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DESIGN AND IN-VITRO EVALUATION OF RASAGILINE ETHOMOSOL DRUG DELIVERY SYSTEM FOR ENHANCED BRAIN TARGETING

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Abstract:

The present study aimed to formulate and evaluate Rasagiline-loaded ethosomes using varying concentrations of lipids to improve drug delivery and therapeutic efficacy. Four formulations (F1–F4) were prepared and characterized for physicochemical properties, drug-excipient compatibility, particle size, zeta potential, entrapment efficiency, in vitro drug release, and stability studies. Preformulation studies confirmed the suitability of Rasagiline for ethosomal formulation development. The drug was found to be a white to off-white crystalline powder with a melting point range of 148–152°C. UV spectrophotometric analysis showed a maximum absorbance at 210 nm in phosphate buffer pH 7.4, and the calibration curve exhibited good linearity within the concentration range of 10–50 µg/mL with an R^2 value of 0.997. FTIR studies confirmed the compatibility between Rasagiline and the selected excipients without any significant interactions. Particle size analysis revealed nanosized vesicles ranging from 186 to 253 nm, while zeta potential values indicated good formulation stability. SEM analysis confirmed the spherical morphology and smooth surface characteristics of the ethosomes. Entrapment efficiency ranged from 79.50% to 85.10%, with formulation F4 showing the highest entrapment efficiency (85.10%). In vitro drug release studies demonstrated sustained drug release, with formulation F4 exhibiting the highest cumulative drug release of 98.32% over 8 hours. Accelerated stability studies performed for three months under ICH conditions confirmed the stability of the optimized formulation. Based on the overall findings, formulation F4 was identified as the optimized ethosomal formulation with desirable physicochemical characteristics, high entrapment efficiency, enhanced drug release, and satisfactory stability. Therefore, Rasagiline-loaded ethosomes may serve as a promising vesicular drug delivery system for improving therapeutic outcomes.

Keywords: *Rasagiline, Ethosomes, Vesicular Drug Delivery System, Entrapment Efficiency, In Vitro Drug Release, Stability Studies.*

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INTRODUCTION:

The definition goes. Ethosomes are a kind of noninvasive medication delivery vehicle that can penetrate several layers of skin and/or the bloodstream. The active substances can be more effectively delivered by means of these pliable, supple vesicles. For a long time, the vesicles' role in cellular communication and particle transport was widely recognised. Because vesicles keep the medication protected from the immune response and other removal systems, they would also make it possible to manage the release rate of the drug over an extended period of time, allowing for the release of precisely the right amount of drug while maintaining that concentration constant. The discovery of a vesicle derivative called an ethosome was a big step forward in the study of vesicles. A little tweak to the tried-and-true drug carrier liposome yields ethosome. Ethosomes are lipid vesicles that contain water, phospholipids, and relatively high concentrations of alcohol (ethanol and isopropyl alcohol). Phospholipids, ethanol (in larger amounts), and water make up the soft vesicles known as ethosomes. Ethosomes can range in size from tens of nanometres (nm) to microns (μ). They have a much higher transdermal flux and can penetrate the skin layers much more quickly.

Composition of Ethosomes

1. **Phospholipids (main vesicle-forming agents)**
   - Examples: Phosphatidylcholine (soy or egg lecithin), phosphatidylserine, phosphatidylglycerol.
   - Role: Form the lipid bilayer that entraps the drug.
2. **High concentration of ethanol (20–45% v/v)**
   - Role:
   - Provides flexibility and fluidity to the lipid bilayer.
   - Acts as a penetration enhancer, increasing permeability of skin lipids.
3. **Water (or aqueous phase)**
   - Purified water or buffer.
   - Role: Hydrates the vesicles and provides the medium for dispersion
   - Optional/Additional Components

- **Drug/Active ingredient** – the therapeutic agent to be delivered.
- **Cholesterol** – sometimes added to improve vesicle rigidity and stability.
- **Propylene glycol or other glycols (optional)** – can act as co-solvents or additional penetration enhancers.
- **Surfactants or stabilizers (optional)** – e.g., poloxamers to prevent aggregation.

