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FORMULATION AND EVALUATION OF METHOTREXATE ETHOSOMAL GEL

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ABSTRACT

Ethosomes are novel lipid-based vesicular carriers created for improved transdermal drug delivery. Ethosomes are mainly made up of phospholipids and elevated levels of ethanol. noted for their capacity to infiltrate the skin's stratum corneum more efficiently than conventional liposomes. This distinctive characteristic is linked to ethanol's capability to fluidify the lipid. bilayers, promoting enhanced drug penetration into the skin layers. Ethosomes provide numerous benefits, such as enhanced bioavailability of therapeutic compounds, precise delivery, and minimized adverse effects. They have demonstrated potential in several applications, ranging from providing systemic medications for addressing localized issues. This summary outlines the formulation and mode of action, and possible uses of ethosomes, emphasizing their significance in improving transdermal drug delivery systems. The aim of this study was to develop and assess topical Methotrexate-loaded ethosomal gel, an effective antimetabolite and chemotherapy drug commonly employed in the therapy of different cancers and autoimmune disorders, including rheumatoid arthritis by reducing immune system activity, manages psoriasis by inhibiting growth of skin cells and addresses cancer by inhibiting the proliferation of cancer cells.

KEYWORDS: Ethosomes, Phospholipids, Cholesterol, Methotrexate, Autoimmune Diseases, Psoriasis.

INTRODUCTION

Transdermal drug delivery is an important research focus in the field of drug delivery because of its convenience, safety, and efficacy as a non-invasive means of administering drugs. It offers multiple advantages, including avoiding the first-pass effect associated with gastrointestinal absorption, enhancing patient adherence, ensuring sustained and controlled release, and minimizing drug metabolism.[1–3] Nonetheless, the skin's inherent barrier greatly limits drug penetration and absorption during transdermal delivery, constraining the effectiveness of some medications. To address this limitation, researchers work to enhance drug permeability and absorption for efficient transdermal delivery.[4,5] In recent years, innovative nanocarriers have demonstrated considerable promise for drug delivery.[2,6–9] Ethosomes are drug formulations created by mixing a drug with a carrier, usually an alcohol or its derivatives. This carrier includes an active alcohol element that offers superior permeability and drug loading ability compared to standard liposomes.[10,11] Ethosomes have shown two key advantages: increasing drug-skin interactions by facilitating drug uptake and penetration, and being easily customizable for different types of drugs, such as water-soluble, fat-soluble, and unstable formulations. Consequently, the use of ethosomes can enhance drug stability while minimizing systemic side effects and drug waste.[12] Additionally, ethosomes offer numerous benefits in transdermal drug delivery and hold potential applications in fields like pharmaceuticals, biotechnology, veterinary care, cosmetics, and nutrition, among others.[13] The majority of products promoted so far are medications. An example is the Decorin cream from Genomic Cosmetics, located in Pennsylvania, USA, which targets anti-aging and pigmentation concerns.[14] Noicellex and Supravir are creams applied topically, developed by Novel Therapeutic Technologies and Trima, respectively. Noicellex is a cream for combating cellulite, formulated to improve the efficacy of its active component by increasing its absorption depth.

The study primarily focuses on the various types of ethosomes, their fundamental mechanisms, production techniques, key factors, and clinical studies. In this discussion, we will examine the challenges and possibilities associated with promoting and improving ethosomes as a method for administering drugs through the skin in transdermal drug delivery.

Definition

Ethosomes are sophisticated drug delivery systems made up of lipid-derived vesicles. comprising phospholipids and an elevated level of ethanol. The ethanol enhances the fluidity of the lipid bilayer, enabling these vesicles to infiltrate the outer layers of the dermis more efficiently. This improved permeability aids in the transport of drugs

into more profound layers of skin or possibly overall circulation. Ethosomes are especially advantageous for topical therapies for skin issues such as psoriasis or eczema, since they improve the uptake and potency of active components in contrast to conventional topical formulations.

Structure of ethsomes

Ethosomes are vesicles derived from lipids, consisting of a phospholipid bilayer, usually formed from phosphatidylcholine or various phospholipids, and containing a significant amount of ethanol. The ethanol, generally present at 30-40% concentration, enhances the fluidity and flexibility of the lipid bilayer. This improved fluidity enables ethosomes to more efficiently penetrate the skin's outer layer, the stratum corneum. Consequently, ethosomes are capable of transporting medications more effectively to the deeper layers of the skin or into the systemic circulation.

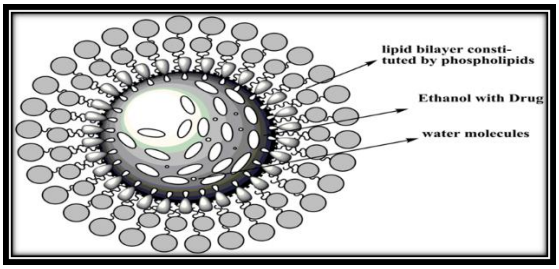


Figure –Ethosome.

