



## DEVELOPMENT AND CHARACTERIZATION FLUOXETINE AND EMBELIN LOADED LIPOSOMES FOR NEUROLOGICAL DISORDERS

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### Abstract

Neurological disorders represent a major global health burden, affecting millions of individuals worldwide and encompassing neurotraumatic, neurodegenerative, and neuropsychiatric diseases. Conventional therapeutic approaches often face significant challenges due to poor drug bioavailability, limited blood–brain barrier (BBB) penetration, systemic side effects, and inadequate targeting of affected neural tissues. Liposomes have emerged as a promising nanocarrier-based drug delivery system capable of overcoming these limitations. Liposomes are spherical vesicles composed of phospholipid bilayers that can encapsulate both hydrophilic and lipophilic therapeutic agents, thereby enhancing drug stability, bioavailability, and targeted delivery. Their biocompatibility, biodegradability, and ability to cross biological barriers make them attractive candidates for neurological applications. Various preparation techniques, including thin-film hydration, reverse-phase evaporation, extrusion, sonication, and detergent removal methods, have been developed to optimize liposomal formulations. Liposomes have demonstrated considerable potential in the treatment of neurological disorders such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, brain tumors, epilepsy, stroke, and other central nervous system disorders. Furthermore, liposomal systems have shown utility in gene delivery, vaccine development, diagnostic imaging, and controlled drug release. This review highlights the classification, preparation methods, mechanisms of action, characterization, evaluation parameters, advantages, and therapeutic applications of liposomes in neurological disorders. The findings suggest that liposomal drug delivery systems offer a promising strategy for improving therapeutic outcomes and advancing the management of neurological diseases.

**Keywords:** Liposomes; Neurological Disorders; Drug Delivery System; Nanocarriers; Blood–Brain Barrier; Neurodegenerative Diseases; Alzheimer's Disease; Parkinson's Disease; Targeted Drug Delivery; Central Nervous System; Nanotechnology; Brain Drug Delivery.

## **Introduction**

Neurological disorders are diseases affecting the central and peripheral nervous systems, which include the brain, spinal cord, cranial and peripheral nerves, and the autonomic nervous system (Farooqui and Farooqui, 2016). These disorders arise from structural, biochemical, or electrical abnormalities in these components, leading to a wide range of symptoms such as loss of sensation, confusion, poor coordination, altered levels of consciousness, seizures, paralysis, muscle weakness, pain, and memory loss (Nguyen *et al.*, 2024). The etiology of these disorders is diverse, encompassing genetic, developmental, acquired, and degenerative causes. According to the World Health Organization, neurological disorders currently affect as many as one billion people worldwide, with this number expected to increase significantly in the coming years, representing a major and growing public health challenge. These disorders occur across all age groups and geographical regions. Major categories include neurotraumatic diseases (such as stroke, traumatic brain injury, and spinal cord injury), neurodegenerative diseases (including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis), and neuropsychiatric diseases (such as depression, schizophrenia, bipolar affective disorders, autism, mood disorders, attention-deficit/hyperactivity disorder, and tardive dyskinesia).

## **Classification and Types of Neurological Disorders**

Neurological disorders are classified into three major groups: neurotraumatic diseases, neurodegenerative diseases, and neuropsychiatric diseases (Farooqui, 2019; Farooqui and Farooqui, 2016).

### **Neurotraumatic Diseases**

Neurotraumatic diseases include stroke, traumatic brain injury (TBI), and spinal cord injury (SCI). Stroke is a metabolic trauma caused by blockage of blood flow to the brain, while TBI and SCI typically result from accidental falls and motor vehicle accidents. The pathogenesis involves rapid depletion of adenosine triphosphate (ATP), loss of ion homeostasis, induction of oxidative stress and neuroinflammation, and abnormal neuron–glial interactions (Farooqui, 2021; Farooqui, 2019).

