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# Nanocarriers for Efficient Drug Encapsulation: Liposomes, Transfersomes, Polymeric Micelles

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A B S T R A C T

Nanocarriers ( 1 to 100 nm ) are nanoparticles used for drug delivery. Transferring of the active medicament at the site of action is efficiently done by the nanocarriers. Various Nanoencapsulation processes are being used for the drug loading in the particular type of nanocarrier. Liposomes, Transfersomes, and Polymeric Micelles are efficient nanocarriers for various types of drugs. In this review their composition, mechanism of action, preparation, surface modification, drug loading and release, encapsulation of various drugs in them, advantages and disadvantages along their applications are been highlighted.

Keywords: Nanocarrier, Nanoencapsulation, Liposome, Transfersome, Polymeric Micelle

## INTRODUCTION

The nanoencapsulation of drugs and small molecules in nanocarriers (NCs) is a potential strategy for nanomedicine evolution. New methods of drug encapsulation enable proper loading of therapeutic agents inside NCs and decrease the ability of the drug to cause health toxicities. NCs can help increase the amount of nanonencapsulated medicine that reaches the affected area [1]. Nanocarriers are colloidal nanoparticles ranging from 1 to 100 nanometres (nm) that are commonly employed to deliver medicinal drugs or other substances to a particular target region [2, 3]. They are biocompatible as they are inactive and are considered to be safe carriers. However therapeutic nanocarriers must be less than 200 nm as the size of the body's microcapillaries is the same [4].

The nanocarriers would bypass the endosome–lysosome process so will have prolonged circulation duration and will release drugs continuously [5]. The surface, composition, shape of nanocarriers' can be altered to increase their activity and reduce their side effects as a result they have good involvement in the field of drug delivery [6]. Despite this, only a handful are capable of transporting the medicine to the desired location. Nanocarriers have enhanced biodistribution and pharmacokinetics, stability and solubility, reduced toxicity, used for Sustained and targeted drug delivery [7].Therapeutic drugs can be nano encapsulated to improve their potency, accuracy, and ability to target [8]. For the production of NCs, various techniques have been documented in the literature. Synthetic methods are recommended based on the drug's chemical composition, kind of treatment [9], and duration of absorption inside of the body [3]. A various matrix can be used to synthesize different sized NCs whereas size and its distribution are significant in knowing their cellular absorption and cross-biological barrier absorption [10]. NCs' in vivo activity is possessed by their physical and chemical properties [11].

Functionalization is the method of adding moiety to the surface of a nanocarrier system. The multivalent surface allows biologically active chemicals or biological macromolecules to be conjugated covalently or non-covalently to provide target-specific interaction and biocompatibility [12].

Controlling the nanocarrier–biosystem interaction and its targeting capabilities throughout the drug delivery process is essential, contemplating its higher payload, binding capability, acute cytotoxicity, and cellular absorption [13, 14]. The structure of the medicinal drug and the type of NCs can also influence the release mechanism [15]. The mononuclear phagocytic system clears traditional NCs from the body (MPS). MPS identifies NCs as foreign substances so they are expeditiously removed from the body. Therefore, surfaces of NCs' should be altered to avoid phagocytosis [16] using tagging

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ligands [17] or hydrophilic polymers [18]. Biological responses are also influenced by the surface charge of NCs, as negatively charged bacterial membranes absorb cationic NCs more readily than neutral or positively charged cell membranes [19, 20].

## 1. LIPOSOMES

### *1.1 Introduction*

Liposomes are phospholipid bilayers that surround an aqueous core, forming a spherical vesicle that may carry both lipophilic and hydrophilic therapeutics to their target sites (Figure No. 1). The bilayer can be classified as a Unilamellar vesicle which has a single bilayer and a Multilamellar vesicle that has many bilayers. Liposomes act as a vehicle for transporting pharmacologically active chemicals to a specific location. In the circulatory system, nevertheless, these compounds have a shorter half-life. [7].