- **Types of the Ethosome**

1. Traditional Ethosomes

Standard ethosomes represent the simplest type of ethosomal formulations, comprising a mix of phospholipids, ethanol, and water. Generally, ethanol levels vary between 20-45%, which is essential for improving skin permeability. Ethanol can alter the lipid composition of the skin's stratum corneum, increasing its permeability to drug substances. In traditional ethosomes, the liposomal structure is usually bigger than other ethosome variants, enabling the inclusion of both hydrophilic and lipophilic medications. The main function of these ethosomes is the fluidization of the lipid bilayer caused by ethanol, which aids in improving the skin absorption of medications. This kind of ethosome is generally utilized for medications that need effective transdermal administration but might not require ultra-deformability or nanoscale features.

2. Ultrasoft Ethosomes

Ultradeformable ethosomes are uniquely designed to possess greater flexibility and deformability compared to traditional ethosomes. They typically include extra elements like glycerol or other permeation boosters, which aid in further decreasing the vesicle's size and improving its deformability. A defining feature of ultradeformable ethosomes is their capability to navigate through narrow intercellular spaces or tight pores in the skin. This renders them perfect for administering medications to the deeper layers of the skin or even aiming for systemic circulation. Owing to their enhanced flexibility, these ethosomes can pass through the skin's micro-pores without breaking, leading to improved transdermal absorption. They are frequently utilized for sizable molecular drugs or substances that typically wouldn't effectively penetrate the skin, providing a controlled release system while reducing irritation.

3. Nanoethosomes

Nanoethosomes are a type of ethosomes distinguished by their reduced particle size, generally in the nanometer scale (less than 200 nm). This reduced size enables nanoethosomes to infiltrate the skin more effectively than traditional ethosomes, as they can readily pass through the skin’s pores and layers. The smaller size also improves stability, increases the solubilization of active components, and facilitates controlled release. Nanoethosomes are frequently utilized for more precise drug delivery, especially when exact targeting is essential. Because of their nanoscale dimensions, they can penetrate the skin more deeply and enhance bioavailability by boosting the solubility of drugs with low water solubility. Additionally, the surface characteristics of nanoethosomes can be adjusted to improve drug targeting and reduce side effects, rendering them a viable option for localized therapies.

4. Micelles Based on Ethosomes

Ethosome-based micelles represent a hybrid formulation that merges ethosomes with micellar structures. Micelles are clusters of surfactant molecules capable of solubilizing hydrophobic medications that would normally have low solubility in water-based solutions. Integrating surfactants into ethosomes allows ethosome-based micelles to improve the delivery of hydrophilic and lipophilic medications. The micellar arrangement enhances the solubility of compounds that are poorly water-soluble, thereby boosting the bioavailability of active pharmaceutical ingredients. These ethosomal micelles also take advantage of ethanol's skin penetration-enhancing properties, facilitating effective transdermal delivery. They are especially beneficial for medications that need solubilization to address solubility problems and for maintaining controlled or prolonged drug release at the application site.

5. Ethosomes Containing Active Compounds

Ethosomes containing active ingredients are a more sophisticated form of ethosome, incorporating extra elements like permeation enhancers or therapeutic agents into the ethosomal mixture. These ethosomes are crafted to both transport drugs through the skin barrier and enhance the permeation of particular molecules. The active compounds, which might consist of additional medications, lipids, or even biological substances, function synergistically to improve the transdermal delivery method. This formulation is perfect for attaining localized drug effects, since the active ingredients can concentrate on particular regions of the skin or tissue, enhancing therapeutic results. In these ethosomes, the

active components may also influence the release rate of the encapsulated medication, ensuring extended therapeutic effects with reduced systemic side effects.

- **Advantages Of Ethosomes[34]**

1. Ethosome enhance permeation of drugs through skin for dermal, transdermal and intracellular delivery.
2. Deliver various molecules with different physicochemical properties, hydrophilic and lipophilic molecules, peptides, proteins and other macromolecules.
3. The components of the ethosomes are generally recognized as safe (GRAS), non-toxic and approved for pharmaceutical and cosmetic use.
4. Low risk profile- Ethosome structure has no largescale drug development risk as the ethosome feature toxicology profiles are well established in the scientific literature.
5. The ethosomal system is passive and non-invasive, and is suitable for immediate marketing.