### **Neurodegenerative Diseases**

Neurodegenerative diseases are characterized by progressive neuronal loss, protein misfolding, oxidative stress, and neuroinflammation. Examples include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS). In AD, neurodegeneration primarily affects

the hippocampus and entorhinal cortex; PD involves degeneration of dopaminergic neurons in the substantia nigra; HD is marked by neuronal death in the basal ganglia and cortex; and MS is a chronic inflammatory demyelinating autoimmune disease characterized by breakdown of the myelin sheath. Demyelinating diseases like MS lead to neurological deficits and disability, especially in young adults in Western countries (Farooqui and Farooqui, 2016; Farooqui, 2019).

### **Neuropsychiatric Diseases**

Neuropsychiatric disorders involve abnormalities in neurotransmitters such as dopamine, serotonin, glutamate, and gamma-aminobutyric acid (GABA), along with mild oxidative stress and neuroinflammation. 536 Examples include major depressive disorder, anxiety, attention-deficit/hyperactivity disorder (ADHD), posttraumatic stress disorder, autism, and schizophrenia. These classifications reflect underlying neural mechanisms and pathology, including structural, neurochemical, and electrophysiological changes in the brain, spinal cord, and nerves.

### **Pathophysiology and Neural Mechanisms**

Protein misfolding and aggregation are central to the pathogenesis of neurological disorders. Key proteins implicated in neurodegeneration include amyloid-beta, tau, and alpha-synuclein. These misfolded proteins accumulate and form toxic aggregates such as amyloid plaques and neurofibrillary tangles in Alzheimer's disease, and Lewy bodies in Parkinson's disease, leading to neuronal dysfunction and degeneration (Sunanda *et al.*, 2025; Hansen *et al.*, 2010; Shirodkar and Nilesh, 2025). Impaired cellular quality control mechanisms, including molecular chaperones, the ubiquitin-proteasome system, and autophagy, exacerbate aggregate formation (Bourdenx *et al.*, 2017; Jerez *et al.*, 2016).

Oxidative stress and mitochondrial dysfunction contribute significantly to neuronal injury. Excessive reactive oxygen species (ROS) production damages cellular components, disrupts mitochondrial function, and leads to energy deficits, DNA mutations, and neuronal death (Kardam *et al.*, 2024; Naveed *et al.*, 2019; Alqahtani *et al.*, 2023). Mitochondrial dysfunction is observed in AD, PD, HD, and ALS, amplifying oxidative stress and accelerating neurodegeneration (Waldbaum and Patel, 2010).

Neuroinflammation, mediated by activated microglia and astrocytes, plays a dual role in neuroprotection and neurotoxicity. These glial cells can adopt pro-inflammatory or anti-inflammatory phenotypes, releasing cytokines such as interleukin-1 $\beta$ , tumor necrosis factor-alpha, and transforming growth factor-beta, which influence neuronal

survival and tissue repair (Wiatrak *et al.*, 2023; Zhang *et al.*, 2024; Coelho and Ana, 2021). Chronic activation leads to sustained inflammation, contributing to neuronal damage and disease progression (Kip and Brownlie, 2022; Bondy, 2020).

## **Diagnosis**

Neuroimaging modalities such as magnetic resonance imaging (MRI), positron emission tomography (PET), and single photon emission computed tomography (SPECT) are central to diagnosis and treatment, enabling identification of structural abnormalities, mass lesions, and physiological changes (Huellner *et al.*, 2023). MRI provides high-resolution images reflecting hydrogen atom concentrations in brain structures, with T1 sequences optimal for investigating gray and white matter changes, and Fluid-Attenuated Inversion Recovery (FLAIR) sequences useful for identifying cerebrovascular and inflammatory conditions (Natale *et al.*, 2023). PET and SPECT quantify biological processes at molecular and cellular levels; PET imaging is validated for neurotransmitter systems, neuroreceptors, protein aggregation, neuroinflammation, glucose metabolism, and synaptic integrity (Subasi *et al.*, 2024). Diffusion tensor imaging (DTI) visualizes white matter microstructural abnormalities by measuring water molecule diffusivity and mapping axonal networks. Functional MRI (fMRI) detects elevated blood oxygen levels in specific regions, mapping neuronal processes during rest or task execution.

