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# Emulsomes drug delivery: A review

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**Abstract**
Emulsomes are developed as a novel lipoidal vesicular system with an internal solid fat core surrounded by a phospholipid bilayer. Hence, this will act as a carrier and vehicle of choice for the poorly soluble drugs. Many techniques has been developed for increasing the solubility of poorly soluble drugs. Among them emulsomes is the most prominent and recent technology. It is designed to overcome the drawbacks associated with current lipoidal formulations. This review addresses the concepts of emulsomal drug delivery system and special attention to its advantages and various recent applications related to the drug delivery.

**Keywords:** vesicular drug delivery system, emulsomes, phospholipid bilayer, sustain release

## Introduction
Vesicular drug delivery system (VDDS) is the system which involves encapsulation of active drug in vesicular structure. Vesicles act as vehicle in the drug delivery system Eg: liposome, nio some, archeo some, transferosome, sphinosome, pharmacosome, ufasome, emulsome, etc [1]. Hence, it enhances the existence of drug in the systemic circulation and also reduce toxicity. The application of novel vesicular technology has changed the definitions of diagnosis and treatment in the different aspects of biomedical field. These types of systems are widely used in the gene delivery, tumour targeting to brain, oral formulations, in stability and permeability problems of drugs [2].

## Objectives of vesicular drug delivery systems
1. Prolong the existence of the drug in the systemic circulation, and hence reduces the toxicity if selective uptake can be achieved due to the delivery of drug directly to the site of infection.
2. [2] Improves the bioavailability especially in the case of poorly soluble drugs.
3. [3] Both hydrophilic and lipophilic drugs can be incorporated.
4. [4] Delays elimination of rapidly metabolizable drugs and thus function as sustained release systems.

## Emulsomes
Emulsomes are the novel lipoidal vesicular system with an internal solid fat core surrounded by a bilayer of phospholipid. Emulsomes are more stable than liposomes. The stability problems associated with convential liposomes or other vesicular delivery systems such as aggregation, susceptibility to hydrolysis and oxidation may be avoided by using emulsomes [3].
Emulsomes have the characteristics of both liposomes and emulsions. This technology is developed to act as a vehicle for poorly soluble drugs. Emulsomes act by encapsulating the active medicament in vesicular structure. Hence, it prolongs the existence of drug in the systemic circulation for a long period of time and reduces toxicity. The convential drug delivery system is unable to meet these needs [4].
Emulsomal formulations are stabilized by cholesterol and soya lecithin. It can encapsulate water-soluble drugs in the aqueous compartments of the outer phospholipid layers, while their cores can be loaded with high levels of hydrophobic drugs. Emulsomes thereby increase the solubility and improve the bioavailability of lipophilic drugs and facilitates sustained and controlled release.[5]The colloidal nature of emulsomes provide passive absorption from the bloodstream by liver and spleen macrophages after intraveneous administration [6].
Emulsomal drug delivery is a liquid based drug delivery system. It has a wide range of therapeutic application in case of parentral drug delivery, which is purely water soluble. In case of lipophilic drugs since it has limited water solubility, large quantity of surfactants and co-solvents has to be used, but it may lead to toxic effects.
Emulsomes are distinct from standard oil in water emulsions. The high phospholipid content of the monolayer of phospholipids that cover the lipid core which is present at the interface thereby stabilizing the emulsions. The particle size distribution of of emulsomes is in the range of 10-250nanometer, which is based on differential weight, making them suitable for intravenous administration. Emulsomal formulation exhibit a sufficiently slow drug release profile that is 12-15% after 24 hours.[7]Emulsomes may serve as efficient drug delivery systems because they exhibit good biocompatibility, stability, high entrapment efficiency and sustain release [8].

## Advantages
- Economical alternative to current lipoidal formulations.
- Increased drug levels at injured tissues.
- Protect drug from gastric environment.
- Increase solubility and bioavailability of poorly aqueous soluble drugs.
- Safe cytotoxicity profile.
- Resist the development of multi drug resistance.
- Modify the pharmacokinetics of drugs.

- Provide improved pharmacological activity and reduce toxicity.
- Slow drug release profile and prolonged drug efficacy.
- Surface modifications can be possible, eg: for cellular targeting.
- High load capacity for poorly water-soluble drugs.
- High stability.
- Low production cost and simplicity of large scale production.

**Disadvantages**
- Low drug loading capacity.
- Causes side effects while parentral delivery.
- Due to the detergent properties, use of surfactants is limited in parentral administration.
- High oil content reduces the stability of the formulation.

**Applications in drug delivery**
The solid lipid core and phospholipid (PL) multilayer surrounding the core of emulsomes allow encapsulation of lipophilic drugswhose medical implementation could be limited owing to thelack of solubility.

