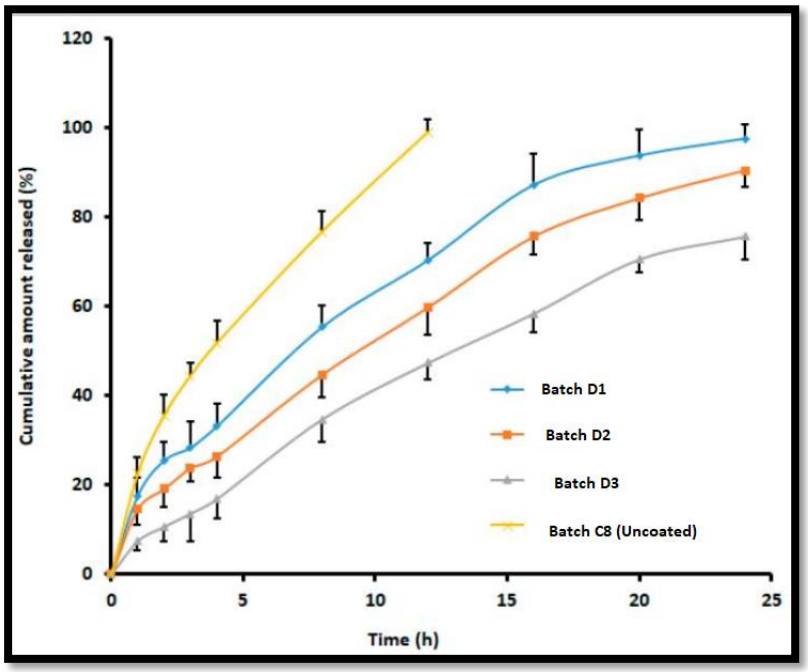

Figure 5: Comparing the cumulative percentage of rivastigmine release between control (uncoated) batches and batches with various core-to-coat ratios. Batch D1 (eudragit nanoparticle, NE 30D 1:1), batch D2 (eudragit nanoparticle, NE 30D 1:3), and batch D3 (eudragit nanoparticle, NE 30D 1:5). The statistics show a mean SD of six trials.

Release kinetics:
The kinetics of release for batch D1 were assessed [87,88]. The r2 value, the sum of squares of residuals (SSR), and the Fischer Ratio (F) were evaluated in order to select the best fit models and avoid errors in the release mechanism prediction. The data indicate that the Korsmeyer-Peppas model has a higher F value (10.34), a lower SSR value (86.72), and a higher r2 value (0.990). The observed n value (0.563) indicates that anomalous transport was the diffusion mechanism. Thus, it was determined that the Korsmeyer-Peppas matrix diffusion-controlled mechanism was used to control the release of rivastigmine from batch D1.

Particle Size, Particle Size Distribution, and Zeta Potential:
Figures 4.18 and 4.19 display the distribution of zeta potential and particle size for coated and uncoated batches, respectively. Nanoparticles with an average size of 144.2 ± 28.4 nm and a polydispersity index (PDI) of 0.24± 0.03 were observed in the designed batch D1 (uncoated), whereas batch C6 (coated) showed nanoparticles with an average size of 175.4± 41.1 nm and a PDI of 0.19 ± 0.03 (indicating a narrow and uniform size distribution of particles).

The zeta potential readings for coated and uncoated nanoparticles showed all positive values and were more than 18± 3.6 mV, demonstrating the stability of the particles and preventing aggregation behaviour.