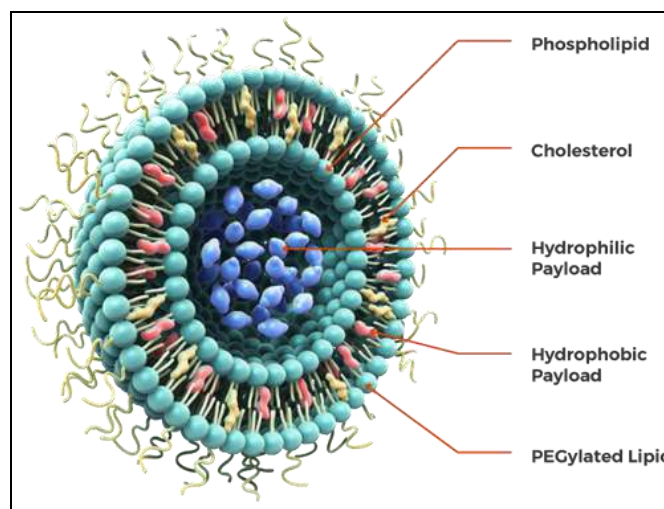
Electrophysiological techniques, including electroencephalography (EEG) and magnetoencephalography (MEG), provide direct measurement of neuronal activity with high temporal resolution (Neuroimaging Modalities, 2013). EEG is widely used for seizure localization, and evoked potential recording is used for cortical mapping and evaluation of sensory, motor, or cognitive functions (Richard *et al.*, 2002). MEG offers excellent temporal resolution and is optimal for detecting electromagnetic sources parallel to the scalp; combining EEG and MEG data improves source localization, though both have relatively poor spatial resolution, especially for deep brain structures (Steele and Stephen, 2010).

Neuropsychological assessments utilize standardized tests to evaluate cognitive, behavioral, and emotional functions, providing objective quantification of neurocognitive deficits and aiding differential diagnosis, treatment planning, and monitoring of disease progression (Timothy *et al.*, 2025). These assessments are instrumental in detecting early signs of neurodegenerative disease and distinguishing among clinical syndromes (Sullivan *et al.*, 2017).

## Liposomes

The Greek words 'Lipos' which means fat and 'Soma' that means body, was combined to form spherical concentric vesicles called liposomes. Liposomes are round sac phospholipid molecules. It encloses a water droplet especially as form artificially to carry drug into tissue membrane. Liposome is a nanoparticle (size-100nm) (Sawant *et al.*, 2021). Liposome were first described by Bangham in 1961, it turned into an accidental discovery in which he scattered the phosphatidyl choline molecule in water, for the duration of this he located that the molecule was forming a closed bilayer shape having an aqueous segment which were entrapped by means of a lipid bilayer (Mishra *et al.*, 2018). Liposomes are useful because they act as carriers for a variety of drugs and have potential therapeutic or other properties. Various carriers such as nanoparticles, microparticles, polysaccharides, lectins, and liposomes can be used to target drug to a specific sites. Liposomal drug delivery is gaining interest due to its contribution to various areas like drug delivery, cosmetics, and biological membrane structure (Sharma *et al.*, 2018). A liposome is a tiny bubble (vesicle), with a membrane composed of a phospholipid bilayer. Membranes are usually made of phospholipids like phosphatidylet-hanolamine and phosphatidylcholine. Phospholipids are amphiphilic with its polar head as hydrophilic and hydrocarbon tail as hydrophobic (Dhandapani *et al.*, 2013).