**Emulsomes in anti-viral therapy**
Azidothymidine (AZT), also called Zidovudine, was the first drug reported to be efficacious in inhibiting human immunodeficiency virus (HIV) replication. [9, 10]
The delivery of AZT, is possible by trilaurin-based emulsomes, or solid lipid nanoparticles stabilized with dipalmitoyl phosphatidylcholine (DPPC) or amixture of DPPC and dimyristoylphosphatidylglycerol (DMPG). DPPC provide theemulsomes a neutral surface charge, whereas DMPG resulted in a net negative charge. An ester prodrug of Zidovudine, AZT palmitate (AZT-P), can be synthesized and incorporated in the emulsomes. AZT-P is an amphiphilic molecule and integrates within the PL bilayers of the Nano formulation than the internal solid core. Negatively charged PL bilayers, i.e. DMPG, enhance the incorporation of AZT-P compared with emulsomes of neutral charge.[11]
Emulsomal formulations for the treatment of intracellular liver infections by sustained and targeted delivery of AZT can also be possible [12]. Trilaurin and tristearin based emulsomes with a positive charge are expected to protect the system from lysosomal degradation and ensure the internalization of the drug. Cationic emulsomes are able to maintain their high drug concentrations in liver for a long period time (at least 6 hours).
Higher bioavailability of lamivudine at lymphatic system can be achieved successfully with lipid based carrier system like emulsome. Lamivudine loaded emulsome may be an effective carrier for anti-HIV drugs. It can be therapeutically more effective for the HIV management as compare to the convential drug delivery system [13].

**Emulsomes in dermal therapy**
Dithranol, also known as anthralin, has been used for the treatment of psoriasis (i.e. a non-contagious autoimmune skin disorder). Its use has fallen steadily due to unwanted side effects such as skin irritation, erythema, peeking and staining.[14]However, encapsulation of dithranol within the lipidic core of emulsomes enhance significantly their permeation across the skin and improve drug retention in skin tissues.[15]Various compritol (glyceryl behenate) based emulsomes can be prepared by using the formulation by design (FbD) approach. Accordingly, the highest entrapment efficacy was achieved for emulsion formulations composed of 63-75% compritol and 25-37% PL. An increase in the amount of PLs decreased the permeation flux through the skin due to the assembly of multilamellar barriers [16]. Antipsoriatic study conducted on mouse-tail models showed that emulsomes has better pharmacodynamics activity than commercial products and no erythema and wrinkles are produced on the mice skin, provide evidence that, emulsomes can diminish potential side effects of dithranol while improving its medical efficacy.

**Emulsomes in Autoimmunity**
If a vaccine composition is combined with
1. Protein or peptide antigens
2. optionally added hydrophobic material and
3. an immune-potentiating membranous carrier such as an emulsome, the antigenic integrity of the protein or peptide epitopes is preserved and the immunogenicity of the vaccine is improved. [17, 18]

Emulsomes can be used as adjuvants for mucosal vaccines.[19] Combination of anti-CD3 mAb and emulsome (as adjuvant) suppress antibody production against type II collagen and improve the severity of joint pathology as a result of reduced inflammatory cytokines in joints. Emulsomes enhance the Th2 response resulting in the induction of LAP+ (latency associated peptide) regulatory T cells and suppression of ongoing arthritis by both nasal and oral anti-CD3 administration.[20] This approach was found to be safe and applicable for mucosal and non-invasive therapy for rheumatoid arthritis.

**Emulsomes in anti-neoplastic therapy**
Anti-neoplastic therapy has severe side effects. Emulomes can alter the metabolism, prolong circulation and half life of the drug and therefore decrease the side effects.
Mainly two drugs, methotrexate (MTX) and curcumin can be used to incorporate in emulsomes.[21,22]MTX is an anti-folate drug against broad spectrum of human cancers including osteosarcoma, lymphoma, choriocarcinoma and leukemia [23]. MTX is also used for psoriasis, rheumatoid arthritis, systemic sclerosis, placenta accreta, and ectopic pregnancy, since it is an anti-metabolite chemotherapeutic agent [24].
For lymphatic delivery of MTX, emulsome formulations are composed of compritol® 888 ATO as the lipid core and soya lecithin as a stabilizing shell.In vitro drug release analysis demonstrated that emulsomes slowly release MTX at pH 7.4 (simulated intestinal fluid), whereas at pH 1.2 (simulated gastric fluid) a burst release of MTX occurs, indicating that in gastrointestinal tract the PL bilayers and compritol® 888 ATO did not provide stability to the formulation.[25]In vivo, emulsome formulations improve the bioavailability of MTX up to 5.7-fold.
Curcumin, (diferuloylmethane) is a hydrophobic polyphenol derived from the rhizome of the herb Curcuma longa (turmeric) of Zingiberaceae family [26]. It has a wide range of therapeutic effect against a broad variety of different cancers including gastrointestinal, genitourinary, breast, ovarian, lung, and neurological cancer; leukemia and

lymphoma; head and neck squamous cell carcinoma; nmelanoma; and sarcoma.[27,28,29] It is mainly affected by its short biological half-life, poor water solubility and low bioavailability after oral administration [26, 30].

