Emulsomes : A Novel Vesicular Platform for Enhanced Drug Delivery and Targeted Therapy

AVADHUT A TALWAR *, SARDAR SHELAKE , DR.N.B.CHOUGALE ,

AVINASH MANGAVE , ADITYA KESARKAR , RADHIKA SUBHEDAR

Ashokrao Mane Institute of Pharmacy, Ambap.

Tal – Hatkanangale Dist – Kolhapur 416112

Abstract

Over the past several decades, there has been a significant increase in interest in the development of innovative drug delivery systems (NDDS), focusing on creating systems that administer drugs at therapeutic rates and target specific action sites. Conventional drug forms, even those with extended release, cannot meet these requirements, while NDDS aims to optimize therapeutic effects and minimize side effects. Emulsomes, a type of NDDS, are lipid-based vesicular systems combining the properties of liposomes and emulsions. They are made up of a phospholipid bilayer enclosing a solid or semi-solid lipid core, enabling the controlled release and encapsulation of both lipophilic and hydrophilic medications. Emulsomes offer stability advantages over traditional liposomes, making them suitable for delivering drugs with a poor water solubility, such as a antifungal and anticancer agents, while reducing toxicity and improving bioavailability. Various preparation methods, such as lipid film formation, reverse phase evaporation, and sonication, contribute to the formation of emulsomes with specific characteristics. The flexibility in emulsome composition allows for tailored applications in drug delivery, enhancing the targeted and sustained release of therapeutic agents.

Keywords: Emulsomes, Novel Drug Delivery Systems, Lipid-Based Vesicles, Controlled Release, Targeted Delivery, Drug Encapsulation.

Introduction

The development of novel drug delivery systems (NDDS) has drawn a lot of interest in recent decades. Two requirements should ideally be met by the NDDS: first, it should route the active component to the site of action; second, it should provide the drug at a pace chosen by the body during therapy. Not even normal extended-release dose formulations can satisfy all of requirements. Novel drug delivery aims to minimize unwanted side effects while maintaining a reasonably constant, effective drug level in the body, or to continue drug activity at a predefined pace. Another way to improve drug efficacy is to place controlled release devices in or close to the organ or tissue that is impacted.

As an alternative, it can target drug action by delivering the medication to certain cell types through the use of carriers or chemical changes.[1] Pharmaceutical carriers come in a variety of forms, including particulate, polymeric, macromolecular, and cellular. Colloidal carrier systems, also known as particulate type carriers, include vesicles, lipid particles, microspheres, nanoparticles, and polymeric micelles.[2] These are colloidal particles called vesicles, in which an aqueous compartment is encircled by an amphiphilic molecule-based concentric bilayer. This efficient vehicle can be used to transport hydrophilic drugs, which are found in the inner aqueous compartment, as well as hydrophobic drugs, which attach to the lipid bilayer. The vesicular

systems like liposomes, emulsomes, sphingosome, niosomes, transferosomes, pharmacosomes, virosomes, ethosomes, aquasomes, bilosomes etc.

Emulsomes

Emulsome is a lipid-based drug delivery system specifically developed to enhance the parenteral delivery of drugs with low water solubility. [3,4] Emulsomes are a unique type of lipid vesicle, featuring an outer phospholipid bilayer and a solid fat core within.(Figure 1). The inner core of emulsomes consists of fats and triglycerides, stabilized as an oil-in-water emulsion through the use of high concentrations of lecithin. The characteristics of emulsions and liposomes are combined in emulsomes. Their solidified or semi-solidified oily core allows for a high concentration of lipophilic drugs and facilitates controlled release. In addition, emulsomes can encapsulate water-soluble drugs within the aqueous compartments formed by the surrounding phospholipid layers.

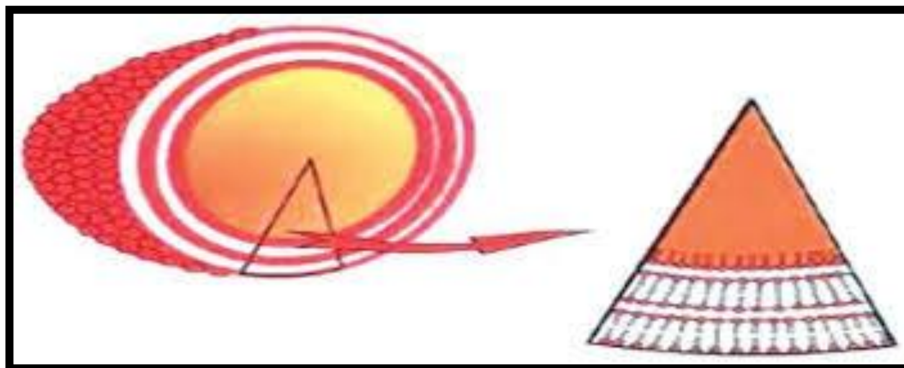

Figure.1 : Emulsome

Emulsomes, free from solvents and surfactants, have demonstrated an impressive capacity to encapsulate water-insoluble antifungal and anticancer drugs, resulting in improved drug delivery and enhanced preclinical efficacy, particularly in oral administration.[5] Emulsomes offer greater stability compared to liposomes, which are often less stable.By adopting emulsomes, you can avoid common problems like oxidation, sensitivity to hydrolysis, and aggregation that are linked to conventional liposomes and other vesicular delivery systems. By encapsulating the active ingredient within a vesicular structure, emulsomes help extend the drug's circulation time in the body and reduce toxicity. Traditional drug delivery methods are often not suited to meet these needs.[6] Since these medications are lipophillic (poorly soluble in water), they cannot be taken or, if they were, would have unfavorable side effects. For this reason, emulsomes are very helpful in this regard. Encapsulating a wide range of medications within emulsomes, such as antifungal, neuroprotective, AZT derivatives, β-blockers, antiepileptic, antibiotic, antineoplastic, and anti-inflammatory agents, is possible.[7] Emulsomes make lipophilic medications more soluble and bioavailable, and their structure permits controlled or prolonged drug release. After loading, the drug is sonicated to produce microscopic emulsomes.[8,9] Emulsomes' positive charge makes it expected that they will impede lysosomal breakdown and guarantee that the medication is taken internally.[9] Research has shown that emulsomes effectively transport a variety of protein and peptide drugs, including curcumin, amphotericin B (AmB), azidothymidine (AZT), methotrexate (MTX), and dithranol.[9,10,11,]

A researcher prepared emulsomes containing amphotericin B, a potent antifungal and anti-leishmanial drug, were used to treat visceral leishmaniasis. This study aims to develop macrophage-targeted emulsomes, specifically for the liver, spleen, and bone marrow, to reduce the adverse effects associated with conventional treatments.[12] For the treatment of psoriasis, Raza et al. created dithranol-loaded emulsomes that exhibit enhanced stability, effectiveness, and biocompatibility.[13] According to Kamboj et al., Vyas et al. created zidovudine-loaded emulsomes with the goal of treating serious viral illnesses such Epstein-Barr virus, HIV, and hepatitis. These emulsomes are intended for targeted and sustained delivery to the liver.[14,4].