### Structure of liposomes:



**Figure: Structure of liposome**

### 1) Phospholipids

#### Naturally occurring phospholipids used in liposome:

- Phosphatidylethanolamine

- Phosphatidylcholine
- Phosphatidylserine

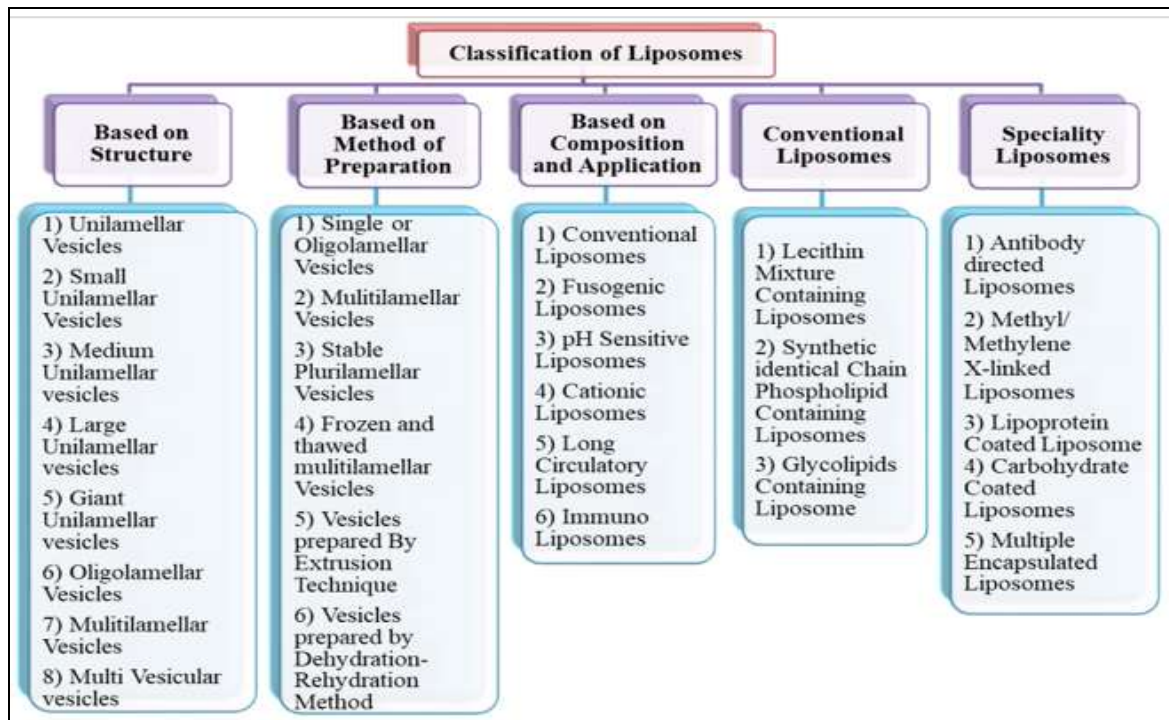
**Synthetic phospholipids used in the liposomes are:**

- Dioleoyl phosphatidylcholine
- Distearoyl phosphatidylcholine
- Dioleoyl phosphatidylethanolamine (Tiwari *et al.*, 2020)

**2) Cholesterol**

Cholesterol may be included into phospholipids membrane in very high awareness up to 1:1 or 2:1 molar ratios of cholesterol to phosphatidylcholine. Being an amphipathic molecule, cholesterol inserts into the membrane with its hydroxyl group of cholesterol orientated towards the aqueous floor and aliphatic chain aligned parallel to the acyl chains inside the center of the bilayers and additionally it growth the separation between choline head organizations and gets rid of the everyday electrostatic and hydrogen bonding interaction (Dwivedi *et al.*, 2014).

**Classification of Liposomes:**



**Figure: Classification of Liposomes**

**Mechanism of formation of Liposomes:**

Liposome performs their motion by four distinct Mechanism-

Endocytosis – This take location via phagocytic cells of reticuloendothelial system together with neutrophils (Nalawade and Patil, 2023).

Adsorption – It occurs to the cellular surface through non precise electrostatic forces or by using interplay with cell surface additives (Lian and Rodney, 2001).

Fusion- It takes place by means of the insertion of liposomal bilayer into plasma membrane with continuous release of liposomal content into the cytoplasm (Gabrijelcic *et al.*, 1990).