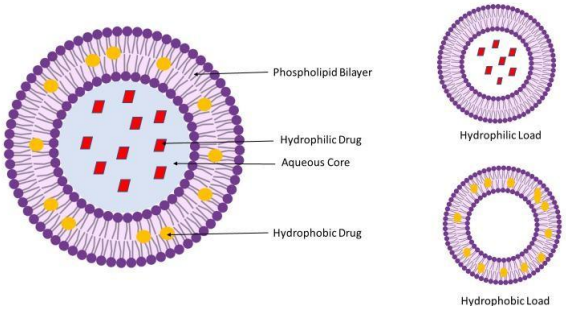


**Figure No. 1. Liposome Structure**

### *1.2 Composition Of Liposomes*

Liposomes have a variety of structural and non-structural components. Phospholipids and cholesterol are the two important structural constituents of liposomes (Table No. 1.).

**Table No. 1. Composition Of Liposomes**

| Phospholipids (Phosphodiglycerides and sphingolipids) | Cholesterol |
|---|---|
| • Phosphatidylcholine (PC)<br>• Phosphatidylethanolamine (PE)<br>• Phosphatidylserine (PS)<br>• Phosphatidyl Inositol (PI)<br>• Phosphatidyl Glycerol (PG) [21]. | • Highly incorporated in phospholipid membranes with the ratio of cholesterol to phosphatidylcholine as 1:1 or even 2:1 [21]. |

### *1.3 Mechanism Of Action of Liposomes*

Liposomes exhibit their action via the endocytic pathway. A ligand will be attached to the outside part of liposomes. These ligands do bind to receptors thereafter taken up by the cells. This process is stated as receptor-mediated endocytosis through which liposomes exhibit their action [22].

### *1.4 Preparation / Formation of Liposomes*

#### *1.4.1 Polycarbonate membrane extrusion method*

Lipid is decreased in chloroform and fine film/ layer is obtained on drying. A buffer having an active ingredient mixed in it is used to dissolve this lipid film. The obtained infusion is then subjected to sonication and freeze-drying. After this extrusion technique is applied ten times to it over polycarbonate membrane (pore size 0.1 µm). This approach produces liposomes of uniform size [23].

#### *1.4.2 High-pressure homogenization*

Lipids are decreased in organic solvents. They are then added to liquid nitrogen. Upon its addition, this will give shock freezing treatment to the solution. After this lyophilization/freeze drying is done to sample. The obtained sample is dissolved in Phosphate Buffer Saline. Then using high pressure, it is blended and liposomes are obtained.

#### *1.4.3 Reversed-phase evaporation method*

Lipid is decreased in chloroform/methanol combination and fine film/layer is obtained on drying. Aqueous diethyl ether is mixed with it to dissolve lipid film. Further, it will be exposed to sonication that will give rise to the oil in water emulsion i.e., o/w emulsion. Then it will undergo a vacuum to let go of the remaining organic solvent in it [24].

#### *1.4.4 Sonication method*

In a nutshell, the lipid is decreased in chloroform and fine film/layer is obtained on drying and then added to Hydrochloride buffer. Unilamellar particles are subsequently generated from multilamellar particles using bath type sonicator[25].

#### *1.4.5 Lipid film hydration sonication extrusion method*

A thin film is formed by drying a lipid solution in an organic solvent that is then soaked in ammonium sulfate. Polycarbonate membrane was used to extrude it after sonicating the solution [26].

### *1.5 Surface Modification of Liposomes*

Liposomes' vague interactivity with larger molecules and biological surfaces results in their short half-life. This is a major disadvantage. Mononuclear systems (MPS) macrophages, notably Stellate Sinusoidal Macrophages in the spleen and liver, remove traditional liposomes quickly. This disadvantage can be remedied by casing the liposome surfaces with water-loving polymers e.g., PEG. When PEG is coated on the surface of liposomes the reactions on the surface will be slowed, hence will increase stability and half-life, resulting in a continuous drug release [7]. In the targeted drug delivery various antibodies, ligands, small amino acid chains, etc., can be added upon this carrier. Considering the attached moiety, liposomes are targeted to the determined area [1].