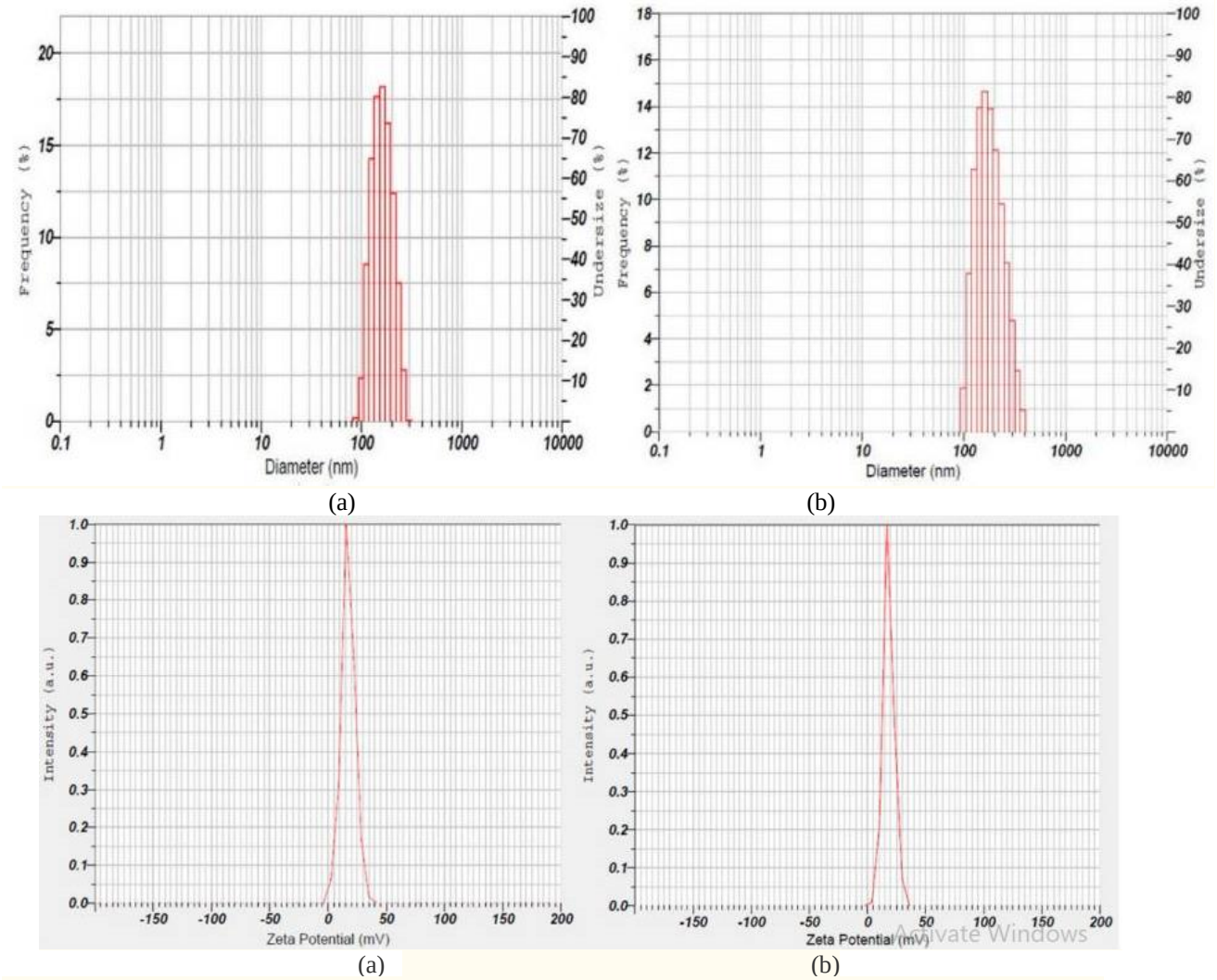

Figure 6: Representative size distribution and zeta potential distribution pictures of (a) uncoated (batch C6), (b) coated nanoparticles (batch d1).

SEM Analysis of the Nanoparticles:

SEM was used to evaluate the surface and form of the produced nanoparticles (Figure 4.20 a, b). The SEM micrographs showed that the optimised uncoated nanoparticles (batch C6) were around 145 nm in size; however, following coating, the size increased to about 175 nm. According to the findings of further analysis, every coated nanoparticle that was produced was less than 200 nm. The information provided in the literature is in agreement with our findings.

Additionally, the SEM pictures show the formed nanoparticles' spherical morphology. Additionally, the image (Figure 4.20 b) shows that the chitosan nanoparticles have a flawless coating, indicating that the coating process was carried out correctly.

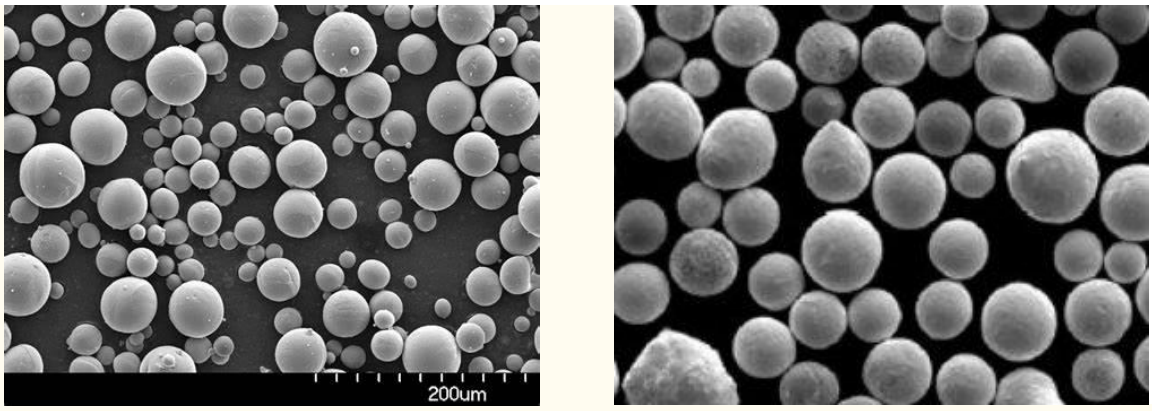

Figure 7: Illustrative images taken using a scanning electron microscope of untreated (batch C6) and coated (batch D1) nanoparticles.

