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Development of Intranasal Deformable Ethosomes of Rasagiline Mesylate for The Effective Management of Parkinsonism

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Abstract
Intranasal deformable ethosomes for Rasagiline mesylate was developed for effective treatment of Parkinson's disease. Ethosomes were prepared by ethanol injection method. D-optimal design was applied for formulation optimization. Ethanol, propylene glycol and phospholipids were selected as independent variables while encapsulation efficiency (EE) of the ethosomes as dependent variable. The optimum formulation of RM ethosomes, in which ethanol (34.3%), propylene glycol (13.2%) and phospholipids (4.1%) has higher EE of 38% with spherical bilayered structure revealed from TEM analysis, average particle size range of 256 nm and zeta potential values obtained as -24.4mV. Further *in- vitro* drug diffusion studies were carried out through nasal mucosa of sheep and the cumulative amount diffused was reported as 766µg/cm^2. These results confirmed that ethosomes has potential for nose to brain delivery system of Rasagiline mesylate for treatment of Parkinson's disease.

Keywords
Intranasal, Ethosomes, Parkinson's disease, Rasagiline mesylate, D- optimal design, Entrapment efficiency.

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INTRODUCTION:
Parkinson's disease (PD) is a progressive neurodegenerative disorder that was first described by Sir James Parkinson as a "shaking palsy" in 1817.[1] an increase in life expectancy, future demographic projections predict a larger population of Indians over age of 60 years with a corresponding increase in the number of PD patients. PD is now known to be caused primarily by destruction of the A9 tract of dopamine neurons that project from the substantia nigra pars compacta (SNc) to the corpus striatum (made up of the caudate nucleus and putamen in primates). These areas of the brain are a major part of the basal ganglia circuitry that is crucial to the extrapyramidal control of movement, as such motor abnormalities (bradykinesia, resting tremor, postural instability, rigidity) are the major symptoms of PD. Generally, when greater than half of these SN dopamine neurons are lost then symptoms of the disease start to manifest in an individual, as 50-60% nigral cell loss results in 70-80% dopamine depletion.[2] This is the greatest problem in curing PD, as the patient is already in an advanced stage of neuronal death when symptoms of the disease

present themselves. At this point, it is too late to undo the loss of dopamine neurons that has already occurred, but not too late to prevent further loss and worsening of symptoms.

Rasagiline (as the mesylate), a propargylamine-based drug indicated for the treatment of idiopathic Parkinson's disease. It is designated chemically as: 1H-Inden-1amine, 2, 3-dihydro-N-2-propynyl-, (1R)-, methane sulfonate. The empirical formula of rasagiline mesylate is $(C_{12}H_{13}N)CH_4SO_3$ and its molecular weight is 267.34..

Ethosomal systems are novel lipid vesicular carriers containing a relatively high percentage of ethanol. These Nano carriers are especially designed for the efficient delivery of therapeutic agents with different physicochemical properties into deep skin layers and across the skin. Different preparation techniques are used in the preparation of these novel carriers. For ease of application and stability, ethosomal dispersions are incorporated into gels, patches, and creams. Highly diverse in vivo models are used to evaluate their efficacy in dermal/ transdermal delivery, in addition to clinical trials. With optimized formulations, intranasal administration presents many benefits when compared to alternative delivery routes. These include: 1) Not only is the nasal cavity easily accessible, it is virtually non-invasive 2) In most cases, intranasal administration is well tolerated 3) Only slight irritation may occur due to the chemical nature of substance delivered 4) Hepatic first-pass metabolism is avoided with intranasal delivery 5) Destruction of drugs by gastric fluid is not a concern 6) Intranasal mucosa has a big number of microvilli, therefore has a high surface area (150 cm^2); Therefore prime aim of this study is to formulate and evaluate deformable ethosomal formulation containing Rasagiline mesylate intended for nose to brain delivery.