### *1.6 Drug Loading and Release of Liposomes*

Encapsulation methods/techniques vary according to the different categories of drugs and different types of liposome synthesis. Passive and active loading of drugs in liposomes are both possible. Drug-loaded liposomes are formed by rehydrating an inactive loading dry lipid film in the presence of a drug [27].Inactive loading, concentration gradient/pH gradient across the membrane is considered to load the drug on premade liposomes [28].

There are four different ways for liposomes to release their contents [1].

1. Charged functional groups of membrane constituents are neutralized in a pH-dependent fashion
2. Non-charged components incorporated in membranes undergo pH-dependent hydrolysis
3. Thiolysis of the disulfide bonds in membrane lipids. Changes in the redox potential of the surrounding environment cause thiolysis
4. The use of temperature to control pharmaceutical release. Thermosensitive liposomes employ this technique to release drugs

### *1.7 Drugs Encapsulated Using Liposomes*

Following are a few drugs which are been encapsulated using liposomes (Table No. 2.).

**Table No. 2. Drugs Encapsulated Using Liposomes**

| Sr. No. | Drug | Category | Modification and Characteristics | Outcome | References |
|---|---|---|---|---|---|
| 1 | methotrexate | Anticancer | inner core i.e., an aqueous portion of liposomes was used to load drug | in the course of storage for 24 hrs at 4 ºC, >90 % of methotrexate was withheld inside the liposome | [29] |
| 2 | doxorubicin | Anticancer | encapsulation on liposomes | withhold time was increased and toxicity of the drug was lower | [30] |
| | | | sterically stabilized liposomes | Significantly retarded tumor growth | [26] |
| 3 | N-butyldeoxynojirimycin | Anticancer | pH-sensitive liposomes were used for filling the drug (dioleoylphosphatidylethanolamine and cholesteryl hemisuccinate) | Dosage was lowered by a factor of 1000 | [31] |
| 4 | Ciprofloxacin | Antibiotic | cysteine is attached to the linkage connecting lipid and PEG | Showed 45 % loading efficiency | [32] |
| 5 | clotrimazole | antifungal | ultra-deformable liposomes were used to load drug | Showed substantial skin penetration | [1] |
| 6 | Tretinoin | Retinoids | Negatively charged liposomes were used for drug loading | tretinoin was significantly withheld in skin | [33] |
| 7 | Insulin | antidiabetic | PEGylation and modification with B12 | more stable, enhanced cellular uptake, higher insulin accumulation in intestine and liver | [34] |
| 8 | Curcumin | Anti-inflammatory, antibacterial | Studied as the implementation of artificial neural network (ANN) | Encouraging drug delivery system is prepared using advanced or better parameters | [35] |
| 9 | Ibrutinib and Curcumin | For psoriasis treatment | Preparation of liposomes with controlled release of drug | Lesions were reduced | [36] |

### *1.8 Advantages And Disadvantages of Liposomes*

Following are the advantages and disadvantages of encapsulating drugs using liposomes (Table No. 3).

**Table No. 3. Advantages And Disadvantages of Liposomes**

| **Advantages** [37] | **Disadvantages** [37] |
|---|---|
| • Increases efficacy and relative safety of the drug.<br>• Increases steadiness of drug.<br>• It is non-toxic, adjustable, biocompatible, biodegradable, and nonimmunogenic.<br>• Reduces the toxicity of the encapsulated agents.<br>• Reduces the vulnerability of perceptive tissues to toxic | • Low dissolvability.<br>• Shorter half-life.<br>• Chances of seepage and intermingling of encapsulated drug.<br>• Possibility of phospholipid oxidation and hydrolysis-like reaction.<br>• High manufacturing cost. |

drugs.
- Do not accumulate in undetermined tissues.
- Improved pharmacokinetic effects.

### *1.9 Applications Of Liposomes*
- Amphiphilic and lipophilic compounds have improved solubility.
- To the immune system's cells, it's an inactive target.
- Amphotericin B nephrotoxicity reduction, and in Doxorubicin liposomes cardiotoxicity reduction.
- Liposomes even can be introduced into the body through punctured/poorly fashioned blood vessels.
- Liposomes with surface-attached ligands can bind to target cells or be introduced into the target tissue via anatomical circumstances such as leaky or poorly formed blood arteries, capillaries, and the basal lamina.
- Improved tissue penetration, especially considering cutaneously active liposomal preparation [21].