Advantage of high alcohol content

There is a significant amount of ethanol (20-50%) in ethosomes, and it is known to be an effective permeability enhancer. Many people thought that vesicles couldn't survive in environments with high concentrations of ethanol because of the way it interdigitated lipid bilayers. Ethosomes were termed by Touitou[20] after the lipid vesicular structures he found and studied that contained ethanol at quite high concentrations. Liposomes and ethosomes differ primarily in their chemical makeup. It was postulated that the improved skin penetration ability of ethosomes was due to the synergistic effect of a mixture of vesicles containing relatively high concentrations of ethanol (20–50%). It is possible that the ethosomal formulation's high ethanol concentration (20-50%) will disrupt the organisation of the skin's lipid bilayer. Hence, it may enable vesicles to cross the SC when contained within their membranes. The ethosomal lipid membrane was also just as stable as normal vesicles, although being packed less densely, because of the high concentration of ethanol. In turn, this made the structure more pliable and supple, which gave the membrane greater leeway and stability, allowing it to fit through the tiny gaps left by the disrupted SC lipids. Furthermore, ethosomal formulations could have their vesicular character altered by adjusting the component ratios and phospholipid chemical structures. Reports showing improved distribution of numerous medications, including acyclovir, minoxidil, triphexyphenidyl, testosterone, cannabidol, and zidovudine, demonstrate the adaptability of ethosomes for systemic delivery.

MATERIALS:

Rasagiline was procured from Synpharma Research Labs, Soya lecithin and Ethanol, were obtained from Synpharma Research Labs, Hyderabad. Other chemicals and the reagents used were of analytical grade.

METHODOLOGY:

Procedure

Using the cold technique, ethosomal formulations were created. When preparing ethosomal material, this is the approach that is most frequently utilised. In a covered jar, the phospholipids and other pharmaceutical ingredients mentioned in the table were dissolved in ethanol while vigorously stirring at room temperature. A closed container was used to gradually add a fine stream of distilled water while stirring continuously at 100 rpm. The liquid was then heated to 300C ± 10C. The mixing process was kept going for another 5 minutes with the system maintained at a temperature of 300 C ± 10C. Following a 30-minute cooling period at ambient temperature, the mixture was subjected to five cycles of sonication at 40 C, with a one-minute interval between each cycle, using a probe sonicator.

S.No	Ingredients	F1	F2	F3	F4
1	Rasagiline	10	10	10	10
2	Phosphotidyl choline	100	200	300	400
3	Ethanol	20	20	20	20
4	Water	q.s	q.s	q.s	q.s

CHARACTERIZATION

Particle size:

The size of each batch of ethosomes was examined under a microscope. The average size of the ethosomes was calculated by collecting a little drop of ethosomes from each batch and measuring them at several locations on the slide.

SEM analysis

Using a scanning electron microscope, the shape of ethosomes was examined. A sputter coater was used to apply a layer of gold particles to the surface of the lyophilised sample that had been deposited on aluminium stubs. A scanning electron microscope (SEM) (XL30, Philips, the Netherlands) operating at 15 kV and 750 mA was used to ascertain the Ethosomes' form.

Zeta Potential:

The charges on the surface of ethosomes are referred to as the zeta potential. How frequently an electron is present on an ethosome's surface. The component or ingredient employed in the production process is the source of this charge. All of the ethosomes in the formulation must have an electrical charge on their surfaces so that the ethosomes can repel each other and prevent the particles from clumping together. We used a zeta sizer equipment with Malvern software to measure the zeta potential of ethosomes. The sample was analysed at 25oC with a detection angle of 90o. A zeta potential value between +30 and -30 mV is good. Within these limits, Ethosomal particles are unable to clump together.

Entrapment efficiency

If you want to know how effective the entrapment process is, you have to divide a known quantity of the created formulation (such a nanoparticle or vesicular suspension) into two parts: the unentrapped drug and the drug linked with the carrier. Centrifugation, ultrafiltration, or dialysis are the primary methods for separation; high-speed centrifugation is often used for vesicular systems such as liposomes or niosomes. It is common practice to use UV-visible spectrophotometry to determine the amount of free drug after meticulously collecting and analysing the supernatant, which includes the unentrapped or free drug. The entire amount of drug in the formulation can be found by dissolving or breaking down the particles or vesicles and then measuring the amount of drug that remains. The formula is then used to calculate entrapment efficiency:

Entrapment efficiency (%)=Total drug−Fre e drug/Total drug×100

As a measure of the loading capacity and overall effectiveness of the formulation, this percentage indicates the amount of the initial medication dose that is really trapped within the delivery system.