- **Disadvantages Of Ethosome[34]**

1. Allergic reaction can be identified if the patients are allergic to ethanol or any of the ethosomal components.
2. Unlike other carriers (solid lipid nanoparticles, polymeric nanoparticles, etc.) which can be used for multiple routes, ethosomal carriers are important only for transdermal use.
3. Due to the fact that ethanol is inflammable, sufficient care should be taken during planning, application, transport and storage.
4. Very poor yield so may not be economical.
5. Loss of product during transfer from organic to water media.
6. It is limited only to potent molecules, those requiring a daily dose of long or less.

- **Salient Features Of Ethosomes**

1. Entrap solutes in a manner analogous to liposomes.
2. Osmotically active and stable.
3. Accommodate the drug molecules with a wide range of solubility.
4. Exhibits flexibility in their structural characteristics (composition, fluidity and size).
5. Performance of the drug molecules is increased.
6. Better availability to the particular site by protecting the drug from biological environment.

- **Methods of preparations**

1. Hydration of Thin Film: Lipids are dissolved in an organic solvent that is then evaporated to create a thin film. Ethanol and water are incorporated to hydrate the film, resulting in ethosomes. This approach is straightforward, economical, and widely utilized.
2. Hot and Cold Method: Phospholipids and ethanol are mixed at a higher temperature, then cooled. Water is gradually added to the mixture, forming ethosomes. This technique improves fluidity and drug encapsulation efficiency.
3. Solvent Injection Technique: Phospholipids and ethanol are mixed with an organic solvent and then introduced into an aqueous phase. The solvent spreads out, creating ethosomes. It is perfect for delivering both hydrophilic and lipophilic medications.
4. Reverse phase evaporation method: A reverse oil-in-water emulsion is formed by dissolving drugs and lipids in an organic solvent. Water is introduced, and the solvent is removed through evaporation, yielding ethosomes. This technique offers excellent drug encapsulation efficiency.

- **MATERIALS AND METHODOLOGY**

Table: Materials.

SR.NO	CHEMICAL	CATEGORY	SUPPLIERS
1	Methotrexate	API	Dolphin Pharmacy Instruments Pvt. Ltd, Mumbai
2	Soya Lecithin	Phospholipid (Emulsifier)	Ozone International (Mumbai), India
3	Ethanol	Penetration Enhancer	Ozone International (Mumbai), India
4	Chloroform	Organic Solvent	Ozone International (Mumbai), India
5	Cholesterol	Stabilizer	Ozone International (Mumbai), India
5	Glycerol	Humectant	Ozone International (Mumbai), India
6	Phosphate Buffer	pH-Regulator	Ozone International (Mumbai), India
7	Carbopol 934	Gelling Agent	Ozone International (Mumbai), India
8	Triethanolamine	Neutralizer	Ozone International (Mumbai), India
9	Distilled Water	Solvent	Ozone International (Mumbai), India

Table: Equipments and Models.

EQUIPMENT	MODEL
Electronic weighing balance	DBK
Electronic rotatory shaker	Remi
Rotational Viscometer	Fungilab
pH meter	Labtronics, India
Heating mantle	Dolphin

UV/ Visible spectrophotometer	Systronics 2201, Ahmedabad
FTIR spectroscopy	Alpha II (410015)
Diffusion tester	Electro lab
Melting point apparatus	Labrotonics, India

- **MATERIALS AND METHODS**

Characterization of Raw material

1. Solubility

To obtain a desirable concentration of the drug in the blood, solubility plays a major role. Varying solvents were taken including, methanol, water, ethanol, and certain buffers such as phosphate buffer (7.4) to determine the solubility.

2. Melting point determination

Melting point to be determined by using Melting Point Apparatus.

3. Determination of (λmax)

Stock solution of (100 µg/ml) for Methotrexate was prepared by dissolving 10 mg of drug in 20 ml of methanol in 100ml volumetric flask, solution was further diluted and analyzed spectroscopically to determine λmax of the drug.

4. Preparation of calibration curve for Methotrexate in 7.4 PH buffer

Accurately weighed 10 mg of Methotrexate was Dissolved in Methanol was Transfered to 100 ml volumetric flask and volume was made up to the mark with 7.4 pH buffer solution to obtain the strength of 100 µg/ml. aliquots of 0.2 ml to 1 ml of stock solution were transferred to 10 ml volumetric flask and the volume was adjusted up to the mark with the 7.4 ph buffer solution representing 2 to 10 µg/ml of drug solution.

5. Compatibility studies

Compatibility Studies is an important step in preformulation study to determine any possible incompatibility between drug and excipients. The samples were subjected to FT-IR.

- **Formulation Of Ethosomes[75]**

Thin Film Dispersion Method

1. Preparation of Lipid Solution: Dissolve phospholipids and cholesterol in a mixture of chloroform and methanol (typically in a 3:1 ratio).