## 2. TRANSFERSOMES

### *2.1 Introduction Of Transfersomes*

Transfersomes can be termed as carriers that have an internal phase of aqueous media that is enclosed by a hydrophobic lipid bilayer. In this outer layer, edge activators are incorporated [38] (Figure No. 2). All this contributes to making transfersomes, ultra-deformable, i.e., these carriers can change their shape and orientation accordingly [39]. As transfersomes are elastic, they can change their shape and compress themselves through pores while maintaining their integrity.

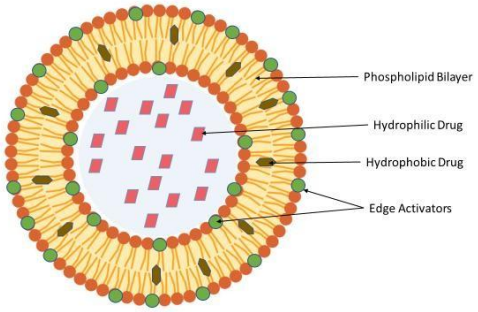


**Figure No. 2. Structure of Transfersomes**

### *2.2 Composition Of Transfersomes*

Following is the composition of transfersomes (Table No. 4).

**Table No. 4. Composition of Transfersomes**

| An amphipathic substance | Surfactants | Solvent |
|---|---|---|
| • It can be a fusion of lipids that constitute the lipid bilayer's vesicle-forming substances.<br>• e.g., soy phosphatidylcholine, egg phosphatidylcholine, etc. [40, 41]. | • They are biocompatible bilayer-softening substances that boost vesicles' outer layer elasticity along with permeability.<br>• e.g., sodium cholates; sodium deoxycholate; Tweens (20,60,80) and Spans (60,65,80) and dipotassium glycyrrhizinate [42].<br>• It is important to maintain an appropriate ratio of different surface-active agents to phospholipids as they contribute to membrane elasticity and reduce the rupture of transfersomes in the skin [43]. | • Ethanol or methanol (approximately 3–10 percent alcohol), and the hydrating medium either water or a PBS having pH 6.5–7 [42]. |

### *2.3 Mechanism Of Action of Transfersomes*

In the aqueous environment, phospholipids come together and make pliable bilayers. These bilayers get sealed and transfersomes are formed [44]. Biocompatible membranes softeners are so-called edge activators that have one chain of surface-active agents, which is absorbed on the transferosome's formation. Wherein it also improves its fluidity and flexibility [42]. Following nonocclusive application, transfersomes follow the natural osmotic gradient over the epidermis [39, 45]. The penetration-enhancing action of these vesicles is determined by surfactant quantities and types, lipid types, and the dimensions, design/shape, and flexibility of the transfersomes.

### *2.4 Preparation / Formation of Transfersomes*

#### *2.4.1 Rotary Evaporation- Thin Film Hydration- Sonication Method*

Phospholipids and edge stimulators are mixed in an evaporative organic solvent mixture of specific volume in which hydrophobic drug is added. The solvent is made to evaporate using a vacuum considering the lipid transformation temperature. This will give a thin layer and to eliminate the last residues of the solvent, keep it under a vacuum. A buffer (pH 7.4) is used in rotating hydrated thin layers for some time at the proper temperature. Then add hydrophilic drug into it. After this, it is sonicated and then extruded using a 0.2µm to 0.1µm polycarbonate membrane. This will make uniform vesicles and uniformly disperse them [46, 47].

#### *2.4.2 Vortexing-Sonication Method*

Phospholipids and edge stimulators were mixed including the drug in Phosphate Buffer. Vortexing is carried out for the same mixture that results in transpersonal suspension which turns out to be milky. After this, it is subjected to sonication followed by extrusion using polycarbonate membranes of pore size 0.45µm to 0.22µm [48, 49].