Curcumin- emulsomes Nano formulations (curcu Emulsomes), improve the solubility of curcumin and facilitate its delivery into cells and tissues.[22] Encapsulation increase the solubility of curcumin by up to 10,000-fold corresponding to a concentration of 0.11 mg/ml. Curcu Emulsomes successfully facilitate the delivery of curcumin into human liver carcinoma HepG2 cells in vitro, and the release of the drug at the target site was prolonged.

**Emulsomes in ophthalmic delivery**

Sparfloxacin belongs to Biopharmaceutical classification scheme class II (BCS CLASS II). It is poorly soluble in aqueous media. The activity of such drugs is dissolution rate-limited. It is a third-generation fluoroquinolones derivative. Sparfloxacin mainly used in external infections of the eye mainly conjunctivitis and bacterial keratitis. It has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. It is available as 0.3 % (w/v) ophthalmic solution. Its dose is 1 to 2 drops every 4 hour or hourly in case of severe infection [31, 32].

Sparfloxacin emulsomes can be dispersed in an in-situ gelling vehicle. It will provide modulated drug release at the ocular surface. The physical barrier provided by the lipid bilayer and the slow diffusion of the emulsomes in the hydrogel will ensure steady, prolonged release and higher trans-corneal permeation of sparfloxacin.

It can overcome the drawbacks associated with conventional sparfloxacinophthalmic formulations like short residence time, drug drainage and frequent instillation by formulating it into novel Emulsomal in situ gelling system, which provide improved patient compliance.[33] The in vivo and in vitro results of Sparfloxacin Emulsomal in situ gel showed that it has promising antimicrobial activity, that suggests its potential for an effective ocular delivery. Hence, it is proved that thermosensitive in situ emulsomal gel can be a viable alternative to convential eye drops.

**Emulsomes in hepatoprotective activity**

Silybin (SIL) is derived from the milk thistle plant, a natural remedy in the treatment of hepatitis and cirrhosis as well as in the protection of the liver from toxic substances. It is also effective in preventing hepatic lipid peroxidation and ischemia.

Several factors such as low aqueous solubility (0.43 mg/ml in water), low oral bioavailability, and poor intestinal absorption limit its clinical use.

SIL can be incorporated into emulsomes. This incorporation improve the bioavailability of SIL. Because it was bound in the internal solid lipid core, which display a sustain-release profile, in vitro and in vivo, in comparison with a control SIL solution. Emulsomes are recommended for the delivery of SIL in therapy of liver disease. SIL emulsomes are expected to be physically stable, due to its high absolute value of the zeta potential, reducing the probability of coalescence.[34]

**Emulsomes in visceral leishmaniasis**

Visceral leishmaniasis (VL) is the most severe form of leishmaniasis. It results from infection of the macrophages of the liver, spleen and bone marrow. Commonly prescribed drugs for the treatment are derivatives of antimony (antimonials), which are in higher concentrations can cause cardiac, liver and kidney damage. Use of emulsome in tests conducted showed that, it was possible to administer higher levels of the drug without triggering side effects, and thus allow greater efficacy in the treatment [35, 36].

**Emulsomes in drug targeting**

Main useful aspects of emulsomes are their ability to target drugs. Usually it can be used to target drugs to the reticulo-endothelial system. Emulsomes can also able to target drugs to organs other than the reticulo-endothelial system. A carrier system (antibodies) can be attached to vesicles to target them to specific organs [36].

**Emulsomes in biotechnology**

Emulsomes can be used to study immune response due to their immunological selectivity, low toxicity and greater stability. They can be used to study the nature of the immune response by antigens [36].

**Emulsomes in anti-fungal therapy**

Amphotericin B (AmB) is a polyene macrolide antifungal antibiotic agent, whose bioavailability by oral route is poor. Antifungal therapy with AmBhas some adverse reactions such as fever, chills, nausea, vomiting, headache and renal dysfunction with associated anemia, hypokalemia and hypomagnesaemia. Lipid based AmB formulations have advantages over convential AmB in terms of reduced renal toxicity [37].

**Emulsomes in anti-inflammatory action**

Lornoxicam is a new Non-Steroidal Anti Inflammatory Drug belonging to oxicam class with analgesic property. It is having plasma half-life about 3 hours. Soya lecithin based emulsomal nanoparticles for percutaneous administration of Lornoxicam is used for the better management against mild to moderate pain and inflammation for musculo-skeletal and joint disorders like rheumatoid arthritis, osteoarthritis and ankylosing spondylitis [38].

**Conclusion**

Emulsomes are a new generation of colloidal carriers. Its internal core is composed of lipid in a solidor liquid at 25˚c. Emulsomes can be used for parentral, oral, ocular, rectal, vaginal, intranasal or topical delivery of either fat-soluble or water-soluble substances. It can increase the solubility, improve the bioavailability of lipophilic drugs, facilitates sustained and controlled release. Hence, emulsomesserve as efficient drug delivery systems because they exhibit good biocompatibility, biodegradability, stability, high entrapment efficiency and sustained drug release.

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