Structure of emulsome

Emulsomes are lipid-based nanoparticles commonly used for drug delivery. their composition, consisting of an oil phase encased in a phospholipid bilayer, can be likened to a hybrid between liposomes and a solid lipid nanoparticles. Emulsomes contain phospholipid bilayers arranged head to tail, with the hydrophilic heads of the two layers facing outward and the hydrophobic tails facing inward. This bilayer functions to prevent the encapsulated oil phase from degrading and provides the emulsomes with a stable structure.[15,16] emulsomes can contain more than just the phospholipid bilayer and oil phase; they can also contain surfactants, stabilizers, and targeting ligands, among other materials.[17,18] These additional chemicals could help improve the emulsomes' ability to target specific tissues or cells, as well as their efficacy and longevity.[19] The general structure of emulsomes is highly flexible, allowing it to be tailored to the specific needs of different drug delivery applications. By carefully selecting the ingredients and refining the formulation, It is feasible to develop emulsomes that are not only effective and stable but also well-tolerated by the body.[20,21] (figure-2)

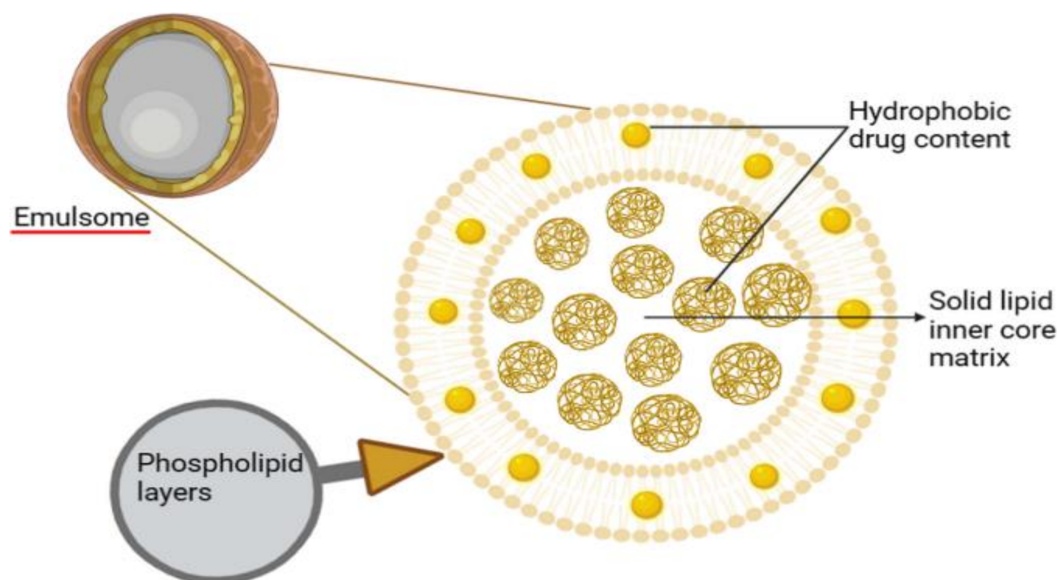

Figure 2 : structure of emulsome

Components or Formulation of Emulsomes –

Antioxidant

The lipid core of the emulsome particles in this invention may optionally contain one or more antioxidants. As members of the vitamin E family, a-tocopherol or its derivatives are the recommended antioxidants. Butylated hydroxytoulinate is one of the other antioxidants (BHT). Antioxidants reduce the production of peroxides, which are results of unsaturated lipid oxidative breakdown. Using saturated fatty acids to prepare the lipid core can help reduce the need for antioxidants.[22]

Lipid core

The internal hydrophobic core, or lipid core, is a key component of emulsomes. It is made up of lipids and can exist in solid, lipid, or a mixed solid and liquid crystal phase at room temperature (25°C). There are many lipids and lipid-like excipients available on the market. In medical terminology, they are collectively referred to as lipids.[23] A single lipid or a blend of lipids can be used.These are molecules that are related to these compounds both functionally and biosynthetically; they are fatty acids and their derivatives. [24,25] In general, lipids are insoluble in water and can be recognized by their hydrophilic-lipophilic balance (HLB), melting point, and fatty acid makeup. For prolonged release, lipids having a high melting point and low HLB are appropriate. On the other hand, excipients with high HLB and semi-solids function as enhancers of bioavailability and immediate release, respectively. [26,27] It is found that triglycerides that

solidify at 25°C make good core materials since they reduce the o/w emulsion's permissible storage life. Emulsomes are composed of unbranched fatty acids with chain lengths varying from c-10 to c-18 and are produced using triglycerides.[22]

Negatively charged particles

Emulsomes can be modified with negatively charged lipid particles, like oleic acid, or negatively charged phospholipids such as phosphatidic acid, phosphatidylinositol, and phosphatidylserine. This enhances the zeta potential of the composition and stabilizes the particles. Additionally, the incorporation of these negatively charged lipids promotes the formation of oppositely charged phospholipid bilayers. [22] As a result, the phospholipid bilayers surrounding the lipid core enhance the loading of the aqueous compartment. The aqueous space between the bilayers generates electrostatic repulsion, driving this effect. The negative charge helps prevent particle aggregation, thereby reducing the chances of coalescence, flocculation, or fusion.[28]

Surfactant

It is important to consider the Hydrophilic Lipophilic Balance (HLB) value when selecting a surfactant. Any surfactant's capacity to produce vesicles can be determined by looking at its HLB number; a number between 4 and 8 was shown to be compatible with vesicle production.[29] Additionally, surfactant transition temperature affects drug entrapment in vesicles. The spans with the highest phase transition temperature are where the medication is most confined, and vice versa.[30,31] A high phase transition temperature and low permeability restrict how much medicine can leak out of the vesicles.[32] A high HLB value of Span 40 and 60 results in a decrease in surface free energy, which allows for the creation of larger vesicles and, in turn, a larger area exposed to the dissolution media.[33,34]

Phosphatidylcholine

One of the main ingredients of lecithin is phosphatidyl choline. The water solubility of phosphatidyl choline is poor. Its phospholipids can form lamellar structures, micelles, or bilayer sheets in aqueous solution based on temperature and moisture content. As a result, a kind of surfactant known as amphipathic is produced. They are a vital part of biological membranes and are readily obtained from a variety of readily available sources, including soy beans and egg yolks. Depending on where they come from, they are referred to as egg lecithin or soy lecithin. The drug entrapment rate increased to 96.1% when lecithin was added, and the vesicles contracted as a result of their increased hydrophobicity.[35]

Cholesterol

Emulsomes need cholesterol as a required component because they are vesicles. Vesicle stability is impacted by the addition of cholesterol.[36,37] The amount of cholesterol present is crucial for the drug's trapping in vesicles.[38,39] There have been indications that an increase in cholesterol content increases entrapment efficiency. It was shown that a very high cholesterol content reduced the amount of drugs that were entrapped in the vesicles.[40] This could be as a result of cholesterol starting to interfere with the natural bilayer structure after a certain point, which causes the loss of drug entrapment.[41] Various materials used for a preparation of emulsomes like a Cholesterol, Triglycerides, Soya lecithin, Stearyl amine, Antioxidants, Surfactants. The materials used to prepare emulsomes are given in a [Table.1]

Sr.no	Material	Uses
1	Cholesterol	Incorporating cholesterol affects the stability of vesicles; however, excessive cholesterol can cause the formulation to become unstable.
2	Surfactants	Assign the drug's maximum entrapment.
3	Triglycrides	Low HLB lipids provide a formulation that is sustainably released when used as a hydrophobic lipid core.
4	Antioxidants	Prevent the lipids from becoming rancid or oxidized.
5	Soya lecithin	Additionally, it improves the entrapment efficiency of lamellar structures, micelles, or bilayer sheets.