Lipid exchange- on this transfer of liposomal lipids to the cellular membrane without association of liposomal contents (Cabral *et al.*, 2004; Bangham and Horne, 1964; Kaur and Kumar, 2018).

### **Method of preparation:**

**1) Thin-Film Hydration Method:** This is one of the most widely used methods for liposome preparation (Hong, 2001; Jesorka *et al.*, 2008; Vemuri *et al.*, 1995).

#### **Steps:**

- Dissolve lipids (phospholipids and cholesterol) in an organic solvent like chloroform or methanol to create a lipid solution.
- Evaporate the solvent under reduced pressure to form a thin lipid film on the walls of a round-bottom flask or a glass vial.
- Hydrate the lipid film by adding an aqueous solution (e.g., buffer or distilled water) and vortexing or sonicating to form multilamellar vesicles (MLVs).
- Optionally, you can reduce the size of MLVs to smaller unilamellar vesicles (SUVs) through extrusion or sonication (Shailesh *et al.*, 2009; Godbole and Mathur, 2018).

**2) Reverse Phase Evaporation Method:** This method is used for preparing liposomes with high encapsulation efficiency.

#### **Steps:**

- Dissolve lipids in an organic solvent along with an aqueous solution containing the substance to be encapsulated.
- Evaporate the organic solvent under reduced pressure to form a water-in-oil emulsion.
- Remove the organic phase, leaving behind liposomes containing the encapsulated substance.

**3) Extrusion Method:** This method is used to prepare liposomes with uniform size and narrow size distribution.

**Steps:**

- Prepare liposomes using the thin-film hydration method to create MLVs.
- Pass the liposome suspension through a series of polycarbonate membrane filters with defined pore sizes using a hand-held extruder or a high-pressure extruder (Kaur and Kumar, 2018).
- This process results in smaller liposomes with a consistent size.

**4) Sonication Method:** This method is used to downsize liposomes or to prepare small unilamellar vesicles (SUVs).

**Steps:**

- Prepare liposomes using the thin-film hydration method or another appropriate method.
- Subject the liposome suspension to high-frequency ultrasound (sonication) to reduce the size of the liposomes (Kirby and Gregoriadis, 1984; Rahman *et al.*, 2018; John *et al.*, 2013).

**5) Detergent Removal Method:** This method is used for preparing liposomes encapsulating hydrophobic substances.

**Steps:**

- Dissolve lipids and the hydrophobic substance in a detergent solution.
- Remove the detergent using techniques like dialysis or chromatography to obtain liposomes with the encapsulated substance (Riaz, 1996; Dwivedi *et al.*, 2015).

**6) Freeze-Thawing Method:** This method is used for preparing liposomes with enhanced stability.

**Steps:**

- Freeze the liposome suspension at a low temperature, typically below the lipid's phase transition temperature (Verma and Sanjay, 2001; Chandraprakash and Verma, 2013; Bangham *et al.*, 1965).
- Thaw the frozen suspension at a higher temperature, repeating the cycle multiple times.
- This process helps to entrap substances within liposomes and reduce leakage.