2. Formation of Thin Film: Transfer the lipid solution to a round-bottom flask. Use a rotary evaporator to remove the organic solvents under reduced pressure at around 35°C, forming a thin lipid film on the flask walls.

3. Hydration of Thin Film: Hydrate the thin film with an aqueous phase containing ethanol, and the drug to be encapsulated. The hydration process can be done at a temperature above the phase transition temperature of the lipids, usually around 40°C.

4. Formation of Ethosomes: The hydration process leads to the formation of ethosomes, which can be further sized and homogenized using techniques like sonication or extrusion.

Formulation of Methotrexate Ethosomes

Table-Formula.

Ingredients	**ME1**% (w/v)	**ME2**% (w/v)
Methotrexate (Active Drug)	1	1
Soya Lecithin (phospholipid)	3	5
Cholesterol	1	0.5
Chloroform	30	30
Methanol	10	10
Ethanol	20	30
Distilled Water	Up to 100 % total	Up to 100 % total

Formulation Of Methotrexate Ethosomal Gel

Table – Formula

Ingredients	**Quantity**% (w/v)
Methotrexate Ethosomes	2
Carbopol 934	1
Triethanolamine	q.s.
Distilled Water	Up to 100 % total

- **Evaluation Of Methotrexate Ethosomes[75-81]**

Morphological characterization: The vesicle formation was confirmed by optical microscopy. The Ethosomal suspension placed over a glass slide and fixed over by drying at room temperature, the dry thin film of Ethosomal suspension observed in the formation of vesicles. The microphotography of the Ethosomes also obtained from the microscope by using a digital camera.[76]

Ethosomal vesicles morphology: The Ethosomal dispersion after hydration was stored under 4°C for

congealing and a drop of dispersion was viewed under an optical microscope to observe the shape and lamellar nature of the vesicle.

Entrapment efficiency: Entrapment efficiency of Ethosomes was determined by exhaustive dialysis method. The measured quantity of Ethosomal suspension was taken into a dialysis tube to which dialysis membrane was securely attached on one side. The dialysis tube was suspended in 100 ml PBS pH 7.4 containing 10% v/v methanol, which was stirred on a magnetic stirrer. The un-entrapped drug was separated from the Ethosomal suspension into the medium through the membrane. every hour, entire medium (100 ml) was replaced with fresh medium (for about 6-7h) until the absorbance reached a constant reading indicating no drug is available in an un-entrapped form. The withdrawn samples were analyzed at 302nm using a UV spectrophotometer. Amount of entrapped drug was obtained by subtracting amounts of un-entrapped drug from the total drug incorporated.

Percent entrapment=
Total drug-Diffused drug/Total drug×100
In-vitro drug release study: The release of Methotrexate from Ethosomal formulations were determined using membrane diffusion technique. The Ethosomes left after removal of un-entrapped drug were dialyzed into a beaker containing 100ml of PBS pH 7.4 containing 10% v/v methanol (to maintain sink condition), which acted as receptor compartment. The temperature of the receptor medium was maintained at 37 ± 0.5°C and agitated using a magnetic stirrer. Aliquots of 5 ml sample were withdrawn periodically and after each withdrawal, same volume of the medium was replaced. The collected samples were analyzed using a UV spectrophotometer at 302nm. The tests were carried out in triplicate.

- **Ethosomal gel Preparation**

Formulation of Ethosomes entrapped Methotrexate gel: Formulation of Ethosomes prepared using Soya containing Methotrexate equivalent to 2 % w/w was incorporated into the gel base composed of Carbopol 940 (1gm) Triethanolamine (quantity sufficient) and distilled water up to 100g.

- **Evaluation Of Methotrexate Ethosomal Gel**

Physical appearance: The prepared gel was examined for clarity, color, homogeneity and the presence of foreign particles.

pH: 2.5g of gel were accurately weighed and dispersed in 25 ml of distilled water. The pH of the dispersion was measured by using a digital pH meter.

- **Rheological study**

Viscosity measurement: Viscosity was determined by Brookfield programmable DV III ultra viscometer. In the present study, spindle no. CP 52 with an optimum speed of 0.01rpm was used to measure the viscosity of the preparation.

Spreadability test: A 0.5 g of gel was pressed between two slides, divided into squares of 5 mm sides and left for about 5 min. The spreading was measured.
$S = M \cdot L/M$

Where,
S = Spreadability, M = Weight tied to upper slide L = Length of glass slide, T = Time taken to separate the slide.

Washability: The washability test was determined by applying a small amount of prepared formulation over the skin and afterwards washed it with water. A small amount of the prepared formulations (gels) was rubbed on the skin and washed it with warm water. The formulations should have good washability.

Content uniformity: The drug content of the gel was estimated, and the results were within the official limits range of 9.3– 9.5mg/g gel. The drug content determination showed that the drug was uniformly distributed throughout the gel.