Table.1 materials used for emulsome preparation with their uses.

Advantages of emulsomes –

- Drug concentration increased in damaged tissue.
- Low systemic absorption.
- Reduced toxicity
- A safe and efficient profile of cytotoxicity.
- Modify the drug's pharmacokinetics.
- Stop the development of resistance to many drugs.
- Slow medication release profile prolongs drug efficacy.
- Exceptional stability
- poorly water-soluble drugs have a high load capacity.
- pharmacological efficacy Improved while lowering toxicity.
- Make medications that are poorly soluble in water more soluble and bioavailable.[42]

Disadvantages of emulsomes -

- In parenteral administration, surfactants are used sparingly because of their detergent-like properties.
- During parenteral administration, it causes adverse effects.
- Drug loading capacity is limited.

• The excessive oil concentration compromises the stability of the formulation.[43]

Methods of preparation

Lipid film formation (Handshaking method)

This method entails casting lipids or surfactants as layers of film that make up their organic solution using a flask rotary evaporator at low pressure (or by hand shaking). After that, an aqueous medium is used to spread the cast films. [44] This procedure calls for constant, mild shaking. It is possible to apply the mechanical energy required to cause the lipid to swell and the cast lipid film to disperse by shaking the film by hand or by exposing it to nitrogen-saturated water steam for fifteen minutes, after which it can swell in the aqueous medium without shaking. While the hand shaking procedure produced multi-lamellar vesicles (MLV), the non-shaking strategy produced large unilamellar vesicles (LMV)

Reserve phase evaporation

The Reserve phase evaporation this technique also called REV method and it is comprised in a two steps. Prepare a phospholipid emulsion in water with an excess of organic phase buffer. With less pressure, remove the organic phase. Usually, mechanical techniques or sonication are used to emulsify the two phases (phospholipids and water). When the organic solvent is removed under vacuum, the water droplets covered with phospholipids clump together to produce a matrix that resembles gel. When the organic solvent is further removed and the pressure is lowered, the gel-like matrix transforms into a smooth paste. This paste is a LUV suspension.[46] This technique can yield drug entrapment efficiencies of 60–65%. Large and small compounds were both encapsulated using this technique.[47] In this process, organic solvents like freon, isopropylether, or chloroform are used to dissolve phospholipids. This procedure calls for constant, mild shaking. It is possible to apply the mechanical energy required to cause the lipid to swell and the cast lipid film to disperse by shaking the film by hand or by exposing it to nitrogen-saturated water steam for fifteen minutes, after which it can swell in the aqueous medium without shaking. While the hand shaking procedure

produced multi-lamellar vesicles (MLV), the non-shaking strategy produced large unilamellar vesicles (LMV).(figure-4)

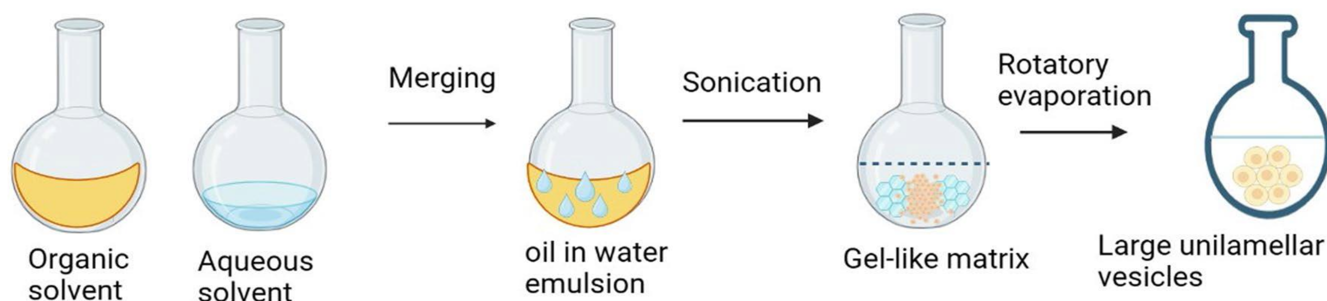

Figure 4: Reserve phase evaporation

Detergent removal technique

This method creates micellar mixtures by combining or mixing phospholipids with a detergent. The detergent was then eliminated from the mixture as the phospholipid content of the micelles increased and, at last, the lipids united to form single bilayer vesicles. These methods, which include adsorption onto bio beads, dialysis, and column chromatography, can remove the detergent from the formulation.[48] Additionally, emulsome preparation can be done using this technique. Typically, high critical micelle concentration (CMC) detergents are utilized for this purpose. Materials with high CMC (between 10 and 20 mM) such as octylglycoside, sodium cholate, sodium deoxycholate, and other detergents are suitable for this purpose.[49] In this method, the phospholipid detergent combination was sent through a dialysis cell to remove the detergent. This method was claimed to create a homogeneous population of single-layered emulsomes with mean sizes between 50 and 100 nm. [50,51] (figure-5)

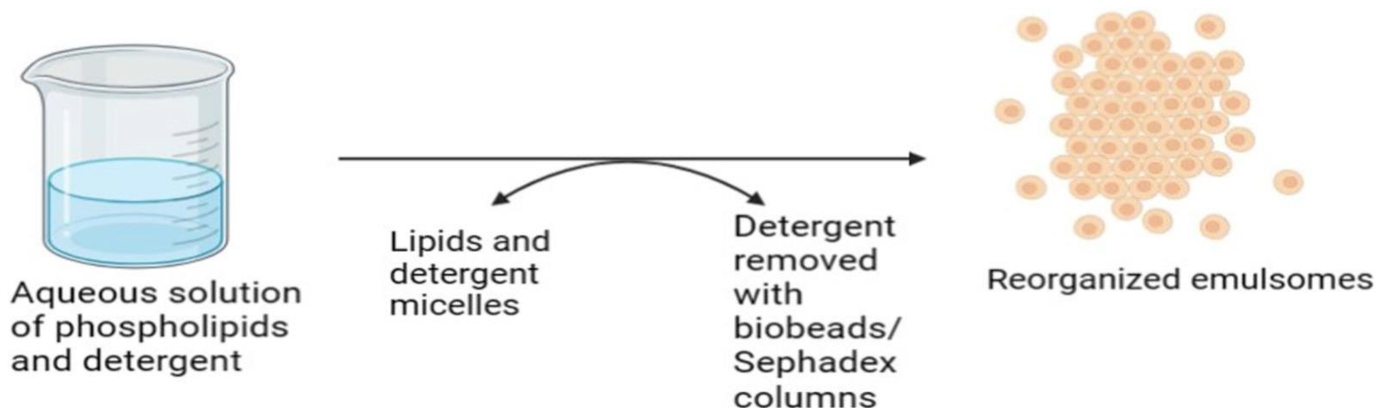

Figure 5: Detergent removal technique

Ethanol injection method

This method is one of the alternatives used to produce small unilammellar vesicles (SUVs), according to documentation. Using a small needle, a surfactant solution composed of ethanol is rapidly injected into an excess of saline or another aqueous media.[52] Ethanol forms vesicles when it evaporates. A tight distribution of tiny liposomes (less than 100 nm) can be created by the ethanol injection method, which involves merely injecting an ethanolic lipid solution in water or in a single step without extrusion or sonication. The right ethanol injection strategy can generate emulsomes with a moderate average radius on their own. [53,54] (figure-6)