### **Advantages of Liposomes:**

- **Targeted Drug Delivery:** Liposomes can encapsulate drugs and deliver them to specific target tissues or cells, allowing for targeted therapy. This minimizes the exposure of healthy tissues to the drug, reducing side effects.
- **Improved Bioavailability:** Liposomes can encapsulate poorly water-soluble drugs, improving their solubility and bioavailability, which can be a critical factor in drug effectiveness.
- **Sustained Release:** Liposomes can release drugs gradually over time, leading to sustained therapeutic effects and reducing the need for frequent dosing.
- **Protection of Sensitive Compounds:** Liposomes can protect sensitive drugs or bioactive compounds from degradation due to environmental factors, such as enzymes, pH changes, or oxidation.
- **Versatility:** They can be tailored in terms of size, composition, and surface modifications to optimize their performance for specific drugs or therapeutic applications.
- **Reduced Toxicity:** Liposomal drug delivery can reduce the toxicity of certain drugs by minimizing their exposure to healthy tissues while targeting diseased cells.
- **Enhanced Cellular Uptake:** Liposomes can improve the cellular uptake of drugs or therapeutic agents, making them more effective in treating diseases (Sawant *et al.*, 2021).
- **Cosmetic Applications:** Liposomes are used in cosmetics to enhance the penetration of active ingredients into the skin, improving their efficacy.
- **Food Technology:** In the food industry, liposomes are used to encapsulate and protect flavors, vitamins, and nutrients, enhancing the quality and shelf life of food products (Dwivedi *et al.*, 2014).
- **Vaccine Delivery:** Liposomes play a crucial role in vaccine development by improving the stability and delivery of antigens, enhancing immune responses.
- **Biocompatibility:** Liposomes are generally well-tolerated by the body, making them suitable for various medical and cosmetic applications (Hens and Fernandez, 2006).
- **Research Tools:** Liposomes are valuable tools in biomedical research for delivering biomolecules, dyes, or other compounds to cells for experimental purposes.

- **Diagnostic Applications:** Liposomes are used in diagnostic assays for drug screening, disease detection, and other diagnostic purposes.
- **Immunogenicity:** Liposomes can enhance the immunogenicity of vaccines, resulting in a stronger and more specific immune response.
- **Customization:** Researchers can customize liposomes for specific applications by modifying their properties, such as size, charge, and surface functionality (Meiwan *et al.*, 2012).

## **Evaluation of Liposomes**

### **1.) Characterization of Liposome Structure:**

#### **a) Morphology:**

- **Transmission Electron Microscopy (TEM):** Provides high-resolution images of liposome size, shape, and lamellarity (Zili *et al.*, 2020).
- **Scanning Electron Microscopy (SEM):** Offers surface information and morphology details.

#### **b) Size and Size Distribution:**

- **Dynamic Light Scattering (DLS):** Measures particle size, size distribution, and polydispersity.
- **Nanoparticle Tracking Analysis (NTA):** Tracks and sizes individual liposomes in a liquid suspension (Pradhan *et al.*, 2015).

#### **c) Zeta Potential:**

- **Electrophoretic Light Scattering:** Determines the surface charge of liposomes, which affects stability and colloidal behavior (Caponigro *et al.*, 2000).

#### **d) Lipid Composition Analysis:**

- **High-Performance Liquid Chromatography (HPLC):** Identifies and quantifies lipids in liposomal formulations (Kaur *et al.*, 2013).

### **2.) Liposome Properties:**

#### **a) Encapsulation Efficiency:**

- **UV-Visible Spectroscopy or Fluorescence Spectroscopy:** Measures the concentration of encapsulated drugs or molecules.

#### **b) Stability:**

- **Assessing changes in size, poly dispersity, and zeta potential over time under various storage conditions (e.g., temperature, pH).**

### **c) Drug Release Kinetics:**

- In vitro release studies to determine the rate and extent of drug release from liposomes.

### **3.) Biological Evaluation:**

#### **a) In vitro Cell Studies:**

- Cell viability assays (MTT, Alamar Blue) to assess liposome cytotoxicity.
- Cellular uptake studies to evaluate liposome internalization and drug delivery efficiency.

#### **4.) Biocompatibility and Toxicity Assessment:**

- **Hemolysis Assay:** Measures the potential for liposomes to cause red blood cell damage.
- **Immunogenicity Assessment:** Investigates the immune response to liposomes.

#### **5.) Drug Release Studies:**

- **Dialysis Method:** Evaluates drug release kinetics under sink conditions by dialyzing liposomal suspensions against a release medium.
- **Franz Diffusion Cell:** Measures drug permeation through a membrane to mimic transdermal drug delivery.

#### **6.) Surface Modification Analysis:**

- **Surface Characterization:** Techniques like X-ray Photoelectron Spectroscopy (XPS) and Fourier-Transform Infrared (FTIR) spectroscopy to analyze modifications made to the liposome surface (Ramkrishna *et al.*, 2014).