#### *2.4.3 Modified Handshaking Process*

Organic solvent and phospholipids including the hydrophobic drug are mixed to get a clear solution. Instead of employing a rotating vacuum evaporator, the organic solvent is removed via evaporation during handshaking. All this is done in a round bottom flask that is kept in a water bath having a temperature of 40º C to 60º C. inside the flask wall a fine layer of lipid will be formed. The flask is kept for the whole night so that all residual solvent gets evaporated. The reaction of Buffer along with a certain amount temperature is to be done with the obtained hydrated layer. This stage allows for the introduction of hydrophilic drugs [47].

#### *2.4.4 Suspension Homogenization Method*

An ethanol extract phospholipid solution is fused with a certain quantity of edge activators to make transferases. After that, the produced matrix is then fused with a buffer to get the total lipid concentration. After that, obtained formulations are sonicated, the freezing-thawing process is continued 2 to 3 times [50, 51].

#### *2.4.5 Centrifugation Process*

The organic solvent is used for the breakdown of phospholipids, edge stimulators, and hydrophobic drugs. The same is then extracted utilizing a rotary vacuum evaporator at an appropriate temperature and under lower pressure. Under vacuum, any leftover residues of solvent are eliminated. By centrifuging at room temperature, the deposited thin film is hydrated using a certain buffer solution. At this time include a hydrophilic medication. At room temperature, the resultant transferases are enlarged and sonicate the vesicles that are multilamellar [51].

#### *2.4.6 Reverse-Phase Evaporation Method*

The phospholipids and edge stimulators are mixed in an organic solvent combination, in it, a hydrophobic drug is added. To get thin films of lipid, the resultant solution is evaporated. In an organic phase, which is largely made of isopropyl ether and/or diethyl ether, lipid films are redissolved. Two phases are formed when an aqueous solution is added to the organic solution. This will be the time to include the hydrophilic medication. Sonication is carried out to yield homogenous emulsion. The organic layer is progressively heated and evaporated to generate gel that is converted to transpersonal suspension [52, 53].

#### *2.4.7 High-Pressure Homogenization Technique*

The phospholipids, edge stimulators, and medication were equally disseminated in buffer or water including alcohol, then agitated simultaneously with ultrasonic shaking. After that, the combination is subjected to ultrasonic shaking regularly. A high-pressure homogenizer is subsequently used to homogenize the resulting mixture. The transfersomes are then kept in the proper conditions [44, 54].

#### *2.4.8 Ethanol Injection Method*

The phospholipids and edge stimulators are mixed in an organic solvent (ethanol), in it hydrophobic drug is added, stirred till it achieves clarity. In the buffer, water-soluble excipients are to be dissolved which generates an aqueous phase. Meantime hydrophilic drugs should be added to it. The first and second solutions are maintained at 45º C to 50º C. The first solution having ethanol is added drop by drop to the second one having buffer. This is carried out by continuous stirring. After this, it is evaporated and then sonicated wherein ethanol is ceased [55, 56].

### *2.5 Surface Modification of Transfersomes*

Transferosomes are supramolecular structures made up of amphipathic substances and edge activators that boost the elasticity and permeability of the lipid bilayer [57]. Alcohol e.g., ethanol or propylene glycol is employed as a permeation enhancer and even as a cosolvent with strong solvating capacity in the compositions of several transferosomes. Ethanol has been shown to cause changes in the hydrophilic head portion of lipid bilayers. It also enhances the liquidity of the lipid material inside the cell after penetration, which shows a lowering in the solidity of the lipid lamellae [58].

### *2.6 Drug Loading and Release Of Transfersomes*

The drug is loaded in the transferosomes during the process of formation of transferosomes itself as mentioned in the above processes.

### *2.7 Drugs Encapsulated Using Transfersomes*

Following are a few drugs that are encapsulated using transfersomes (Table No. 5).