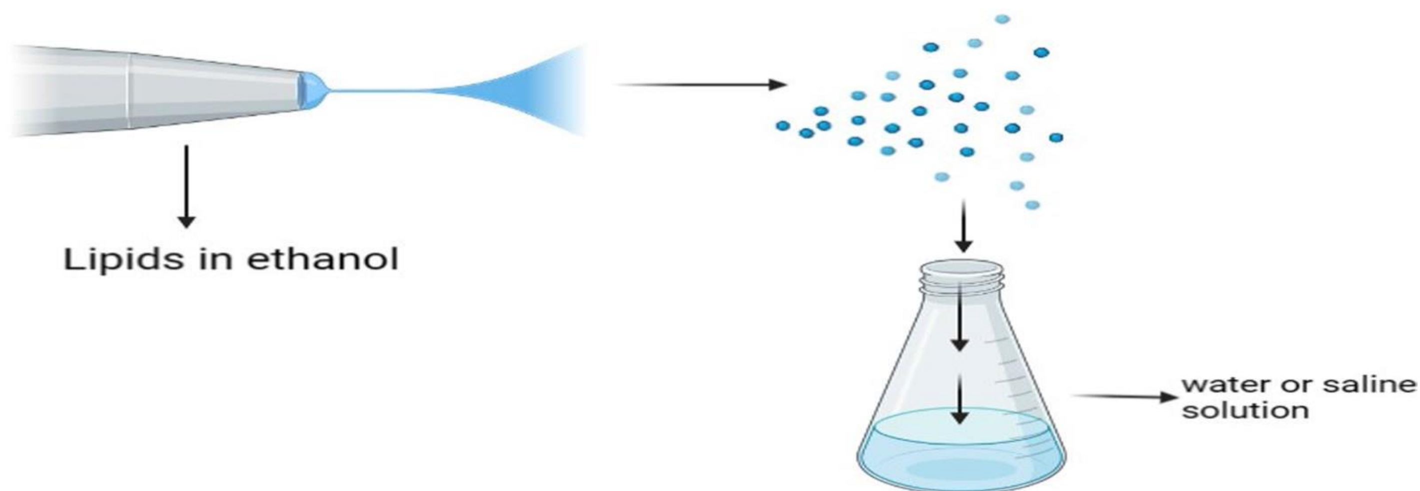

Figure 6 : Ethanol injection method

High-pressure extrusion technique

Numerous studies have demonstrated that when MLV are repeatedly transferred under high pressure through very small pore polycarbonate membranes (0.8 to 1.0 pm), the average diameter of the vesicles progressively shrinks, reaching a minimum of 60 to 80 nm after five to ten passes. When vesicles lose their typical size, they tend to become unilamellar.[55,56,57] Similar results have been reported by other studies when MLV is passed through a microfluidizer. A microfluidizer is a machine that forces feed material through a tiny hole using high pressure. Similar to how onion skin layers separate during peeling, it appears that when MLV are forced through the microscopic opening, bilayer layers are taken from the vesicular structure. Furthermore, it was suggested that the layer separation mechanism only applied to vesicles made of positively charged phospholipids and larger than 70 pm.[58] (figure-7)

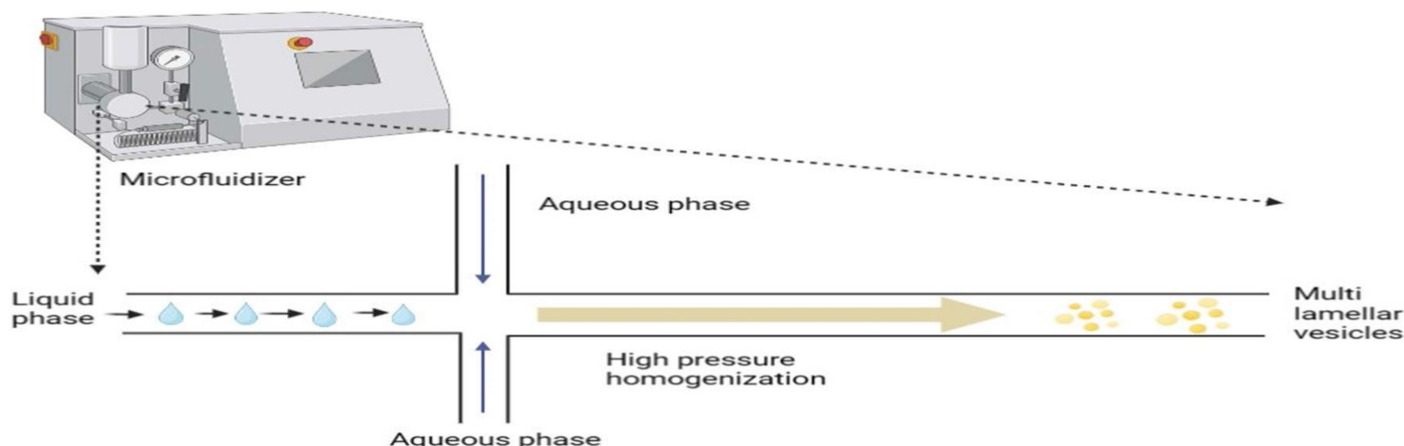

Figure 7 : High-pressure extrusion technique

Cast film method

When combined with phospholipids at a weight ratio of 0.5:1.0, triglycerides can undergo a phase transition from solid to liquid at temperatures over 25°C. The combination must be suspended in an aqueous solution at a temperature lower than the solid-to-liquid transition temperature in order to produce emulsomes. The liquid particle nano-emulsion that makes up these emulsomes has a mean diameter of 10–250 nm and a frequency of 50–150 nm. Usually, the particles fall between 20 and 180 nm in size.It is preferable to define the size range based on weight percentage as opposed to particle number. The lipid component may typically be a volatile organic solvent that is chemically non-reactive, such as dichloromethane or diethylether. A low-pressure rotary evaporator or an inert gas stream are typically used to remove the solvent. To hydrate and disseminate the resulting lipid layer, cover and shake with an aqueous solution. If the drug component wasn't in the organic solution, it may be added to the aqueous hydration solution. After that, the lipid suspension or dispersion is typically sized at pressures of up to 800 bar using a high shear homogenizant.[19]