In vitro drug diffusion study: Drug release studies were performed in Franz diffusion cell applied on dialysis membrane which is used in diffusion media of phosphate buffer solution pH 7.4 withdrawn 2ml sample diluted in PBS pH 7.4 at 10min time interval absorbance measured in determining a max at 303 nm by UV spectrophotometer in all formulation. The in vitro test was performed to ensure the uniform and accurate permeability of the drug.

- **RESULTS AND DISCUSSION**

Melting point determination: Melting point of Methotrexate taken by Melting point apparatus and results are shown in Table.

Table-MTX Melting Point.

Reported M.P.	Observed M.P.
182°C to 189°C	185-190° C

Melting point of Methotrexate was found in the range of 185-190° C which is in the reported range that is 182°C to 189°C indicated absolute purity of drug sample.

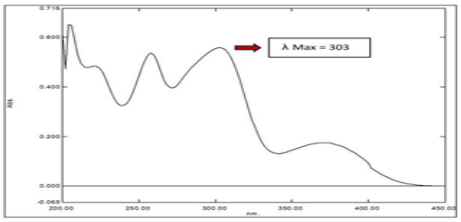
Determination of λmax: Determination of λmax of Methotrexate done by UV-Spectrophotometer and Results are shown in Table.

Table - λmax of MTX.

Parameters	Results
λmax	303nm

The wavelength of maximum absorbance (λmax) of solution of Methotrexate prepared in buffer solution i.e. pH 7.4 which is shown in Figure and was concordant

with the given literature. The max for Methotrexate was observed at 303nm.



Standard Calibration curve for Methotrexate in 7.4 pH Buffer: Absorbance of 2-10µg/ml of Methotrexate solution were measured on UV-Visible. Spectrophotometer at 303nm and plotted against absorbance vs concentration the results are shown in table.

Table - absorbance vs concentration.

Concentration(µg/ml)	Absorbance
2	0.206
4	0.410
6	0.608
8	0.802
10	1.060

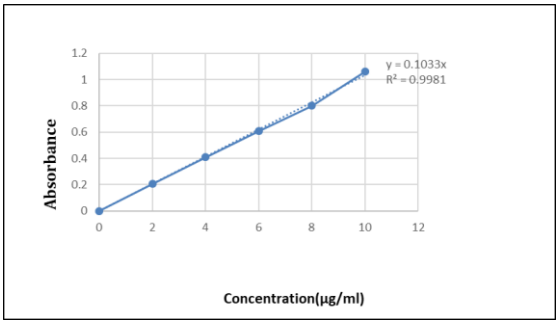


Figure - absorbance vs concentration.

- **Drug Excipient Compatibility Studies**

Fourier Transform-Infra Red spectrophotometric study

The IR spectra of Methotrexate, Carbopol 940, Cholesterol, Soya Lecithin, Methotrexate+Soya Lecithin, Methotrexate+Carbapol 940 and its physical mixture are shown in the following figures.

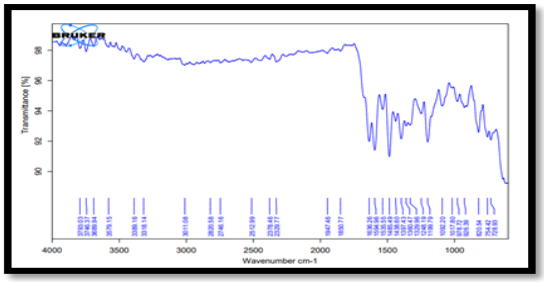


Figure-: FTIR Spectra Of Methotrexate.

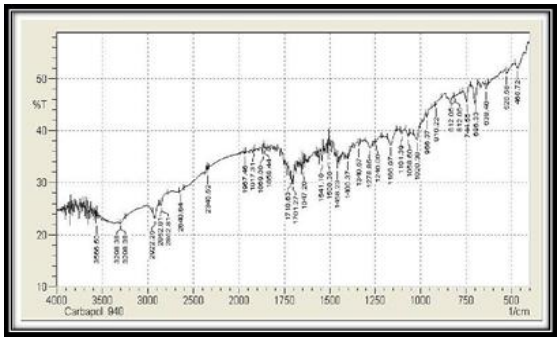


Figure-: FTIR Spectra Of Carbopol 940.

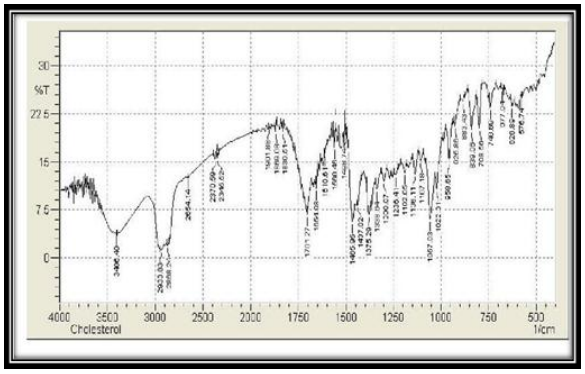


Figure-: FTIR Spectra Of Cholesterol.