### **Application for Liposomes**

#### **Drug Delivery:**

- Liposomes are commonly used as drug delivery vehicles to encapsulate and deliver both hydrophobic and hydrophilic drugs.
- They can improve drug solubility, stability, and bioavailability.
- Liposomal drug formulations can target specific tissues or cells, reducing systemic side effects (Marripati *et al.*, 2014).

#### **Vaccines:**

- Liposomes are used as adjuvants or carriers for vaccines to enhance immunogenicity (Shashi *et al.*, 2012; Keller, 2001).

- They can improve antigen delivery to immune cells, leading to a stronger immune response (Rao and Alving, 2000; Lian *et al.*, 1999).

#### **Cosmetics and Skincare:**

- Liposomes are utilized in cosmetics and skincare products for controlled release of active ingredients, such as vitamins and antioxidants (Bui *et al.*, 1994; Gluck, 1995).
- They can enhance the penetration of ingredients into the skin, improving their efficacy.

#### **Gene Delivery:**

- Liposomes can be used to deliver genetic material, including DNA and RNA, for gene therapy applications.
- They protect and facilitate the transport of genetic cargo into target cells.

#### **Diagnostics:**

- Liposomes can serve as carriers for contrast agents in medical imaging, such as magnetic resonance imaging (MRI) and ultrasound (Gabrijelcic and Sentjure, 1995; Johnston *et al.*, 2007).
- They enable targeted imaging of specific tissues or cells.

#### **Cancer Therapy:**

- Liposomal formulations of chemotherapy drugs, like Doxil (liposomal doxorubicin), are used to treat cancer.
- They can improve drug circulation time and reduce damage to healthy tissues.

#### **Food Technology**

- Liposomes are applied in the food industry for encapsulating and protecting sensitive ingredients, such as vitamins, flavors, and antioxidants.
- They can improve the stability and bioavailability of these additives in food products.

#### **Biotechnology**

- Liposomes are used in research and biotechnology applications for drug screening and delivery to cells *in vitro*.
- They are valuable tools for studying cell membrane interactions and drug transport mechanisms (Atrooz, 2011; Hatwar *et al.*, 2023).

### **Transdermal Drug Delivery:**

- Liposomal formulations can be applied topically to deliver drugs through the skin.
- They offer controlled release and can avoid the first-pass metabolism in the liver (Deulkar *et al.*, 2024).

### **Personal Care Products**

- Liposomes are employed in personal care products such as sunscreens and moisturizers to enhance the delivery of active ingredients.

### **Veterinary Medicine**

- Liposomes are used in veterinary medicine for drug delivery to animals, similar to their applications in human medicine.

### **Environmental Remediation:**

- Liposomes can be utilized for the controlled release of remediation agents in environmental cleanup efforts.

### **Intracellular Delivery:**

- Liposomes are valuable tools in research for delivering molecules into specific organelles within cells (Liu *et al.*, 2015).

### **Nutraceuticals:**

- Liposomes are used to enhance the bioavailability of nutraceutical compounds in dietary supplements.

### **Wound Healing**

- Liposomal formulations can be applied to wound dressings to promote the controlled release of wound-healing agents (Shashi *et al.*, 2012).

## **CONCLUSION**

Liposomes represent a promising and innovative drug delivery system with a wide range of applications in the field of pharmaceuticals. Over the years, extensive research has demonstrated their potential to overcome various challenges associated with traditional drug delivery methods. Liposomes have emerged as a promising class of drug delivery systems that offer significant advantages for enhancing the therapeutic efficacy and safety of various drugs. While challenges remain, the continued innovation and refinement of liposomal technologies hold great promise for the future of drug

delivery in the pharmaceutical industry. Liposomes represent an exciting and versatile approach to drug delivery, with the potential to revolutionize the pharmaceutical industry by improving drug efficacy, reducing side effects, and enabling precise targeting of therapies. Further advancements in liposomal technology are likely to expand their use in a wide range of medical applications.

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