Sonication method

This procedure involved dissolving solid lipids, cholesterol, and phosphatidylcholine in a little amount of chloroform that contained three or four drops of methanol in a round-bottom flask. The additions were made in different molar ratios. In this solution, a precisely weighed quantity of drug was dissolved. Using a rotary evaporator, the organic solvent was evaporated until it was entirely dry at reduced pressure, forming a thin lipid layer on the walls of the round bottom flask. [59,60,61] In order to produce nanoscale emulsomes, 10 milliliters of phosphate-buffered saline (pH 7.4) were used to hydrate the dry film. After that, ultrasonication was used for 15 minutes at 40% frequency to homogenize it.[62,63] (figure-8)

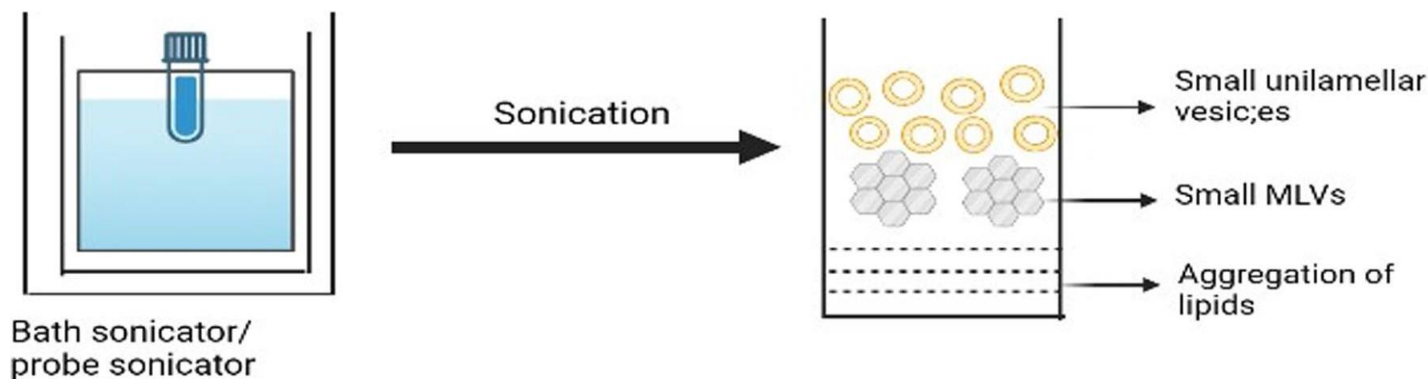

Figure 8: Sonication method

Evaluation of emulsomes –

1) Entrapment efficiency (EE%)

Centrifugation was used for 1 hour at 15,000 rpm at 4°C to separate the non-entrapped medication from the emulsomes in the cooled samples.[64] Using 1% Triton X to dissolve emulsomes and spectrophotometrically detecting the drug's concentration at l max 305 nm, the EE% of oxcarbazepine was ascertained.[65] The following formula was used to determine the EE%

$$EE\% = Entrapped\ drug\ /\ Total\ drug \times 100$$

2) Transmission electron microscopy (TEM)

A drop of 1% phosphotungstic acid was then added to the emulsomes to negatively stain them. A 50 mL drop of the vesicular dispersion was put on a carbon-coated grid, left to adsorb on the carbon film for two minutes, and any extra liquid was wiped out with fiber-free, toughened filter paper to image a sample of the generated emulsomal particles. The grid was cleaned with distilled water, any leftover discoloration was removed with filter paper, and it was then allowed to air dry. The sample underwent a 200 kV TEM analysis with a magnification of X 25000.[66]

3) Drug release

OX-bearing emulsomes' permeability through the cellophane membrane was investigated in Franz-type diffusion cells.Three milligrams of medication's worth of emulsomes were present in the donor compartmentThe receptor compartment, which was maintained at 37 + 0.2 °C by a flowing water jacket, contained 7.5 mL of phosphate buffer (pH 6.8) that was continuously mixed by a small magnetic bar rotating at 50 rpm.[67] In order to replicate the low mixing conditions found in the nose, this low stirring rate was used.[68]

4) Particle characterization

The freshly manufactured emulsomes' average particle size and size distribution were estimated using dynamic light scattering (DLS) and represented by the polydispersity index (PDI). To find the zeta potential, or z, electrophoretic light scattering was employed with a Zetasizer Nano ZS fitted with 4 mW 633 nm He-

Ne lasers. Samples were allowed to equilibrate at 25°C after being suitably diluted with deionized water to avoid multi-scattering. Analysis was conducted at an angle of 173 degrees.[69]

Stability of emulsomes

The ability of the nanocarrier to sustain its biophysical properties over time, such as size, zeta potential, and drug retention, is known as stability in relation to DDSs mediated by nanoparticles. Because of their high absolute levels of zeta potential, emulsomes are consequently predicted to be physically stable, which lowers the likelihood of coalescence. [70] Emulsomes' superior stability in suspensions over liposomes and other lipid-based formulations may prove to be very advantageous in therapeutic settings.[71] Two essential components are combined to create emulsomes: phospholipid, which gives the lipidic core its vesicular steric stability by enclosing it. It is feasible to create a pharmaceutically stable emulsomal formulation without the need for an extra surfactant or solubilizer. PEGylation of the emulsome surface will therefore help to increase steric stability and extend circulation time.[72,73]

The stability of the nanocarrier is significantly influenced by the physicochemical characteristics of the lipids used and the storage temperature.[74] Zeta potential is a crucial component of stability, and in order to study the storage stability of electrostatically stabilized vesicles and comprehend the workings of dispersion and aggregation processes, it is unquestionably vital to measure the zeta potential in these containers. When the kind of lipid was altered, the zeta potential improved, but it was shown to be notably negative for the fats used in emulsomes, such as tristearin, compritol ATO 888, and trilaurin. More energy is added during sonication, resulting in a decrease in particle size and zeta potential and the production of stable, tightly packed emulsomes. [72,75]

Biopharmaceutical aspects

The solubility of inefficient luminal medicines is increased with the help of emulsomes. The GI tract's lipids increase the secretion of endogenous biliary lipids, including phospholipid and cholesterol. This leads to the formation of intestinal mixed micelles that contain phospholipid, cholesterol, and bile salts and improves the GI tract's ability to solubilize substances. But when exogenous lipids are added to these bile salt complexes, either directly or indirectly through digestion, the micellar structures grow and can become more soluble. [76] When intestinal lymphatic transport is stimulated, lipids may either directly or indirectly increase bioavailability by decreasing first-pass metabolism or by increasing lymphatic transport.