**Table No. 5. Drugs Encapsulated Using Transfersomes**

| Sr. No. | Drug | Category | Modification and Characteristics | Outcome | References |
|---|---|---|---|---|---|
| 1 | epigallocatechin-3-gallate (EGCG) and hyaluronic acid | Antioxidant | high-pressure merging was carried out after new thin-film hydration | Enhanced efficacy | [59] |
| 2 | resveratrol | Antioxidant | high-pressure fusion method was used | Showed steadiness, good bioavailability, dissolvability, and non-toxicity. | [55] |
| 3 | paclitaxel | Anticancer | Transfersomes embedded oligopeptide hydrogels | effectively penetrated tumor tissues | [40] |
| 4 | triamcinolone-acetonide | Corticosteroids | older thin-film hydration method was used | Increased biological capabilities and extended effect with decreased quantity effective dose | [60, 61] |
| 5 | Diclofenac sodium, celecoxib, mefenamic acid and curcumin | Anti-Inflammatory | Used for topical route | improved stability and efficacy | [42] |
| 6 | berberine chloride | antibiotic | transfersomal emulgel for transdermal delivery | Effective permeation of drug through the skin was | [62] |

| | | | | | |
|---|---|---|---|---|---|
| | | | | observed | |
| 7 | Nystatin | antibiotic | transferosomes were formulated utilizing the thin-film hydration method | exhibited significant eradication of candida infestation | [63] |
| 8 | Trifluralin | herbicidal | localized and targeted dermal delivery of TFL | improved its solubility, improved cutaneous permeability, improved macrophage targeting, and enhanced targeted assassination | [64] |
| 9 | carvedilol | β-blocker | Used for topical dosage | An effective method to avoid skin cancer having very less systemic effects | [65] |
| 10 | Tempranillo Grape Extract | Antioxidant | Spherical unilamellar vesicles around 100 nm | Good antioxidant effect and was not toxic to cells | [66] |

### *2.8 Advantages And Disadvantages of Transfersomes*

Following are the advantages and disadvantages of transfersomes (Table No. 6).

**Table No. 6. Advantages And Disadvantages of Transfersomes**

| **Advantages** [42] | **Disadvantages** [42] |
|---|---|
| • It can be used for the delivery of drugs with expansive solubility.<br>• Have ultra-deformability and elastic properties.<br>• It is used to deliver drugs through the skin without changing the shape of vesicles.<br>• Applicable in topical as well as systemic drug delivery<br>• Drugs with different sizes, formations, weight, and hydrophilicity can be efficiently transported.<br>• Are biocompatible and biodegradable.<br>• Sustained drug release with a long-time effect can be obtained.<br>• Site responsive type of drug delivery<br>• Steer clear of the first-pass metabolism.<br>• Reduces the unwanted side effects of the drug<br>• Comparative, effective entrapment (90 percent) of hydrophobic drugs.<br>• Easy to scale up. | • Oxidative degradation makes it unsteady.<br>• Expensive raw materials and equipment are needed to increase manufacturing.<br>• Difficult to achieve the purity of innate phospholipids. |

### *2.9 Applications Of Transfersomes*

Transferosomes can carry the following cargo [42] :

- Proteins And Peptides
- Anticancer Medicines
- Insulin
- Interferons
- Corticosteroids
- Antioxidants
- Anesthetics
- Herbal Medications
- Non-Steroidal Anti-Inflammatory Drugs.

## 3. POLYMERIC MICELLES

### *3.1 Introduction Of Polymeric Micelles*

When the surface-active agent is added to water, it creates a suspension of clustered particles, terming Micelle. These carriers are amphiphilic as they have water-loving heads and lipid-loving tails. Heads will be facing outside and tails will be facing inside the micelle [67]. Vice versa can be termed as inverse micelle (Figure No. 3). Micelles occur only if the concentration of surface-active agents i.e., surfactants exceed the threshold. This threshold is defined as Critical Micelle Concentration [68].

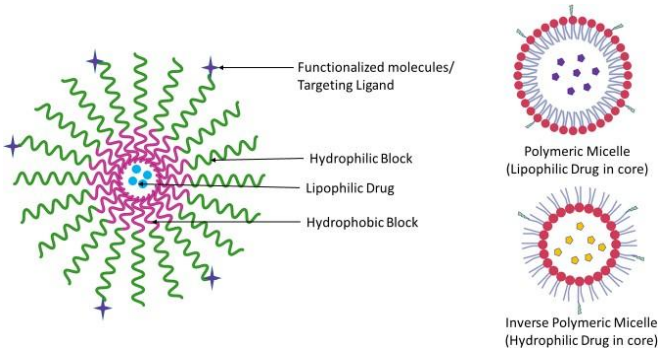


**Figure No. 3. Structure of Polymeric Micelles**

### *3.2 Composition Of Polymeric Micelles*

Polymeric micelles are two-phase gatherings that have a spherical lipophilic inner core and lipophobic outer shell formed by physically assembling amphiphilic molecules or copolymers and revealing its hydrophilic segments to neighbouring fluid while trapping the hydrophobic portions in the center[69].