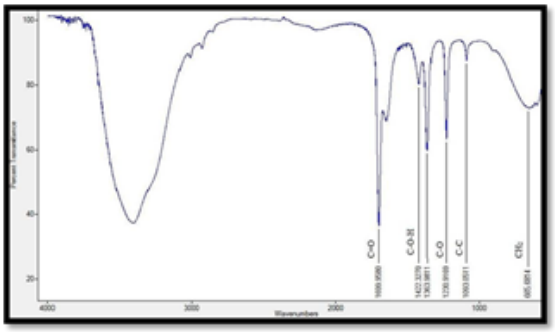


Figure -: FTIR Spectra of Methotrexate + Soya Lecithin.

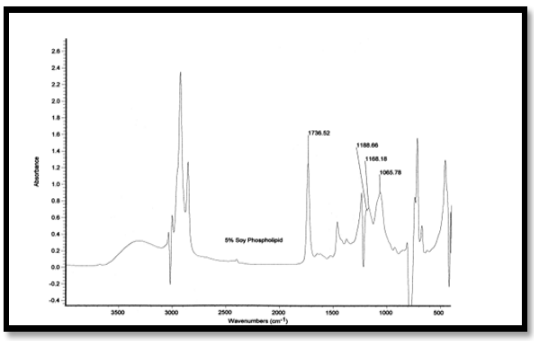


Figure-: FTIR Spectra of Soya Lecithin.

Ethosomes Formulation code	Partical size	Percentage entrapment efficiency	Cumulative percent drug released (after 6h)
ME1	6.12±2.20	55.14±2.29	72.371±0.592
ME2	5.76±2.06	59.08±3.27	68.113±0.545

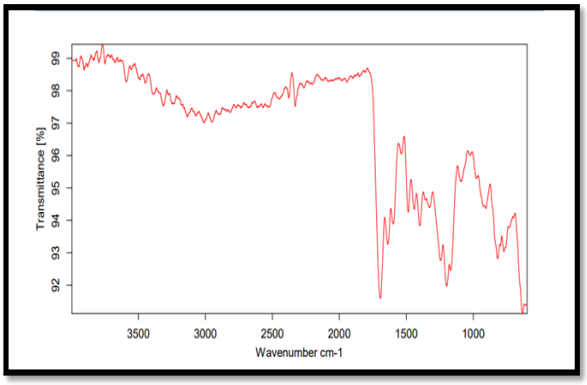


Figure- FTIR Spectra of Methotrexate-Carbapol 940.

- **Evaluation And Result Of Methotrexate Ethosomes**
- **Morphological Characterization**

The vesicle formation was confirmed by optical microscopy 45× resolution. The Ethosomal suspension placed over a glass slide and fixed over by drying at room temperature, the dry thin film of Ethosomal suspension observed in the formation of vesicles. The microphotography of the Ethosomes also obtained from the microscope by using a digital camera.

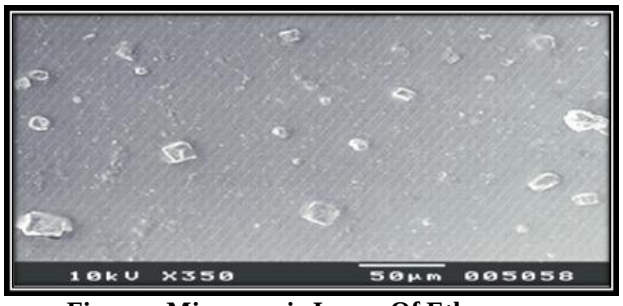


Figure-: Microscopic Image Of Ethosomes.

Entrapment efficiency: Entrapment efficiency of Ethosomes was determined by exhaustive dialysis method. The measured quantity of Ethosomal suspension was taken into a dialysis tube to which dialysis membrane was securely attached on one side. The dialysis tube was suspended in 100ml PBS pH 7.4 containing 10% v/v methanol, which was stirred on a magnetic stirrer. The un-entrapped drug was separated from the Ethosomal suspension into the medium through the membrane. At every hour, entire medium (100ml) was replaced with fresh medium (for about 6‑ 7h) until the absorbance reached a constant reading indicating no drug is available in an un-entrapped form. The withdrawn samples were analyzed at 303nm using a UV spectrophotometer. Amount of entrapped drug was un-entrapped drug from the total drug incorporated. The result shown in table.