Emulsomes have the potential to improve bioavailability by altering the GI tract's biochemical barrier function. As demonstrated by the p glycoprotein efflux pump, it is evident that the lipids and triglycrides included in the emulsomal preparation may lessen the amount of enterocyte-based metabolism as well as the activity of intestinal efflux transporters.[77,78]

The physical barrier function of the GI tract may be changed by emulsomes. Certain mixtures of lipids and triglycerides have been shown to have properties that increase permeability. [79,80]

Application of Emulsomes

Drug targeting

The ability of emulsomes to target medications is one of their greatest benefits. The reticulo-endothelial system is a target for medication delivery via emulsomes. Emulsome absorption is favored by the reticuloendothelial system. Circulating blood factors known as opsonins regulate the consumption of Emulsomal vesicles. To be cleared, these opsonins identify the vesicles. Drugs with this specific location are used to treat malignancies in animals whose liver and spleen are known to metastasis. Hepatic parasite infections can also be treated with this drug fixing method. In addition to the reticuloendothelial system, emulsomes can be utilized to direct medications to other organs. Vesicles have the ability to be targeted to particular organs by attaching a carrier system to them.[81,82]

Increase bioavailability of lipophillic drugs

Emulsomes have been shown to be an effective drug delivery vehicle for lipophillic medicines, which have low water solubility in biological fluids and hence low drug absorption and bioavailability. Emulsomes are made of solid lipid at their center, which entraps lipophillic medicines and releases them gradually. Emulsomes also benefit from having a higher drug content, which lowers dosage frequency and improves entrapment efficiency.[83]

Anti-neoplastic treatment

The adverse effects of most antineoplastic drugs are immediate. By altering a drug's metabolism, lengthening its half-life, and boosting its circulation, emulsomes might lessen the negative effects of the medication. When compared to the unentrapped medicines, methotrexate exhibited favorable effects from enzymatic entrapment, including a slowed rate of tumor development and increased plasma levels that were followed by a delayed clearance.[81,84]

Leishmaniasis

Leishmaniasis is caused by a parasite from the genus Leishmania that infects the cells of the liver and spleen. Antimony compounds, which can harm the kidneys, liver, and heart in excessive doses, are commonly prescribed medications for the condition. Emulsome was used in experiments to demonstrate that bigger dosages of the medication may be given without causing side effects, increasing treatment efficacy.[81,85]

AIDS treatment

The medication ziduvodine is a approved to treat AIDS. Due to its high lipophillicity, the medication has altered pharmacokinetics and some major adverse effects. Low bioavailability of zidovudine and other side effects have been resolved by encapsulating the drug in emulsomes.

Dermal therapy

Dithranol has been used to treat psoriasis, yet the medication has unfavorable side effects that include erythema, peeping, staining, and skin irritation. However, the addition of dithranol to emulsomes improves medication retention in skin tissue and increases skin penetration while reducing negative effects. [86]

Future Aspects

Emulsomes represent a potentially effective method for the formulation of pharmaceutical substances exhibiting variable oral bioavailability and poor aqueous solubility. Emulsomes can facilitate the oral delivery of hydrophobic medicines, since they have demonstrated a significant improvement in oral bioavailability. Emulsome renaissances throughout the last few decades are drawing more and more attention. the last few decades are drawing more and more interest. An increase in oral bioavailability cannot be predicted using many in vitro models, and most emulsome development is still empirical. The creation of in vitro methods for predicting the dynamic changes involving the drug in the gut is necessary for tracking the medication's solubilization condition in vivo.The interactions between the pharmacologically active ingredient and lipid systems also require consideration. In order to create recommendations that enable the early identification of viable candidate formulations, it is also necessary to comprehend the characteristics of diverse lipid formulations. Both further basic research on the mechanisms of action of this fascinating and diverse collection of formulations and future studies or research on human bioavailability are required.

Conclusion:

Emulsomes' distinct structural makeup and adaptable properties make them a promising development in the realm of medication delivery systems. Emulsomes combine the advantages of liposomes with emulsions to provide sustained release profiles, increased stability, and better drug loading capacity. They are extremely

versatile for a range of therapeutic applications, such as controlled release systems and targeted drug administration, because they can encapsulate both hydrophilic and hydrophobic medications. Additionally, site-specific targeting can be accomplished by functionalizing emulsomes, increasing therapeutic efficacy while reducing adverse effects. Even with these encouraging characteristics, more research is required to improve their formulation, look into long-term stability, and assess their efficacy and safety in clinical settings. In conclusion, emulsomes have a lot of promise as a new vesicular platform for targeted therapy and improved drug delivery, opening the door for more developments in pharmaceutical formulations in the future.

Refrences-

1] Biju S.S., Talegaonkar S., Mishra P.R., Khar R.K. Vesicular systems: An overview. Ind. J. Pharma. Sci. 2006; Vol. 68 (2):141-153.

2] Goldberg E.P.Eds., In;, 2nd edn, Wiley, Newyork, (1983) 312.

3] Bhatt DA, Pethe AM (2010) Lipoidal technology-a promising drug delivery for poorly water soluble drugs.Int J Pharm Res Dev 2(7): 1-11.

4] . Sunil Kamboj, Vipin Saini, et al. (2013) Vesicular drug delivery systems: A novel approach for drug targeting. International Journal of Drug Delivery 5(2): 121-130.

5] Kumar D, Sharma D, Singh G, Singh M, Rathore MS. Lipoidal soft hybrid biocarriers of supra molecular construction for drug delivery. Int. Scholar Res Network Pharm. 2012; 2012:1-14

6] Nair AS, Vidhya KM, Saranya TR, Sreelakshmy KR, Nair SC. Emulsomes: a novel liposomal formulation for sustained drug delivery. Int Res J Pharm Appl Sci. 2013;3(5):192-6

7] Amselem AS, Friedman D. Solid fat nanoemulsion. 1997, United States Patent no. 5,662,932(02-09-1997).

8] Choudhury H, Zakaria NFB, Tilang PAB, Tzeyung AS, Pandey M, ChatterjeeB, Alhakamy NA, Bhattamishra SK, Kesharwani P, Gorain B (2019) Formulation development and evaluation of rotigotine mucoadhesive nanoemulsion for intranasal delivery. J Drug Deliv Sci Technol 54:101301

9] Yilmaz EN, Bay S, Ozturk G, Ucisik MH (2020) Neuroprotective effects of curcumin-loaded emulsomes in a laser axotomy-induced cns injury
model. Int J Nanomed 15:9211–9229.

10] Erdő F, Bors LA, Farkas D (2018) Evaluation of intranasal delivery route of drug administration for brain targeting. Brain Res Bull 143:155–170

11] Ghode PS, Ghode DP (2020) Applications perspectives of emulsomes drug delivery system. Int J Med Pharm.

12]Kumar MS, Khurana B, Arora D, Mahadevan N. Development of amphotericin B loaded modified emulsomes for visceral leishmaniasis: in vitro. Int J Recent Adv Pharm Res2011; 2:14-20

13] Raza K, Katare OP, Setia A, Bhatia A, Singh B. Improved therapeutic performance of dithranol against psoriasis employing systematically optimized nanoemulsomes; J Microencapsul. 2012:1-12.

14] Vyas SP, Subhedar R, Jain S. Development and characterization of emulsomes for sustained and targeted delivery of an antiviral agent to liver. J Pharm Pharmacol.2006; 58:321-326.

15] Amselem, Shimon, Zawoznik E, Yogev A, Friedman, D (2018) Emulsomes, a new type of lipid assembly. In Handbook of Nonmedical Applications
of Liposomes: Volume III: From Design to Microreactors, CRC Press, pp

209-223

16] Maher S, Casettari L, Illum L (2019) Transmucosal absorption enhancers in the drug delivery field. Pharmaceutics 11(7):339.