MATERIALS AND METHODS:

Rasagiline Mesylate was gift sample from Dr. Reddy's Pharma Pvt. Ltd India. Soya lecithin was procured from Sonic Biochem Extractions Limited, Indore. Ethanol, Propylene glycol Sodium chloride, Potassium dihydrogen ortho phosphate, Sodium hydroxide pellets, Anhydrous-di sodium hydrogen phosphate was purchased from from S.D. Fine chemicals, Mumbai. All other chemicals were of analytical grade.[3,4]

Method of preparation:

The ethosomal formulation was prepared according to the method reported by Touitou *et al.* The ethosomes system prepared here was comprised of 1-5% phospholipids, 17-50% ethanol, drug, 0-30%propylene glycol and water to 100% w/w. Phospholipids and drug were dissolved in ethanol-propylene glycol mixture. The mixture was heated to 30^0c in a water bath.[26,27,28] The double distilled water heated to 30^0c was added slowly in a fine stream with constant mixing at 700 rpm in a closed vessel. Mixing was continued for an additional 15mins. The system was kept at 30^0c throughout preparation. The formulation was sonicated at 4^0c using bath sonicator for 20 mins. Then again preparation was sonicated at 4^0c using probe sonicator in 3 cycles of 5min with 5min rest between cycles at 40W[5,6,7]

Evaluation of of Rasagiline mesylate ethosomes

1.Determination of encapsulation efficiency (EE)

The encapsulation efficiency (EE) of ethosomes was determined by an ultracentrifugation method. First, Ultra centrifugal units were filled with 2ml vials samples of ethosomes.[31,33] After centrifugation at 15,000 rpm for 60 min in a cooling microfuge ("Microfuge" M/S Remi instruments Pvt. Ltd. Maharashtra, India), the supernatant was diluted with buffer and UV spectrometry analysis was carried out. The EE of the vesicles was then calculated, based on the following formula:

EE% = (1–Concentration of free drug/total Concentration of drug) ×100%

The results are expressed as the means of three independent measurements of Rasagiline mesylate was quantified using a UV visible spectrophotometer. [8]

2. Vesicle size distribution

The size distribution and polydispersity index (PDI) of vesicular delivery systems were determined by Malvern Mastersizer 2000 (Malvern Instruments, UK). Principle on which instrument works is laser diffraction. Measures particle size distributions by measuring the angular variation in intensity of light scattered as a laser beam passes through a dispersed particulate sample. Large particles scatter light at small angles relative to the laser beam and small particles scatter light at large angles.[9] The angular scattering intensity data is then analyzed to calculate the size of the particles responsible for creating the scattering pattern, using the Mie theory of light scattering. The particle size is reported as a volume equivalent sphere diameter.[37,38,41]

3. Zeta-potential determination.

Zeta potential of the vesicles was determined using Zetasizer (Nano-ZS, Malvern, U.K.). The magnitude of the zeta potential gives an indication of the potential stability of the colloidal system. If all the particles in suspension have a large negative or positive zeta potential then they will tend to repel each other and there will be no tendency for the particles to come together.[10] However, if the particles have low zeta

potential values then there will be no force to prevent the particles coming together and flocculating. The measurements were made in triplicate.

Morphological characterization.

Morphological analysis of RM loaded ethosomes was performed using transmission electron microscopy (Tecnai G2 Spirit Bio Twin; FEI, Czech Republic).[11] Samples of ethosomes formulation (10µl) were dropped onto copper grids. After complete drying, the samples were stained using 2 wt. % aqueous uranyl acetate. After staining images was captured by Veleta camera fitted with instrument.[44,46,47]

5. Reproducibility test

Once all the process parameters were assessed, the experiment under the optimum conditions was repeated three times in order to study the technique reproducibility

6. *Ex vivo* permeation studies of ethosomes:

The ex vivo permeation study was carried out following the procedure described by Steffen Lang et al[51]. Tissue with nasal mucosa was excised from the noses of freshly slaughtered sheep. After removing the skin, tissue containing nasal mucosa was cut off with a sharp knife from the frontal part of the nasal conch (conchae nasals dorsales) above the os incisivum starting from the incisura nasoincisiva.[12] The excised tissue was stored on ice during transport to the laboratory. At no more than 30 min after the excision, the mucosa was separated from the underlying cartilage by blunt stripping using a pair of tweezers. Samples were taken and inserted into the diffusion chambers, the apical side of the tissue typically facing the donor compartment.[13] The ethosomes equivalent to 2 mg of Rasagiline mesylate was place on the upper side of the nasal mucosa. The donor and the receiver compartment containing 10 ml of pH 7.4 phosphate buffer saline were kept in intimate contact and the temperature was maintained at 32^0C. The whole assembly was kept on a magnetic stirrer and stirred continuously. The samples were withdrawn at definite time intervals and equal amount of the phosphate buffer saline was replaced. The transport rate k was determined from the slope obtained by linear regression of the fraction of the drug absorbed as a function of time.[14]

RESULT AND DISCUSSION:

Optimization:

The mathematical models generated were validated by preparing three new formulations which differed totally in composition and processing time from the model formulations. A numerical optimization technique employing desirability approach was used to locate the optimum setting of the new formulation various feasibility and grid searches were executed to establish the composition of these optimized formulations.[15] The three new formulations developed were evaluated and the experimental value of the responses was compared with those predicted and by the mathematical models. The optimized formulation of Rasagiline mesylate loaded ethosomes was having composition with ethanol 34.5%, propylene glycol 13.2%, and phospholipids 4.1% was found to fulfill the requisites of an optimum formulation**.**

Effect on encapsulation efficiency:

EE is expressed as fraction of drug incorporated into ethosomes relative to total amount of drug used. EE for all batches was found to be in the range of 13-38%. The process variables were found to have an insignificant effect on EE. However observed high EE may be attributed to optimum concentration of ethanol (34.2%) and phospholipids (4.1%) in formulation.[16]

Particle size analysis:

PSD (particle size distribution), is a list of value or mathematical function that defines the relative amount of particles present according to the size. Particle size analysis has shown that particles have average diameter 256 nm which is suitable for passive targeting of the ethosomes following nasal administration to brain. The peak obtained from analysis indicates uniformity of the particle size.[17,18]

Transmission Electron Microscopy (TEM):

Transmission Electron Microscopy (TEM) studies were carried out for optimized formulations. Ethosomes of batch with optimized amount of ethanol and phospholipid were found to be spherical with bilayer and existed as discrete entities.[19] The picture showed the morphology of ethosmes which was revealed by transmission electron microscopy as shown in Figure.

In vitro diffusion study of Rasagiline mesylate Ethosomes formulations:

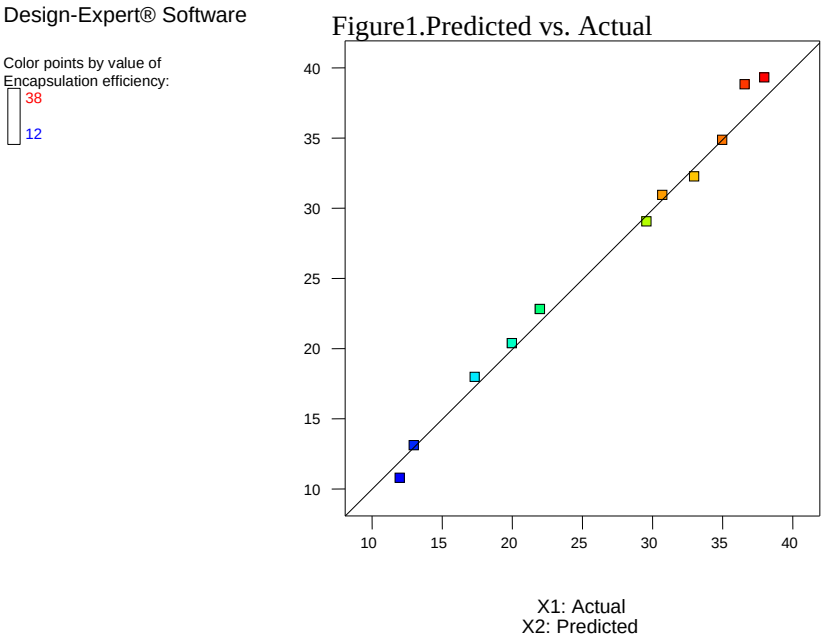
Diffusion studies of optimized ethosomal formulation were performed using nasal mucosa as a barrier. In an optimized ethosomal formulation the amount of drug diffused through nasal mucosa showed better result that is 766µg/cm^2 within time interval of 6 hours with comparison to rasagiline mesylate solution.[20] This may be explains by the fact that dead nasal mucosa cells are not capable of undergoing the endocytosis process which could enhance the permeation of ethosomes *in-vivo.* Incorporation of drug to ethosomal formulation is likely enhance the permeation through nasal mucosa. Ethanol and phospholipids both has inherent property to act as permeation enhancer