DSC Analysis of Nanoparticle Formulation

The drug, physical mixture, and nanoparticle formulation (batch D1) DSC thermograms are shown in Figure 4.21. Rivastigmine tartrate's melting point is verified by the thermogram, which shows a noticeable endothermic peak at 126.02 ℃. The physical mixing confirms that there are no interactions between the medication and polymers. The drug has a definite endothermic peak at 126.02 ℃, whereas chitosan and eudragit EPO exhibit broad and reduced endothermic peaks in the region of 180-220 ℃ and 260-300 ℃, respectively.

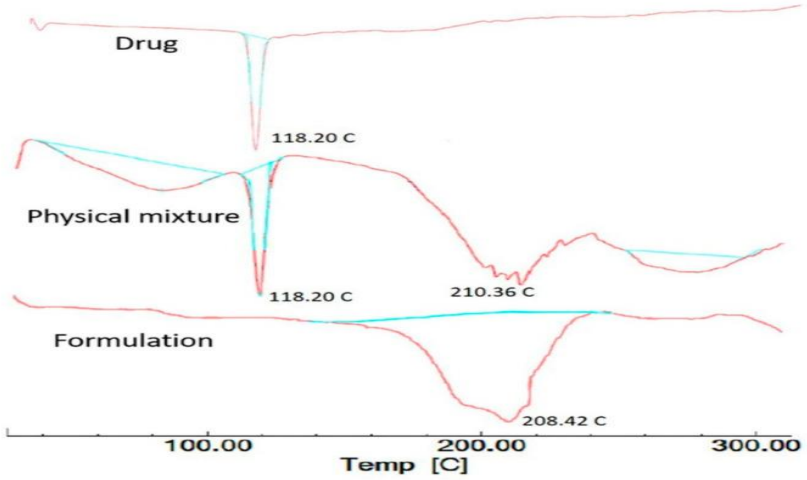

Figure 8: DSC patterns of rivastigmine tartrate, physical mixture, and optimized nanoparticle formulation (batch D1).

Stability studies:

The optimised loaded formula's stability analysis during a three-month period, tested monthly at two distinct temperatures. At 25 ℃, the average Nano size was 172.59± 40.33 nm, while at 4 ℃, it was 197.57± 33.40 nm. There was no appreciable change in Zeta potential and the PDI was around 0.02.

Table 3: Stability Study of the optimum loaded nano dispersions (D1) over three months at 4 °C and ambient room temperature; (n=3)

At 4 °C	Particle size (nm)	PDI	Zeta potential (mV)
On the spot	198.4 ± 41.1	0.28 ± 0.03	22± 3.34
1st Month	198.12±25.12	0.28±0.031	21.93±0.535
2nd Month	197.43±30.51	0.27±0.0245	21.34±0.750
3rd Month	196.34±36.90	0.27±0.045	20.98±0.512
At room temperature			
On the spot	173.4 ± 41.1	0.24 ± 0.03	19.56± 3.4
1st Month	172.8±20.11	0.23±0.127	18.89±0.52
2nd Month	172.2±45.00	0.22±0.043	18.53±0.91
3rd Month	171.96±55.13	0.22±0.065	17.9±0.76

n= number of determination; mean±Standard Deviation

SUMMARY AND CONCLUSION:

Nanoformulations have the potential to greatly improve our understanding of the causes and treatments for neurodegenerative and other disorders. Many factors were effectively tuned in the development of novel nanoformulations for the treatment of Alzheimer's disease using this approach. Pharmaceutical quality by design was used to successfully optimise rivastigmine-loaded chitosan nanoparticles. The preliminary optimization procedure revealed the impact of formulation factors, including various medication and polymer concentrations, stirring speed, and crosslinking duration on the product quality. The coated nanoparticles were created using a set core-to-polymer ratio of 1:1, which controls the release pattern of the drug contained for an extended length of time.

The produced coated nanoparticles had a size of less than 200 nm and slowly released the drug from the 66.83% drug-entrapped nanoparticles over 24 hours (98.46%). The best formula was selected because it was physically and chemically stable throughout three months at various temperatures. Thus, to get around the drug's low bioavailability problems, produced rivastigmine nanoparticles could be employed as an alternative delivery mechanism.