Two copolymers are used to make polymeric micelles. One copolymer is solvent-soluble, whereas the other is solvent insoluble. The core is made up of insoluble copolymers, whereas the shell is made up of soluble copolymers, with the copolymers forming a chain or micellar aggregate [70].

### *3.3 Mechanism Of Action of Polymeric Micelles*

By the EPR effect, polymeric micelles made from polyethylene glycol/phosphatidyl-ethanolamine conjugates (PEG-PE) gathered with an efficiency more than 8-fold greater in the localized necrosis area than that in a non-damaged region of the cardiac muscle [71]. Folate conjugated micelles showed higher absorption in MCF-7 cells after coming in contact with overexpressed folate receptors upon cancer cells. According to [72, 73] it was found that folate-linked poly (L-histidine)–poly (L-lactic acid) micelles were superior in destroying cancer cells. And [74] found that poly(dimethyl aminoethyl methacrylate), poly(butyl methacrylate) polymeric micelles could infect COS-7 and OVCAR-3 cells with minimal harm.

### *3.4 Preparation / Formation of Polymeric Micelles*

#### *3.4.1 Solvent extraction technique*

Polymers are decreased in dimethyl ketone and then dropped into double distilled water with continuous stirring. After purging with dry nitrogen, the organic solvent is removed. This employed solvent extraction approach creates polymeric micelles that have efficient loading capacity, are stable, and show sustained release [75].

#### *3.4.2 Dialysis method*

Here polymers are decreased in organic solvents that form a homogenous mixture with water. And dialysis is carried out against water. And dialysis is carried out against water. Micelle production is caused by the slow elimination of organic solvent [76].

#### *3.4.3 Solution casting method*

Polymers that have been decreased in an organic solvent are evaporated to form a thin layer. To create micelles, the thin film is rehydrated in a hot aqueous solvent [76].

### *3.5 Surface Modification of Polymeric Micelles*

The exterior part of micelles is to be altered to increase blood circulation time. The most often utilized polymer for surface refashioning is hydrophilic i.e., Polyoxyethylene Glycol. This will help in improving blood steadiness. According to [76] PEG creates a brush-like corona on the exterior portion of these carriers. The hydrophilic PEG corona plays a crucial role in inhibiting opsonin adhesion and removal by the reticuloendothelial system [77]. The backstairs characteristics and half-life of acetaldehyde functionalized PEG-b-PDLLA micelles were improved as their surface got attached with the peptidyl ligand. This ligand is negatively charged so on gave same to the micelles [78].

### *3.6 Drug Loading and Release of Polymeric Micelles*

Physically enclosing or chemically conjugating can be used as methods to incorporate drugs into polymeric micelles [76]. Using organic solvents, the medication is injected into the core of these nanocarriers via oil by water emulsion, dialysis, and physical mixture.

Many factors influence drug release from polymeric micelles, comprising the length of the center polymer segment, drug-core affinity even the amount of drug-loaded [79]. The release of the drug that is physically accumulated on these nanocarriers is controlled by its diffusion from the core and its partition coefficient.

### *3.7 Drugs Encapsulated Using Polymeric Micelles*

Following are a few drugs encapsulated using Polymeric Micelles (Table No. 7).