In-vitro Drug release studies:

Utilising a modified Franz type glass diffusion cell, an in-vitro investigation of drug penetration through the Dialysis membrane was conducted. To keep the sink state, the modified cell is used, which has a higher capacity of 10 ml. The spectrophotometric analysis was used to determine the drug content in the samples. Refilling the receptor phase with phosphate buffer of the same volume was done with each sample removal.

Stability studies:

To define an appropriate shelf life and suggested storage conditions, stability studies are conducted to ascertain the quality variations of a medicinal substance or medication product over time in response to environmental elements including light, humidity, and temperature. Preparation of a stability protocol outlining the quantity of batches, type of packaging, storage conditions, testing intervals, and acceptability criteria is the first step in the study, as per ICH Q1A(R2) recommendations. The batches that will be sold or used as a pilot are sealed in the designated commercial container and kept in stability chambers under specific conditions. These conditions can be long-term (25 ± 2 °C / 60 ± 5% RH for 12-24 months), accelerated (40 ± 2 °C / 75 ± 5% RH for 6 months), or intermediate (30 ± 2 °C / 65 ± 5% RH) in nature.

RESULTS AND DISCUSSION:

Particle Size Analysis

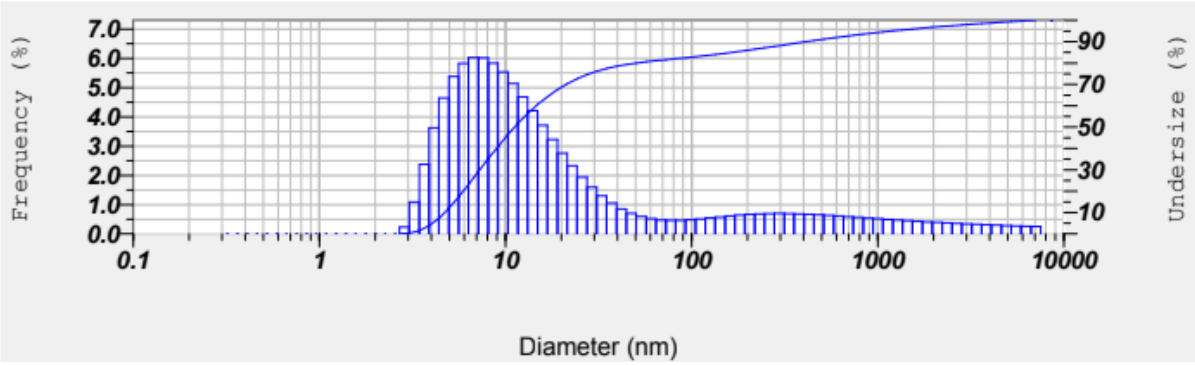


Fig-1: Particle size analysis of Optimized ethosomes

Zetapotential

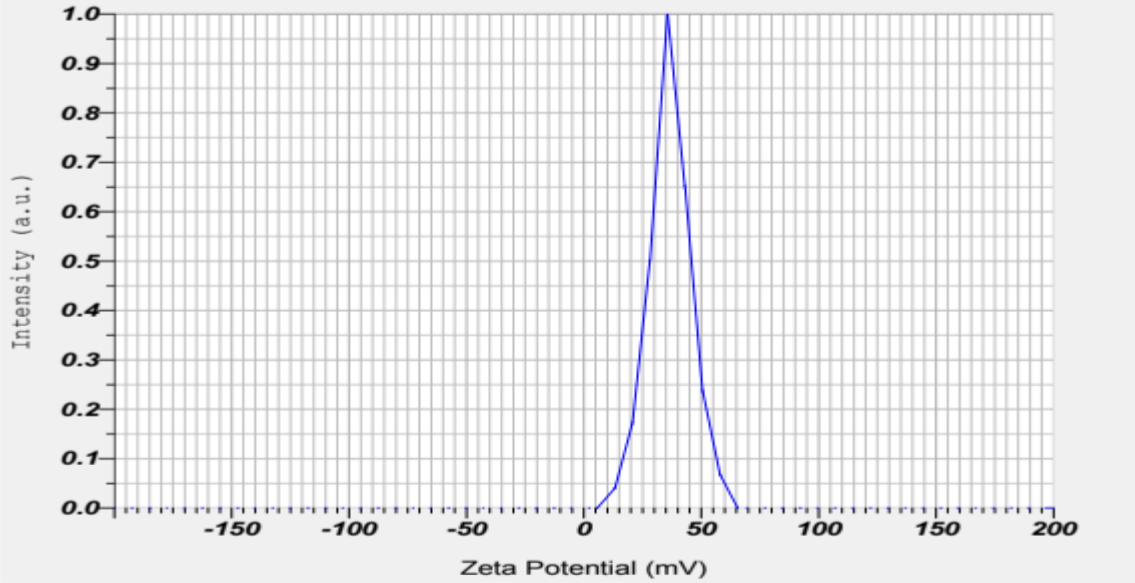


