CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187
https://doi.org/10.5281/zenodo.23860261

Available online at: http://www.iajps.com Research Article

DESIGN AND IN VITRO EVALUATION OF FLUOXETINE ETHOSOMAL DRUG DELIVERY SYSTEM FOR BRAIN DELIVERY

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Abstract:

The present study was aimed at the formulation and evaluation of Fluoxetine-loaded ethosomes using varying concentrations of lipids to enhance drug delivery. Four formulations (F1–F4) were prepared and evaluated for physicochemical characteristics, drug-excipient compatibility, particle size, zeta potential, entrapment efficiency, in vitro drug release, and stability studies. Preformulation studies confirmed the purity and suitability of Fluoxetine for formulation development. FTIR studies demonstrated the compatibility between the drug and selected excipients without any significant interactions. The prepared ethosomes exhibited particle sizes ranging from 163 to 228 nm and zeta potential values between −21 and −32 mV, indicating good stability. SEM analysis confirmed the spherical morphology of the vesicles. Entrapment efficiency ranged from 65.80% to 84.50%, with formulation F4 showing the highest entrapment efficiency (84.50%). In vitro drug release studies revealed sustained release behavior, with F4 exhibiting the highest cumulative drug release of 94.2% over 8 hours. Accelerated stability studies conducted on the optimized formulation (F4) demonstrated satisfactory stability over a period of three months. Based on the overall findings, formulation F4 was identified as the optimized ethosomal formulation with desirable physicochemical properties, enhanced drug entrapment, sustained drug release, and good stability. Thus, Fluoxetine-loaded ethosomes may serve as a promising vesicular drug delivery system for improved therapeutic efficacy.

Keywords: *Fluoxetine, Ethosomes, Vesicular drug delivery system, Entrapment efficiency, In vitro drug release, Stability studies.*

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Please cite this article in press ***Bathini Santhoshi*** *et al.,* **Design And In Vitro Evaluation Of Fluoxetine Ethosomal Drug Delivery System For Brain Delivery",.** *Indo Am. J. P. Sci, 2026; 13(10).*

INTRODUCTION:

Ethosomes are soft, malleable, phospholipid-based vesicular drug delivery systems that contain a high concentration of ethanol (usually 20–45%) along with water. They are modified liposomes in which ethanol acts as a penetration enhancer, increasing the flexibility of the vesicles and improving their ability to deliver drugs through the skin.Ethosomes are designed primarily for topical and transdermal drug delivery, as their unique composition allows them to penetrate deeply into the skin layers more effectively than conventional liposomes. The presence of ethanol disrupts the lipid structure of the stratum corneum and enhances vesicle deformability, thereby facilitating improved drug permeation.

Advantages of Ethosomal Drug Delivery

1. Enhanced Skin Penetration

Ethosomes contain a high concentration of ethanol, which disrupts the lipid structure of the stratum corneum and increases membrane fluidity. This allows deeper penetration of the drug into the skin layers.

2. Improved Drug Entrapment Efficiency

Ethosomes can encapsulate both hydrophilic and lipophilic drugs effectively, resulting in higher drug loading capacity compared to conventional liposomes.

3. Increased Vesicle Flexibility

The presence of ethanol makes the vesicles soft and deformable, enabling them to pass through narrow skin pores and intercellular spaces.

4. Sustained and Controlled Drug Release

Ethosomal formulations provide prolonged drug release, reducing the frequency of application and improving therapeutic effectiveness.

5. Reduced Systemic Side Effects

By delivering the drug locally and efficiently to the target site, ethosomes minimize systemic absorption and related adverse effects.

Disadvantages

1. Skin Irritation

High concentration of ethanol (20–45%) may cause skin dryness, irritation, or burning sensation, especially in sensitive individuals.

2. Limited Stability

Ethosomal formulations may undergo vesicle aggregation, fusion, or drug leakage during long-term storage if not properly stabilized.

3. Cost of Phospholipids

Phospholipids used in formulation can be expensive, increasing the overall production cost.

4. Ethanol Evaporation

Loss of ethanol during storage may affect vesicle structure, size, and drug entrapment efficiency.