REFERENCES:

1. Qiao R, Jia Q, Huwel S, Xia R, Liu T, Gao F, Galla HJ, Gao M. Receptor-mediated delivery of magnetic nanoparticles across the blood-brain barrier. *ACS nano*. 2012Apr24;6(4):3304-10
2. Hladky SB, Barrand MA. Mechanisms of fluid movement into, through and out of the brain: evaluation of the evidence. *Fluids and Barriers of the CNS*. 2014Dec;11:1-32
3. Pinheiro RG, Coutinho AJ, Pinheiro M, Neves AR. Nanoparticles for targeted brain drug delivery: what do we know?. *International Journal of Molecular Sciences*. 2021Oct28;22(21):11654
4. Teixeira MI, Lopes CM, Amaral MH, Costa PC. Current insights on lipid nanocarrier-assisted drug delivery in the treatment of neurodegenerative diseases. *European journal of pharmaceutics and biopharmaceutics*. 2020Apr1;149:192-217
5. Pardridge WM. Brain drug targeting: the future of brain drug development. *Cambridge University Press*. 2001 May 31
6. Li X, Tsibouklis J, Weng T, Zhang B, Yin G, Feng G, Cui Y, Savina IN, Mikhalovska LI, Sandeman SR, Howel CA. Nano carriers for drug transport across the blood-brain barrier. *Journal of drug targeting*. 2017Jan2;25(1):17-28
7. Patel M, Souto EB, Singh KK. Advances in brain drug targeting and delivery: limitations and challenges of solid lipid nanoparticles. *Expert opinion on drug delivery*. 2013Jul1;10(7):889-905
8. Bicker J, Alves G, Fortuna A, Falcão A. Blood-brain barrier models and their relevance for a successful development of CNS drug delivery systems: a review. *European Journal of Pharmaceutics and Biopharmaceutics*. 2014Aug1;87(3):409-32
9. Abbott NJ. Blood-brain barrier structure and function and the challenges for CNS drug delivery. *Journal of inherited metabolic disease*. 2013May;36:437-49
10. Naqvi S, Panghal A, Flora SJ. Nanotechnology: a promising approach for delivery of

neuroprotective drugs. *Frontiers in Neuroscience*. 2020Jun9;14:494
11. Feng L, Wang H, Xue X. Recent progress of nanomedicine in the treatment of central nervous system diseases. *Advanced Therapeutics*. 2020May;3(5):1900159
12. Nguyen TT, Nguyen TT, Vo TK, Nguyen MK, Van Vo T, Van Vo G. Nanotechnology-based drug delivery for central nervous system disorders. *Biomedicine & Pharmacotherapy*. 2021Nov1;143:112117
13. Dhiman N, Awasthi R, Sharma B, Kharkwal H, Kulkarni GT. Lipid nanoparticles as carriers for bioactive delivery. *Frontiers in chemistry*. 2021Apr23;9:580118
14. Haider M, Abdin SM, Kamal L, Orive G. Nanostructured lipid carriers for delivery of chemotherapeutics: A review. *Pharmaceutics*. 2020Mar;12(3):288
15. Duan Y, Dhar A, Patel C, Khimani M, Neogi S, Sharma P, Kumar NS, Vekariya RL. A brief review on solid lipid nanoparticles: Part and parcel of contemporary drug delivery systems. *RSC advances*. 2020;10(45):26777-91
16. Salunkhe SS, Bhatia NM, Bhatia MS. Implications of formulation design on lipid-based nanostructured carrier system for drug delivery to brain. *Drug Delivery*. 2016May3;23(4):1306-16
17. Costa CP, Moreira JN, Lobo JM, Silva AC. Intranasal delivery of nanostructured lipid carriers, solid lipid nanoparticles and nanoemulsions: A current overview of in vivo studies. *Acta Pharmaceutica Sinica B*. 2021Apr1;11(4):925-40
18. Costa CP, Barreiro S, Moreira JN, Silva R, Almeida H, Sousa Lobo JM, Silva AC. In vitro studies on nasal formulations of nanostructured lipid carriers (NLC) and solid lipid nanoparticles (SLN). *Pharmaceuticals*. 2021Jul23;14(8):711
19. Costa C, Moreira JN, Amaral MH, Lobo JS, Silva AC. Nose-to-brain delivery of lipid-based nanosystems for epileptic seizures and anxiety crisis. *Journal of Controlled Release*. 2019Feb10;295:187-200
20. Satapathy MK, Yen TL, Jan JS, Tang RD, Wang JY, Taliyan R, Yang CH. Solid lipid nanoparticles (SLNs): an advanced drug delivery system targeting brain through BBB. *Pharmaceutics*. 2021Jul31;13(8):1183.