Fig-2: Zetapotential of Optimized formulation

Table-2: Evaluation Studies of particle size and Zeta potential Ethosomes

F. No	Particle size (nm)	Zeta potential
F1	232	-21
F2	253	-24
F3	201	-28
F4	186	-32

SEM Analysis

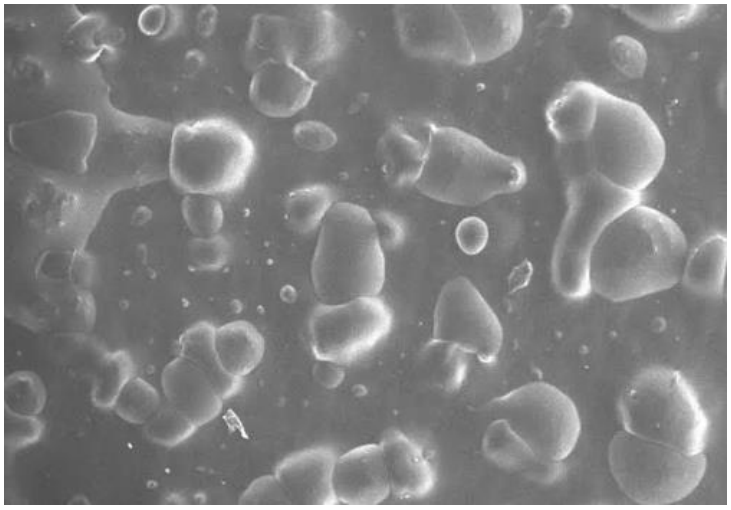


Fig-3: SEM Analysis of Ethosomes

SEM images confirm the spherical morphology of ethosomes.Smooth surfaces suggest uniform vesicle formation without significant aggregation.The vesicle sizes observed under SEM are consistent with particle size measurements, confirming reliability of results.

Entrapment Efficiency:

Table-3: Drug entrapment efficiency

F. code	Drug entrapment efficiency
F1	82.63
F2	79.50
F3	81.36
F4	85.10

Drug entrapment efficiency (EE) ranged from 79.50% to 85.10% .Higher EE indicates effective incorporation of Rasagiline into the lipid bilayer of ethosomes.F4 (85.10%) showed the highest entrapment, possibly due to optimal lipid-to-drug ratio.Higher EE% contributes to improved drug stability and controlled release.

In vitro release study:

Phosphate buffer pH 7.4 was used as medium for the release studies and good linearity was observed in the plotted standard graph with a correlation coefficient of 0.998.

Table-4: In vitro drug release profiles of Rasagiline Ethosomes (F1-F4)

Time	F1	F2	F3	F4
0	0	0	0	0
1	16.10	16.54	17.25	19.20
2	27.09	28.65	29.66	29.55
3	36.38	37.05	38.05	38.10
4	42.55	44.92	45.25	48.47
5	54.98	55.94	56.50	58.92
6	67.10	68.69	69.10	78.21
7	81.23	81.34	82.10	85.82
8	92.69	93.20	95.32	98.32