leads to higher permeation through nasal mucosa. Hence, concentration of drug to be delivered to brain through nasal route can be assumed to be higher.[21,22]

Standard deviation	2.26
Mean	25.63
CV%	8.81
R square	.9641
Adjusted R square	.9385
Predicted R square	.8703
Adeq. Precision	18.593

Table: 1 Summary of results of regression analysis for response encapsulation efficiency

Figure1.Predicted vs. Actual



Equation as follows:

Encapsulation efficiency	=
-0.21457	* A
-0.99751	* B
-161.92281	* C
+0.041571	* A * B
+3.57474	* A * C
+3.60616	* B * C

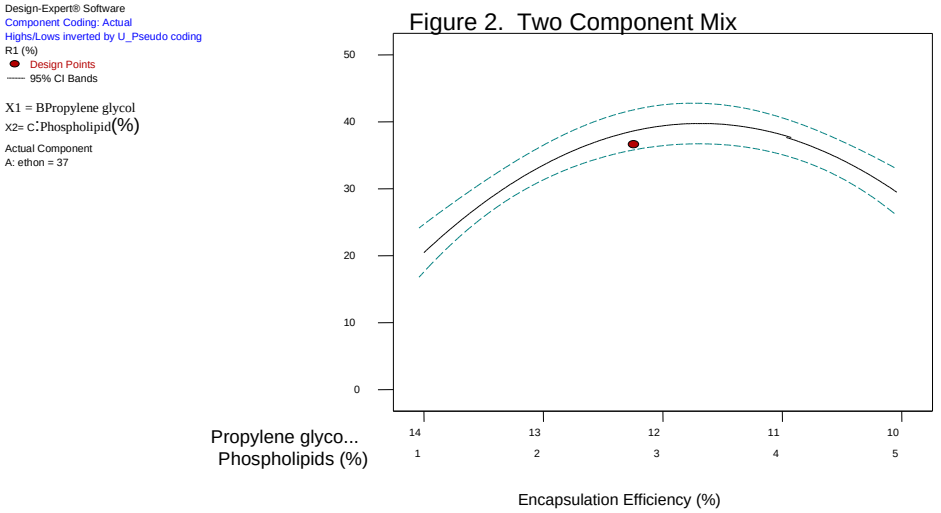


Figure 2. Two Component Mix

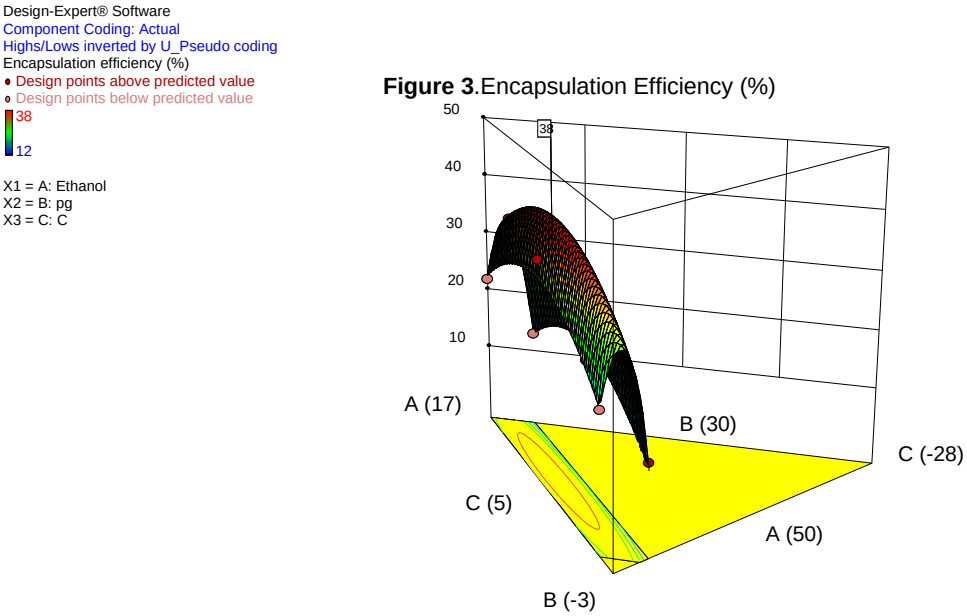


Figure 3.Encapsulation Efficiency (%)

Component	Name	Units	Type	Minimum	Maximum	Std. Dev.
A	Ethanol	%	Mixture	17	50	11.8488
B	Propylene glycol	%	Mixture	0	30	11.7478
C	Phospholipids	%	Mixture	1	5	1.70268