MATERIALS:

Fluoxetine was procured from Hetero drugs, Hyderabad, Phosphotidyl choline and Ethanol were obtained from Synpharma Research Labs, Hyderabad. Other chemicals and the reagents used were of analytical grade.

METHODOLOGY:

Formulation development

Table-1: Composition of Fluoxetine Ethosomes (F1 to F4)

S.No.	Ingredients	F1	F2	F3	F4
1	Fluoxetine (mg)	20	20	20	20
2	Phosphotidyl choline (mg)	200	300	400	500
3	Ethanol (ml)	3.0	3.0	3.0	3.0
4	Water (ml)	10	10	10	10

Fluoxetine-loaded ethosomes were prepared by the cold method. Accurately weighed quantities of phosphatidylcholine were dissolved in ethanol under continuous magnetic stirring at 700 rpm to obtain a clear alcoholic phase. Separately, Fluoxetine Hydrochloride was dissolved in distilled water to prepare the aqueous phase. The aqueous drug solution was then added slowly in a fine stream to the alcoholic phase under continuous stirring to facilitate the spontaneous formation of ethosomal vesicles. The resulting dispersion was stirred continuously for 30–45 minutes at room temperature to ensure complete mixing and vesicle formation. Subsequently, the formulation was subjected to sonication for 5–10 minutes to reduce vesicle size and obtain a homogeneous dispersion with

improved uniformity. Finally, the prepared Fluoxetine-loaded ethosomal suspension was transferred into suitable airtight containers and stored under refrigerated conditions at 4 ± 2°C until further characterization and evaluation studies.

CHARACTERIZATION

1.Vesicle Size

The average vesicle size of the ethosomal formulation were determined using a particle size analyzer after suitable dilution with distilled water.

2. Zeta Potential

Zeta potential was measured using a zeta sizer to assess the surface charge and physical stability of the ethosomal vesicles.

3. Entrapment Efficiency (%)

Entrapment efficiency of Fluoxetine in ethosomes was determined by separating the unentrapped drug using centrifugation followed by estimation of drug content in the supernatant using a suitable analytical method.

Determination of particle size Size

4. Surface Morphology

The shape and surface morphology of ethosomal vesicles were examined using Scanning Electron Microscopy (SEM).

5. In-Vitro Drug Release Study

In-vitro drug release was carried out using a Franz diffusion cell with an appropriate dialysis membrane and receptor medium maintained at 37 ± 0.5°C.

6. Stability Studies

Stability studies were conducted on the optimized ethosomal formulation under different storage conditions as per ICH guidelines, and changes in vesicle size, entrapment efficiency, and drug content were evaluated.

RESULTS AND DISCUSSION:

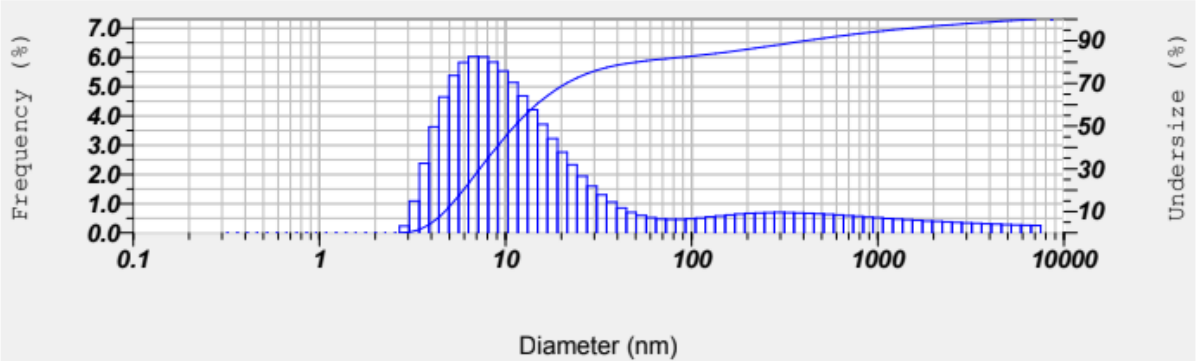


Fig-1: Particle size analysis of Optimized ethosomes

Zetapotential

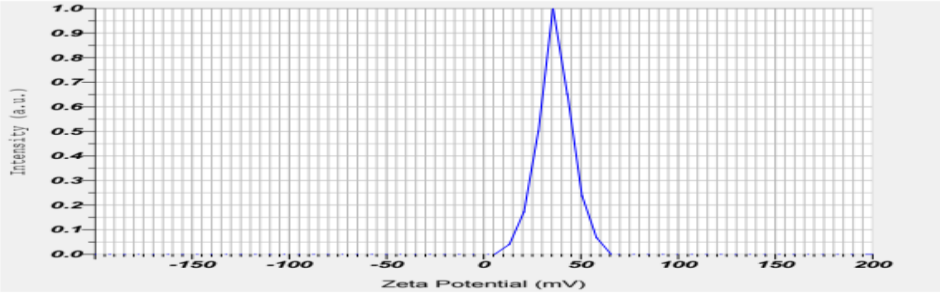


Fig-2: Zetapotential of Optimized formulation

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

F. No	Particle size (nm)	Zeta potential
F1	228	-21
F2	198	-24
F3	176	-28
F4	163	-32

SEM Analysis

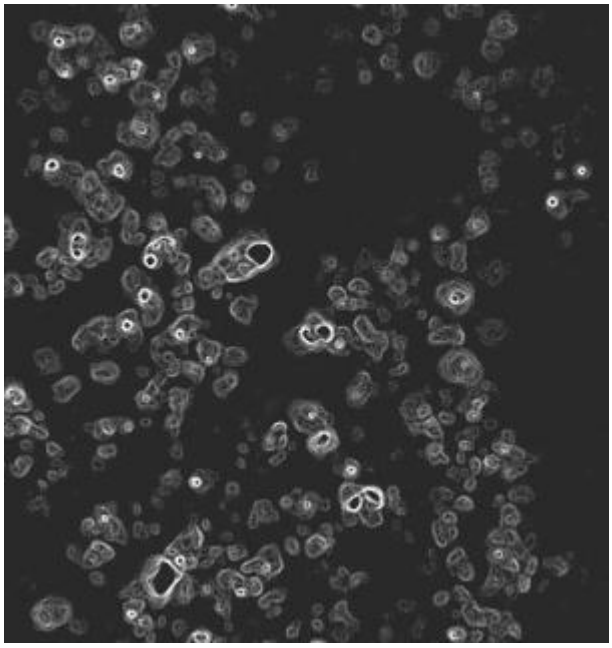


Fig-3: SEM Analysis of Ethosomes

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	65.80
F2	72.30
F3	78.60
F4	84.50

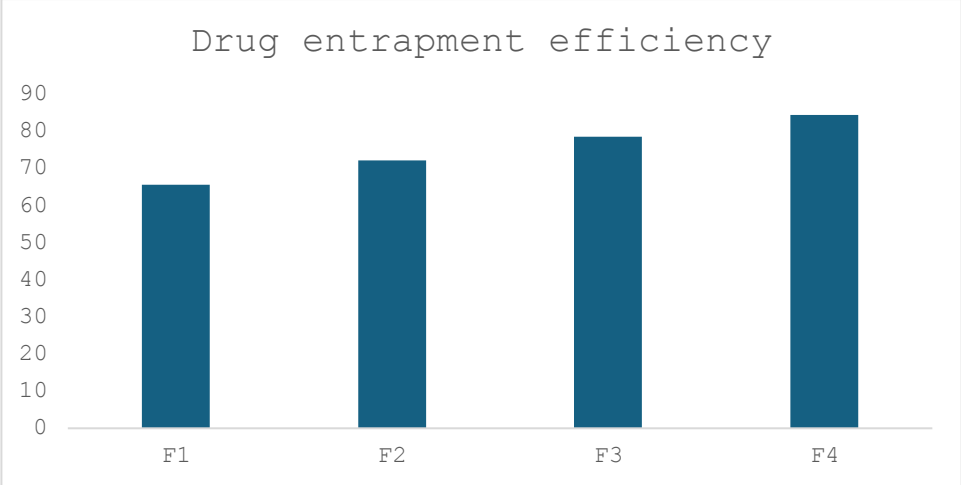


Fig-4: Drug entrapment efficiency of all formulation

Drug entrapment efficiency (EE) ranged from 65.80% (F1) to 84.50% (F4).Higher EE indicates effective incorporation of Fluoxetine into the lipid bilayer of ethosomes.F4 (84.50%) 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 Fluoxetine Ethosomes (F1-F4)