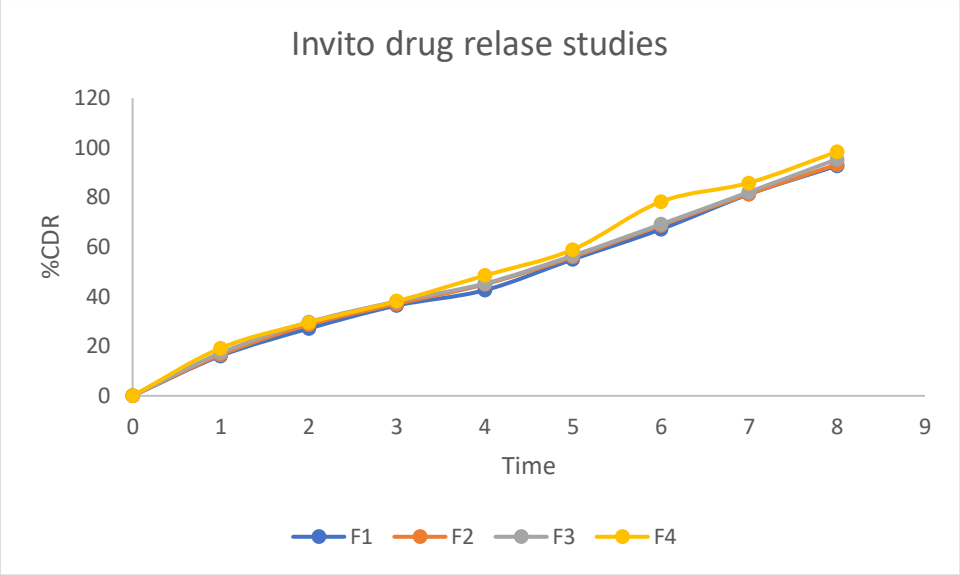


Fig-4: In vitro drug release studies of F1-F4 formulations

Stability studies

Optimized formulations F4 was selected for accelerated stability studies as per ICH guidelines.

Table-5: Stability studies of optimized formulations at 40 ± 2 ^{0}C and 75 ± 5% RH for 3 months

Formulation Code	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-4	98.32	96.45	95.52	94.69	Not less than 85 %
F-4	98.32	96.40	95.43	94.32	Not less than 85 %
F-4	98.32	96.38	95.20	94.12	Not less than 85 %

SUMMARY AND CONCLUSION:

The present study was undertaken to formulate and evaluate Rasagiline-loaded ethosomes using varying concentrations of lipids. Four formulations (F1–F4) were successfully prepared and evaluated for their physicochemical properties, drug-excipient compatibility, particle size, zeta potential, entrapment efficiency, in vitro drug release, and stability.Preformulation studies confirmed the suitability of Rasagiline for ethosomal formulation development. Organoleptic evaluation revealed that Rasagiline was a white to off-white crystalline powder, which was odorless and tasteless in nature. The melting point was found to be in the range of 148–152°C, indicating the purity of the drug sample. Solubility studies demonstrated that Rasagiline was freely soluble in water and methanol, soluble in ethanol (95%), and practically soluble in chloroform. The calibration curve of Rasagiline in phosphate buffer pH 7.4 showed good linearity at 210 nm within the concentration range of 10–50 µg/mL, with a correlation coefficient (R^2) value of 0.997, confirming adherence to Beer-Lambert's law.

FTIR studies demonstrated the compatibility between Rasagiline and the selected excipients. No significant shifts, disappearance, or appearance of new peaks were observed in the physical mixture, confirming the absence of chemical interactions and indicating the stability of the drug during formulation.Particle size analysis revealed that the ethosomal vesicles were in the nanometric range of 186–253 nm. Among all formulations, F4 exhibited the smallest particle size (186 nm) and a zeta potential value of -32 mV, indicating good physical stability and reduced vesicle aggregation. SEM analysis confirmed the spherical morphology and smooth surface characteristics of the prepared ethosomes.Entrapment efficiency values ranged from 79.50% to 85.10%, with formulation F4 exhibiting the highest entrapment efficiency (85.10%), indicating effective incorporation of Rasagiline into the ethosomal vesicles.In vitro drug release studies carried out using phosphate buffer pH 7.4 demonstrated sustained drug release from all formulations over a period of 8 hours. Formulation

F4 showed the highest cumulative drug release of 98.32%, indicating superior release characteristics compared to other formulations.Accelerated stability studies conducted on the optimized formulation (F4) under ICH-recommended conditions of 40 ± 2°C and 75 ± 5% RH for three months demonstrated no significant changes in the formulation characteristics. The optimized formulation maintained drug release above the specified limit of 85%, confirming its stability throughout the study period.Based on the overall evaluation, formulation F4 was identified as the optimized ethosomal formulation due to its desirable particle size, high entrapment efficiency, suitable zeta potential, enhanced in vitro drug release profile, and satisfactory stability. Therefore, Rasagiline-loaded ethosomes may serve as a promising vesicular drug delivery system for improving therapeutic efficacy and patient compliance. However, further in vivo studies are recommended to establish the clinical potential and therapeutic effectiveness of the developed formulation.

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