Percent entrapment=Total drug-Diffused drug/Total drug×100

obtained by subtracting amounts of un- entrapped drug from the total drug incorporated. The result shown in table.

Percent entrapment=Total drug-Diffused drug/Total drug×100

Table- Result of Methotrexate Ethosomes.

In-vitro drug release study: The release of Methotrexate from Ethosomal formulations were determined using membrane diffusion technique. The Ethosomes left after removal of un-entrapped drug were dialyzed into a beaker containing 100ml of PBS pH 7.4 containing 10% v/v methanol (to maintain sink condition), which acted as receptor compartment. The temperature of the receptor medium was maintained at 37 ± 0.5°C and agitated using a magnetic stirrer. Aliquots of 5 ml sample were withdrawn periodically and after each withdrawal, same volume of the medium was replaced. The collected samples were analyzed using a UV spectrophotometer at 303nm. The tests were carried out in triplicate. The result shown in table 8. Result shows that **ME1 has a more drug entrapment efficiency than ME2**

Figure-: Methotrexate Ethosomes.

Evaluation of Methotrexate Ethosomal Gel

Physical appearance

The prepared gel was examined for clarity, color, homogeneity and the presence of foreign particles result are shown in table.

Table- Physical appearance.

Parameters	Results
Clarity	Clear
Colour	White
Homogeneity	Good
Presence Of Foreign Particles	None

pH: 2.5 g of gel were accurately weighed and dispersed in 25 ml of distilled water. The pH of the dispersion was measured by using a digital pH meter (pH is 5.5± 0.3)

Rheological study

Viscosity measurement: Viscosity was determined by Brookfield programmable DV III ultra viscometer. In the present study, spindle no. CP 52 with an optimum speed of 0.01rpm was used to measure the viscosity of the preparation result (Viscosity is 3220 cps).

Spreadability test

A 0.5 g of gel was pressed between two slides, divided into squares of 5mm sides and left for about 5min. The spreading was measured result (Spreadability is 5.6).

Washability

The washability test was determined by applying a small amount of prepared formulation over the skin and afterwards washed it with water. A small amount of the prepared formulations (gels) was rubbed on the skin and washed it with warm water. The formulations (washability is Good).

Content Uniformity

The drug content of the gel was estimated and the results were within the official limits range of 9.3 9.5 mg/ gel. The drug content determination showed that the drug was uniformly distributed throughout the gel.

In-vitro drug release study

The release of Methotrexate from Ethosomal gel formulation were determined using membrane diffusion technique.

Figure: Methotrexate Ethosomal Gel.

Table- In-vitro drug release study.

Ethosomes Formulation code	Cumulative percentdrug released (after 6hr)
ME2	63.95

Cumulative % drug release of MTX from Ethosome Formulations

Table: Cumulative % drug release of MTX from Ethosome Formulations.

Time (hrs)	%Cumulative Drug Release
0.5	20.34%
1	28.35%
2	33.21%
3	42.42%
4	52.35%
5	60.64%
6	63.95%

In Vitro Drug Release Data For Methotrexate Ethosomal Gel Formulation

Table- In Vitro Drug Release Data For Methotrexate Ethosomal Gel Formulation.

S.No.	Time (Hr)	Square root of Time	Log Time	Cumulative Percentage Drug Release +_ (SD)	Log Cumulative Percentage Drug Release	Cumulative Percent Drug Remaining	Log Cumulative Percent Drug Remaining
1	0.5	0.707	-0.301	20.34%	-0.6902	79.66%	-0.0987
2	1	1.000	0.000	28.35%	-0.5470	71.65%	-0.1449
3	2	1.414	0.301	33.21%	-0.4783	66.79%	-0.1754
4	3	1.732	0.477	42.42%	-0.3747	57.58%	-0.2374
5	4	2.000	0.602	52.35%	-0.2810	47.65%	-0.3214
6	5	2.236	0.698	60.64%	-0.2185	39.36%	-0.4041
7	6	2.449	0.778	63.95%	-0.1958	36.05%	-0.4447