Time	F1	F2	F3	F4
0	0	0	0	0
1	19.6	21.3	22.8	23.4
2	33.2	35.4	37.1	38.7
3	42.8	43.2	44.3	45.2
4	50.3	51.2	51.9	52.8
5	60.1	63.4	64.9	65.8
6	70.2	72.8	73.9	74.3
7	78.4	81.8	82.7	83.5
8	88.5	91.0	92.4	94.2

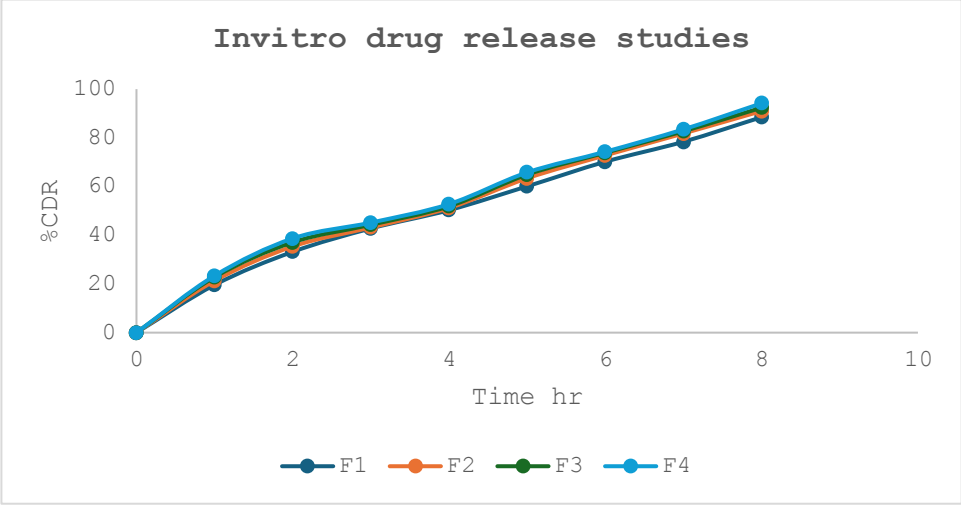


Fig-5: In vitro drug release studies of F1-F4 formulations

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	97.58	96.45	95.52	94.69	Not less than 85 %
F-4	97.58	96.40	95.43	94.32	Not less than 85 %
F-4	97.58	96.38	95.20	94.12	Not less than 85 %

SUMMARY AND CONCLUSION:

The present study was undertaken to formulate and evaluate Fluoxetine-loaded ethosomes using varying concentrations of lipids. FTIR studies demonstrated the compatibility between Fluoxetine and the selected excipients. The characteristic peaks of the drug were retained in the physical mixture without any significant shifts or the appearance of new peaks, confirming the absence of chemical interactions and indicating the stability of the drug within the formulation.Particle size analysis showed that the ethosomal formulations possessed nanosized vesicles ranging from 163 to 228 nm. The optimized formulation F4 exhibited the smallest particle size (163 nm) and the highest negative zeta potential (−32 mV), suggesting good physical stability and reduced vesicle aggregation. SEM analysis confirmed the formation of spherical vesicles with smooth surfaces and uniform morphology.Entrapment efficiency values ranged from 65.80% to 84.50%, with formulation F4 exhibiting the highest entrapment efficiency (84.50%), indicating efficient incorporation of Fluoxetine into the ethosomal vesicles.The in vitro drug release studies performed using phosphate buffer pH 7.4 demonstrated a sustained release pattern for all formulations over 8 hours. Formulation F4 showed the highest cumulative drug release of 94.2%, indicating superior release characteristics among the developed formulations.Accelerated stability studies of the optimized formulation (F4) conducted at 40 ± 2°C and 75 ± 5% RH for a period of three months showed no significant changes in drug release characteristics, with the formulation maintaining drug release above the specified limit of 85%, indicating good stability.

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, and satisfactory stability profile. Therefore, the developed Fluoxetine ethosomes may serve as a promising vesicular drug delivery system for improving drug delivery and therapeutic effectiveness. Further in vivo studies are recommended to establish their clinical potential.

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