				Total =	52.00	

Table 2. Factors and the corresponding levels for the preparation of ethosome formulation by ethanol injection method as per d-optimal design

Optimised formulation composition(x_1:x_2:x_3)	Experimental value	Predicted valve	Percentage prediction error
34.5:13.2:4.1[#]	38	41	-7.31%
31.0: 16.7: 4.2	36	34	5.88
37.3: 12.82: 1.87	34	32.22	5.52

Table 3. Composition of checkpoint formulation, the predicted and experimental value of response and percent prediction error

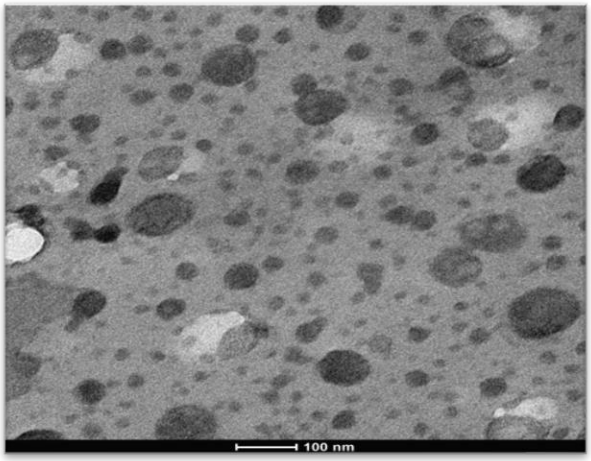


Figure:4 SEM images of Rasagiline mesylate Ethosomes

Time(hours)	Rasagiline mesylate solution(ug/cm^2)	Ethosomes optimized formulation(µg/cm^2)
1	30.66±2.01	115.60±3.10
2	125±1.06	226.87±1.6
3	220.09±1.8	339.10±2.1
4	301.019±2.8	458.27±1.2
5	365.08±3.1	614.34±1.8
6	450.3±1.2	766.56±2.7

Table 4: *In Vitro* Drug Diffusion through Nasal Mucosa:

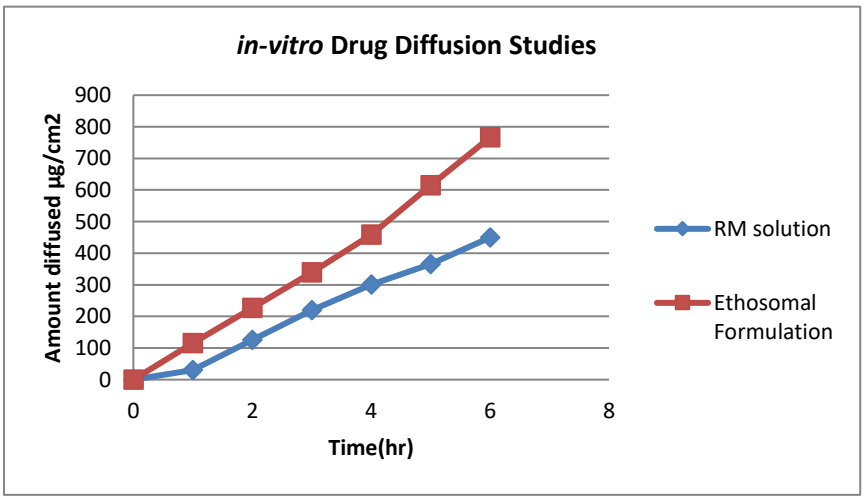
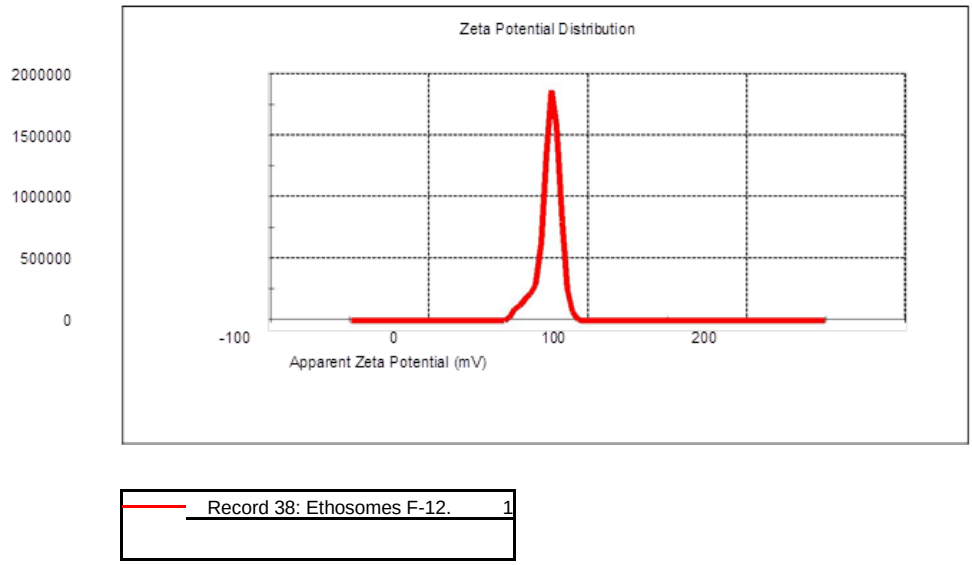


Figure.5 *in- vitro* drug diffusion studies

Zeta potential results for optimised formulation:



	Mean (mV)	Area (%)
Zeta potential (mV): -24.4	Peak 1: -24.4	100.0
Zeta deviation (mV): 6.84	Peak 2: 0.00	0.0
Conductivity (mS/cm): 0.394	Peak 3: 0.00	0.0

Result Quality: Good

CONCLUSION:

This study of rasagiline mesylate loaded ethosomes revealed amelioration in the encapsulation efficiency upon increasing the amount of ethanol and phospholipids to certain extent in preparation .*In-vitro* permeation study through nasal mucosa of goat of RM loaded ethosomes containing Ethanol: propylene glycol: phospholipids (34.5%:13.2%:4.1%) showed superior permeation results as the presence of ethanol in the aqueous compartment of the ethosomal vesicles favoured the encapsulation of RM and enhanced its permeation through nasal mucosa.[23,24,25] Demonstrations of direct delivery of RM into the brain in significant quantities might help further research and more preclinical and clinical studies should also be performed in the near future to establish these formulations in the market on the basis of low risk/high benefit ratio as compared to high risk /low benefit ratio in their present forms.

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