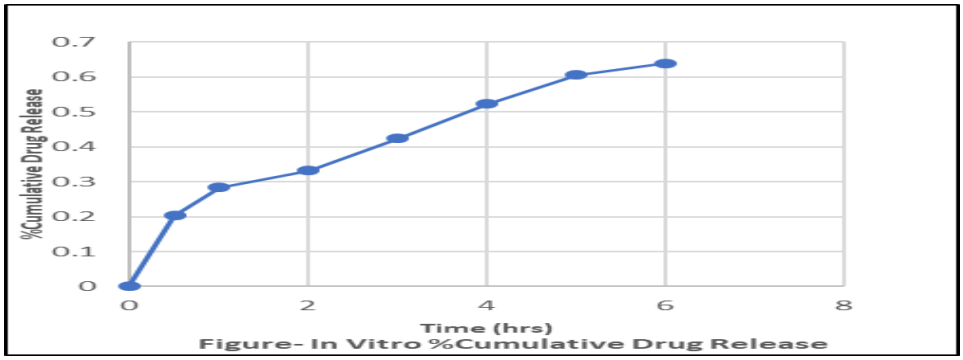


Figure- In Vitro %Cumulative Drug Release

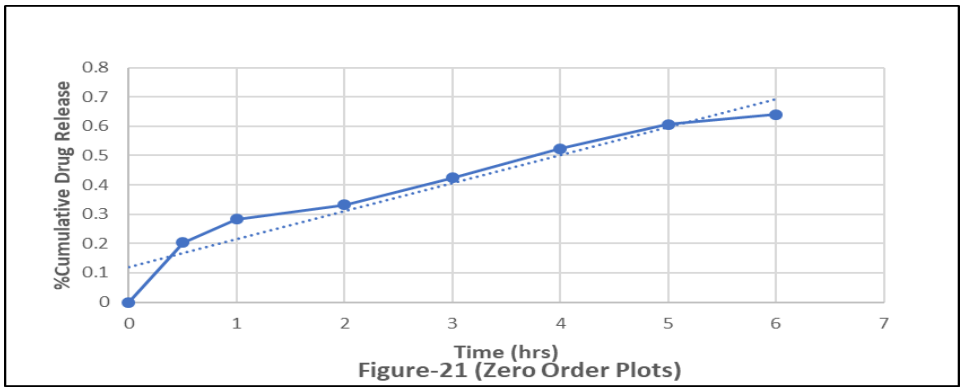


Figure-21 (Zero Order Plots)

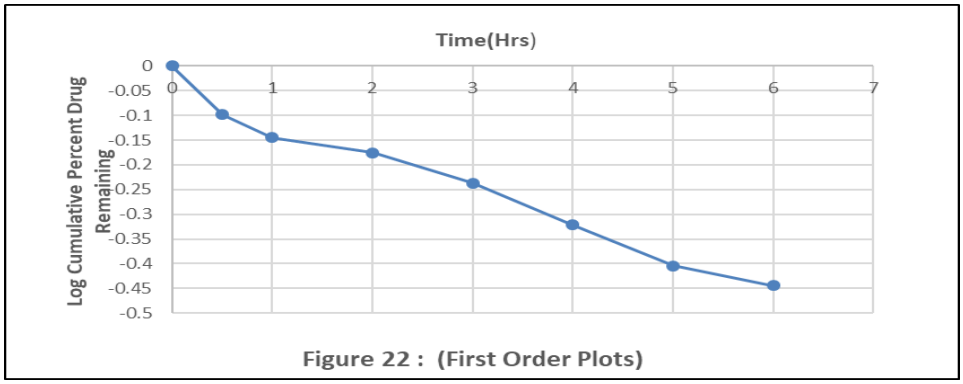


Figure 22 : (First Order Plots)

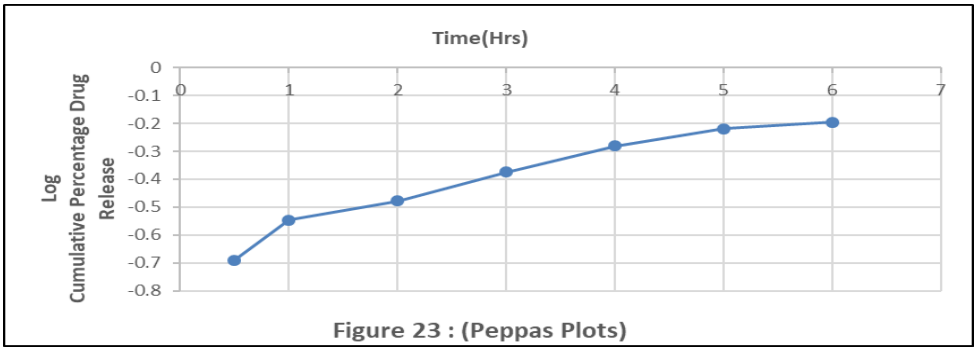


Figure 23 : (Peppas Plots)

CONCLUSION

The results of this study showed that the concentration of Phospholipids altered the entrapment efficiency and drug release rate from Ethosomes. Formulation having higher concentration of Phospholipids exhibited higher drug release. The concentration of phospholipids increases vesicle stability and drug entrapment, while higher ethanol levels reduce vesicle size, enhancing skin permeation From this studies, it can be concluded that a gel formulation containing Ethosomes loaded with Methotrexate (ME2) showed prolonged action and it can be developed successfully to improve Management of Autoimmune Diseases like rheumatoid arthritis and psoriasis.

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