17] Hadel A, El-Enin A, Mostafa ER, Ahmed FM, Naguib AI, Abdelgawad A,Ghoneim MM, Abdou ME (2022) Assessment of nasal-brain-targeting efficiency of new developed mucoadhesive emulsomes encapsulating an anti-migraine drug for effective treatment of one of the major psychiatric
disorders symptoms. MDPI; Pharmaceutics 14:410

18] Schwarz C, Mehnert W, Lucks JS, Muller RH (1994) Solid lipid nanoparticles (SLNs) for controlled drug delivery: I. production, characterization and sterilization. J Control Releas 30:83–96

19] Mehmet H Ucisik, Uwe B Sleytr, Bernhard Schuster (2015) Emulsomes meet S-layer proteins: an emerging targeted drug delivery system 16(4):392-405.

20] Patel, R. R., & Patel, K. D. (2018). Emulsomes: A novel drug delivery system. *Journal of Drug Delivery Science and Technology*, 44, 137-144. DOI: 10.1016/j.jddst.2018.04.002

21] Kumar R, Nirmala KHLS (2013) Emulsomes: an emerging vesicular drug delivery system. J Drug Deliv Ther 3(6):133–142

22] Solid Fat Nanoemulsions As Drug Delivery Vehicles-Patent 5576016. Available from: http://www.docstoc.com/docs/48874511/Solid-Fat-Nanoemulsions-As-Drug-Delivery-Vehicles-Patent-5576016.

23] Hauss DJ. Oral lipid based formulations. Adv Drug Deliv Rev 2007;59:667- 76.

24] Hofmann AF, Borgstrom B. The intraluminal phase of fat digestion in man: The lipid content of the micellar and oil phases of intestinal content obtained during fat digestion and absorption. J Clin Invest 1964;43:247-57.

25] Pouton CW. Formulation of poorly water-soluble drugs for oral administration: Physicochemical and physiological issues and the lipid formulation classification system. Eur J Pharm Sci 2006;29:278-87.

26] Chambin O, Jannin V. Interest of multifunctional lipid excipients: Case of Gelucire 44/14. Drug Dev Ind Pharm 2005;31:527-34.

27] Vilhemsen T, Eliasen H, Schaefer T. Effect of a melt agglomeration process on agglomerates containing solid dispersions. Int J Pharma 2005;303:132-42.

28] Banerjee A, Roychoudhury J, Ali N. Stearylamine-bearing cationic liposomes kill leishmania parasites through surface exposed negatively charged phosphatidylserine. J Antimicrob Chemother 2008;61:103-10.

29] Sudhamani T, Priyadarisini N, Radhakrishna. Proniosomes-A promising drug carriers. Int J PharmTech Res 2010;2:1446-54.

30] Sek L, Porter CJH, Charman WN. Characterisation and quantification of medium chain and long chain triglycerides and their in-vitrodigestion products, by HPTLC coupled with in situ densitometric analysis. J Pharm Biomed Anal 2001;25:651-61.

31] Mujoriya R, Bodla RB, Dhamande K, Singh D, Patle L. Niosomal drug delivery system: The magic bullet. JAPS 2011;1:20-3.

32] Ruckmani K, Sankar V. Formulation and optimization of zidovudine niosomes. AAPS PharmSciTech 2010;11:1119 27.

33] Venkatesan N, Vyas SP. Polysaccharide coated liposomes for oral immunization: Development and characterization. Int J Pharm 2000;203:169-77.

34] Hood E, Gonzalez M, Plaas A, Strom J, VanAuker M. Immunotargeting of nonionic surfactant vesicles to inflammation. Int J Pharm 2007;339:222- 30.

35] Azeem A, Anwer MK, Talegaonkar S. Niosomes in sustained and targeted drug delivery: Some recent advances. J Drug Target 2009;17:671-89.

36] Barry BW. Novel mechanisms and devices to enable successful transdermal drug delivery. Eur J Pharm Sci.

37] Devaraj GN, Parakh SR, Devraj R, Apte SS, Rao BR, Rambhau D. Release studies on niosomes containing fatty alcohols as bilayer stabilizers instead of cholesterol. J Colloid Interface Sci 2002;251:360-5.

38] Kirby C, Clarke J, Gregoriadis G. Effect of cholesterol content of small unilamellar liposomes on their stability in vivo and in vitro. Biochem J 1980;186:591-8.

39] Pires, A. D. S., da Silva, R. M., & de Lima, D. R. (2018). The influence of cholesterol on the stability and drug entrapment efficiency of liposomes. *Journal of Liposome Research*, 28(1), 55-63. DOI: 10.1080/08982104.2017.1357044

40] Harder T, Simons K. Caveolae, digs, and the dynamics of sphingo-lipid cholesterol microdomains. Curr Opin Cell Biol 1997;9:534-42.

41] Papahadjopoulos D, Cowden M, Kimelberg H. Role of cholesterol in membranes, effects on phosphor lipid protein interactions, membrane permeability and enzymatic activity. Biochim Biophys Acta 1973;330:8-26.

42] Gill B, Singh J, Sharma V, Kumar SH. Emulsomes: An emerging vesicular drug delivery system. Asian J Pharm. 2014;6(2):87-94.

43] Khan, M. I., Ullah, N. F., & Awan, M. M. (2020). Formulation and stability of emulsions: Effect of oil content and emulsifier type. *Journal of Dispersion Science and Technology*, 41(1), 23-32. DOI: 10.1080/01932691.2019.1654580

44] Snjezana S. PLGA nanoparticles prepared by nanoprecipitation: Drug loading and release studies of water soluble drug. J Control Release 1999;57:171-85.

45] Ibrahim MMA, Sammour OA, Hammad MA, Megrab NA. In vitro evaluation of proniosomes gel as A drug carrier for flurbiprofen. AAPS PharmSciTech 2008;9:782-90.

46] Fang JY, Hong CT, Chiu WT, Wang YY. Effect of liposomes and niosomes on skin permeation of enoxacin. Int J Pharm 2001;219:61-72.

47] Dipali SR, Kulkarni SB, Betageri GV. Comparative study of separation of non-encapsulated drug from unilamellar liposomes by various methods. J Pharm Pharmacol 1996;48:1112-5.

48] Domazou A, Luisi PL. Size distribution of spontaneously formed liposomes by the alcohol injection method. J Liposome Res 2002;12:205- 20.

49] Kagawa Y, Racker E. Partial resolution of the enzymes catalyzing oxidative phosphorylation. J Biol Chem 1971;246:5477-87.

50] Milsmann MHW, Schwendner RA, Weder H. The preparation of large single bilayer liposomes by a fast and controlled dialysis. Biochim Biophys Acta 1978;512:147-55.

51] Enoch HAG. Strittmatter P. Formation and properties of 1000 A diameter, single-bilayer phospholipid vesicles. Proc Natl Acad Sci U S A 1979;76:145-9.