**Table No. 7. Drugs Encapsulated Using Polymeric Micelles**

| Sr. No. | Drug | Category | Modification and Characteristics | Outcome | References |
|---|---|---|---|---|---|
| 1 | Doxorubicin | Anticancer | encapsulated on pluronic micelles | Reduction by double in the intake of the drug by normal cells | [80] |

| | | | | | |
|---|---|---|---|---|---|
| 2 | Paclitaxel | Anticancer | methoxy poly(ethylene glycol) (MPEG) and poly(ε-caprolactone) (PCL) were used as copolymers | greater cytotoxicity to cancer cells | [72] |
| 3 | Camptothecin | Anticancer | poly(ethylene glycol)-poly(benzyl aspartate) was used as a copolymer | inhibited tumor growth after a singlein vivoinjection<br>highly accumulated in tumors and withheld good in blood | [81] |
| 4 | Oxaliplatin | Anticancer | poly(ethylene glycol)-ß-poly(glutamic acid) was used | enhanced antitumor activity | [82] |
| 5 | ß-lapachone | plant-derived anticancer | PEG-PLA was used | The steady and extended-release was observed | [83] |
| 6 | Amphotericin B | Antifungal | poly(ethylene oxide)-block–poly(N-hexyl-L-aspartame) was used | sustained-release was observed | [84] |
| 7 | Geldanamycin | Antitumor antibiotic | poly(ethylene glycol)-b-poly(ε caprolactone) (PEG-b-PCL) was used | Water dissolvability and effectiveness was increased | [75] |
| 8 | Adriamycin | Anticancer | poly(L-histidine) poly(L-lactic acid) was used | the pH-dependent release was observed | [73] |
| 9 | Cyclosporin A | immunosuppressive agent | methoxy poly(ethylene oxide)-ß-poly(ε-caprolactone) was used | The steady and extended-release was observed | [85] |
| 10 | Rapamycin | macrolide antibiotic | 1. PEG-PCL was used | the slow and sustained release was observed | [75] |
| | | | 2. A combination of TPGS and poloxamer was used | Showed more significant influence on skin | [86] |
| 11 | capecitabine | Anticancer | nano PMs and cyclodextrin was used | Targeted drug release was observed and was in command | [87] |
| 12 | Hyaluronic acid | Antioxidant, anti-inflammatory, analgesic | poly(L-lysine)-b-polylactide (PLys+-b-PLA) and Hyaluronic Acid was used | Was found to be steady in thin blood, effective carrier | [88] |
| 13 | Daunorubicin | Anticancer | POEGMA-b-P(ABMA-co-AMA) was used | Cancer cells were destroyed effectively | [89] |
| 14 | Niclosamide | antitumor | PEG2K-Fmoc-Ibuprofen micelles, PEG2K-FIbu) were used | Reduction in tumor size and liver injury was observed | [90] |

### *3.8 Advantages And Disadvantages of Polymeric Micelles*

Following are the advantages and disadvantages of polymeric micelles (Table No. 8).

**Table No. 8. Advantages And Disadvantages of Polymeric Micelles**

| **Advantages** [69] | **Disadvantages** [91] |
|---|---|
| • It can be used for drugs that have poor solubility.<br>• Extended-release can be obtained.<br>• Nanosize helps in proper filtration as well as metabolism.<br>• Prevents disruption of the cargo loaded in it. | • It is generally used for lipophilic drugs.<br>• It has limited Drug-loading capability.<br>• This technique is dependent on Critical micelle concentration. |

### *3.9 Applications Of Polymeric Micelles*

- Pharmaceutical uses
- Delivery methods for therapeutic drugs (drugs, genes, and proteins), as well as medical diagnostics.
- Almost every route of medication administration (parenteral, oral, nasal, and ocular) has benefited from micellar versions of pharmaceuticals in terms of higher bioavailability or reduced side effects [92].

## 4. CONCLUSION

Nanocarriers are potential agents for the delivery of drugs and so are promising systems. Nanocarriers have many advantages over conventional drug delivery, hence have a good therapeutic index. The surface modifications of the nanocarriers

make them more potent carriers by reducing their limitations. Liposomes are good nanocarriers but have a shorter half-life, which can be modified using various processes. Transfersomes are deformable nanocarriers that have plenty of advantages and applications. Polymeric micelles are amphiphilic molecules whose blood circulation can be modified with PEG polymer. In such a way nanocarriers which are nontoxic, biocompatible, inactive are been used for nanoencapsulation of various drugs and have a very high range of applications.

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