52] Dayan N, Touitou E. Carriers for skin delivery of Trihexyphenidyl HCl: Ethosomes vs. Liposomes. Biomaterials 2000;21:1879-85

53] Sugarman SM, Zou YY, Wasan K, Poirot K, Kumi R, Reddy S, et al. Lipid-complexed camptothecin: Formulation and initial biodistribution and anti-tumor activity studies. Cancer Chemother Pharmacol 1996;37:531-8.

54] Vemuri S, Yu C, Wangsatorntanakun V, Roosdorp N. Large-scale production of liposomes by Microfluidizer. Drug Dev Ind Pharm 1990;16:2243-56.

55] Ljeoma FU, Vyas SP. Non-ionic surfactant based vesicles in drug delivery. Int J Pharm 1998;172:33-70

56] Szoka F, Papahadjopoulos D. Procedure for preparation of liposomes with large internal aqueous space and high capture by reverse-phase evaporation. Proc Natl Acad Sci U S A 1978;75:4194-8.

57] Vemuri S, Rhodes CT. Preparation and characterization of liposomes as therapeutic delivery systems: A review. Pharm Acta Helv 1995;70:95-111.

58] Balasubramaniam A, Kumar VA, Palliai KS. Formulation and in-vivo evaluation of niosomes encapsulated daunorubicin hydrochloride. Drug Dev Ind Pharm 2002;28:1181-93.

59] Hope MJ, Bally MB, Webb G, Cullis P. Production of large unilamellar vesicles by rapid extrusion procedure: Characterization of size distribution, trapped volume, and ability to maintain a membrane potential. Biochim Biophys Acta 1985;812:55-65.

60] Batzri S, Korn ED. Single bilayer liposomes prepared without sonication. Biochim Biophys Acta 1973;298:1015 9

61] Fry DW, White JC, Goldman ID. Rapid separation of low molecular weight solutes from liposomes without dilution. Anal Biochem 1978;90:809-15.

62] Gao, Y., Zhang, H., & Chen, J. (2019). Preparation and characterization of emulsomes for drug delivery: Optimization of the formulation. *Drug Delivery*, 26(1), 103-110. DOI: 10.1080/10717544.2019.1560325

63] Gupta S, Vyas SP. Development and characterization of Amphotericin B bearing emulsomes for passive and active macrophage targeting. J Drug Target 2006;15:206-17.

64] Chandrika, M., Babul, K., 2014. Design and development of Candesartan cilexetil emulsomal drug delivery systems for the effective management of cardiovascular diseases. Indian J. Res. Pharm. Biotechnol. 2320–2347, 1284– 1288.

65] Enéas, P.C., Barbosa de Oliveira, R., Pianetti, A., 2010. Oxcarbazepine: validation and application of an analytical method. Braz. J. Pharm. Sci. 46, 265–272.

66] El Zaafarany, G.M., Awad, G.A.S., Holayel, S.M., Mortada, N.D., 2010. Role of edge activators and surface charge in developing ultra deformable vesicles with enhanced skin delivery. Int. J. Pharm. 397, 164–172.

67] Florence, K., Manisha, L., Kumar, B.A., Ankur, K., Kumar, M.A., Ambikanandan, M., 2011. Intranasal clobazam delivery in the treatment of status epilepticus. J. Pharm. Sci. 100, 692–703.

68] Amidi, M., Romeijn, S.G., Borchard, G., Junginger, H.E., Hennink, W.E., Jiskoot, W., 2006. Preparation and characterization of protein-loaded N-trimethyl chitosan nanoparticles as nasal delivery system. J. Controlled Release 111, 107–116.

69] Seju, U., Kumar, A., Sawant, K.K., 2011. Development and evaluation of olanzapine-loaded PLGA nanoparticles for nose-to-brain delivery: in vitro and in vivo studies.Acta Biomater. 416, 9–4176.

70] Zhou X, Chen Z (2015) Preparation and performance evaluation of emulsomes as a drug delivery system for silybin. Arch Pharm Res 38(12):2193–2200.

71] Dubey S, Vyas PS (2021) Emulsomes for lipophilic anticancer drug delivery: development, optimization and in vitro drug release kinetic study. Int J App Pharm 13(2):114–121.

72] Mishra, A., & Lathwal, S. (2021). Emulsomes: A promising drug delivery system. *Pharmaceutical Development and Technology*, 26(7), 830-845. DOI: 10.1080/10837450.2020.1826872

73] Zakaria MY, Zaki I, Alhomrani M, Alamri AS, Abdulaziz O, Abourehab MA (2022) Boosting the anti MERS-CoV activity and oral bioavailability of resveratrol via PEG-stabilized emulsomal nano-carrier: factorial design,in-vitro and in-vivo assessments. Drug Deliv 29(1):3155–3167.

74] Ghosh A, Kaur CD, Gupta A, Saraf S (2017) Surface engineered lamivudine loaded emulsome for targeting drug delivery to lymphatic system for effective treatment of hiv. Int J Appl Pharm Biol Res 2(1):25–37

75] Priya S, Desai MV, Singhvi G (2023) Surface modification of lipid-based nanocarriers: a potential approach to enhance targeted drug delivery. ACS Omega 8(1):74–86.

76] Porter CJH, Charman WN. Uptake of drugs into the intestinal lymphatics after oral administration. Adv Drug Deliv Rev 1997;25:71-89.

77] Dintaman JM, Silverman JA. Inhibition of P-glycoprotein by Dalpha-tocopheryl Polyethylene Glycol 1000 Succinate (TPGS). Pharm Res 1999;16:1550-6.

78] Nerurkar MM, Burton PS, Borchardt RT. The use of Surfactants to Enhance the Permeability of Peptides Through Caco-2 Cells by Inhibition of An Apically Polarized Efflux System. Pharm Res 1996;3:528-34.

79] Aungst BJ. Intestinal permeation enhancers. J Pharm Sci 2000;89:429-42.

80] Muranishi S. Absorption enhancers. Crit Rev Ther Drug Carrier Syst 1990;7:1-33.

81] Bhawandeep Gill, Jatinder Singh, et al. (2012) Emulsomes: An emerging vesicular drug delivery system. Asian Journal of Pharmaceutics 6: 87-94.

82] Erion MD, Van Poelje PD, et al. (2005) Liver-targeted drug delivery using hepdirect prodrugs. J Pharmacol Exp Ther 312: 554-560.

83] Liu, Y., & Chen, H. (2015). "Emulsomes: A novel approach to deliver poorly soluble drugs." *Journal of Controlled Release*, 205, 154-162. DOI: 10.1016/j.jconrel.2015.03.021

84] Moghbel A, Zand Moghaddam A, et al. (2003) High performance liquid chromatography determination of methotrexate in plasma. Iran J Pharm Res 2: 149-152.

85] Sanchez-Brunete JA, Dea MA, , et al. (2004) Treatment of experimental visceral leishmaniasis with amphotericin B in stable albumin microspheres. Antimicrob Agents Chemother 48: 3246-3252

86] Ali, J., & Khar, R. K. (2013). "Role of emulsomes in drug delivery." *European Journal of Pharmaceutical Sciences*, 48(3), 661-672. DOI: 10.1016/j.ejps.2012.10.008