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A Review on Long-circulatory Liposome and Magic Bullet Concept

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ABSTRACT

The long circulatory liposome means shows action towards target organ longer period of time. Liposome are the concentric bilayer in which aqueous volume entirely envelope by the lipid bilayer used to transfer enzymes, protein and drugs to targets cancer cell or tissue. These are chemical moieties in which action towards target organ. It was first discovered by 1965 and soon was proposed drug delivery system. There are numerous application like anti fungal, anti cancer, anti inflammatory and anesthetic drugs. The magic bullet concept of Poul-Ehrlich et al; through very late, offers a logical solution to the age old problem unrelated and unwanted effect of therapeutic agent and optimizing the drug therapy in its true sense. The controlled, sustained and controlled drug delivery can be considered as the magic bullet concept. The long circulatory liposome gives the stealth effect called as killer bomber to cancer cell and arrest the Mitosis of M-phase and G-phase.

Keywords: Stealth liposome, Magic bullet, Liposome, Target, Vesicle

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INTRODUCTION

Liposome can be significantly used as drug carrier in drug delivery system hence efficacy can be increases [28]. In the case of PL-DOX is less cardiotoxic than unencapsulated doxorubicin, higher at cumulative dose the cardiac lesion in rabbits are similar to humans and dogs are histological same like humans. The therapeutic activity shows doxorubicin when increasing the encapsulation of long circulatory effect by pegylated method [29]. In cancer treatment, passive targeting accomplishes using liposome as a carrier of anticancer agents [30]. The 4% of PEG-HS-CHEM action shows result by pH sensitivity, serum stability and tissue uptake significantly shows the theronostic application. The fujogenic and pH sensitive lipid combination used to ensure cytoplasmic delivery [31]. The long circulatory liposome with a lies uptake by cells of reticulo-endoplasmic system (RES) usually prepared by modification of surface of liposome with the help of hydrophilic polymer such as PEG [32].

Liposome [1, 2]

The name liposome is derived from two Greek words: 'Lipos' meaning fat and 'Soma' meaning body. Structurally, liposomes are concentric bleeder vesicles in which an aqueous volume is entirely enclosed by a membraneous lipid bilayer. Membranes are usually made of phospholipids, which are molecules that have a hydrophilic head group and a hydrophobic tail group. The head is attracted to water, and the tail, which is made of a long hydrocarbon chain, is repelled by water. In nature, phospholipids are found in stable membranes composed of two layers (a bilayer). In the presence of water, the heads are attracted to water and line up to form a surface facing the water. The tails are repelled by water, and line up to form a surface away from the water. In a cell, one layer of heads faces outside of the cell, attracted to the water in the environment, and another layer of heads faces inside the cell, attracted by the water inside the cell. The hydrocarbon tails of one layer face the hydrocarbon tails of the other layer, and the combined structure forms a bilayer. When membrane phospholipids are disrupted, they can reassemble themselves into tiny spheres, smaller than a normal cell, either as bilayers or monolayers. The bilayer structures are liposomes. The monolayer structures are called micelles.

Advantages

- Provide controlled drug delivery
- Biodegradable, biocompatible, flexible
- Non ionic
- Can carry both water and lipid soluble drugs

- Drugs can be stabilized from oxidation
- Improve protein stabilization
- Controlled hydration
- Provide sustained release
- Targeted drug delivery or site specific drug delivery
- Stabilization of entrapped drug from hostile environment
- Alter pharmacokinetics and pharmaco-dynamics of drugs
- Can be administered through various routes
- Can incorporate micro and macro molecules
- Act as reservoir of drugs
- Therapeutic index of drugs is increased
- Site avoidance therapy
- Can modulate the distribution of drug
- Direct interaction of the drug with cell

Disadvantages

- Less stability
- Short half life
- Phospholipids undergoes oxidation, hydrolysis
- Leakage and fusion
- High production cost
- Quick uptake by cells of R.E.S
- Allergic reactions may occur to liposomal constituents
- Problem to targeting to various tissue due to their large size

Stealth Liposome [3]

Step in which the development of long circulatory liposome with the help of synthetic polymer (PEG) poly ethylene glycol in liposome composition. The 'Stealth liposome' is the spherical vesicle in which with a membrane composed of phospholipids bilayer used to deliver drug or genetic material in to cell. Pharmacologically shows the action of long circulation drug like vasopressin. To improve the blood circulation time of liposome PEG widely used as a polymeric stabilizer. PEG is a linear polyether-diol with many useful to biocompatibility, solubility in aqueous and organic media. The property gives a stealth behavior or long circulatory action of liposome [4]. The stealth action shows drug -carrier homing device see figure 1.

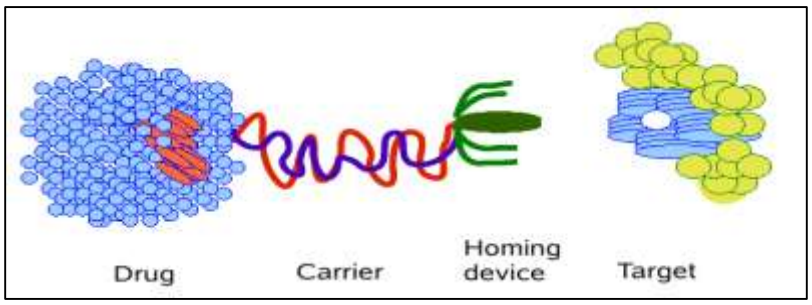

Figure 1: Drug carrier targeting phenomenon

Composition of stealth liposome [5]

1. Polyhydroxyethyl L-aspargines coated
2. PEG coating
3. H-PG-PEG coated
4. Dope coated

We need drug delivery carriers that are able to deliver the killer bomb inside the tumor cell and destroy them, just like the killer bomb of 'stealth liposome' [5] . A stealth liposome is a spherical vesicle with a membrane composed phospholipids bilayer used to deliver drug or genetic materials into cells. Liposome can be composed of naturally derived phospholipids with mixed lipid chains coated or stabilized by polymers of PEG and colloidal nature.

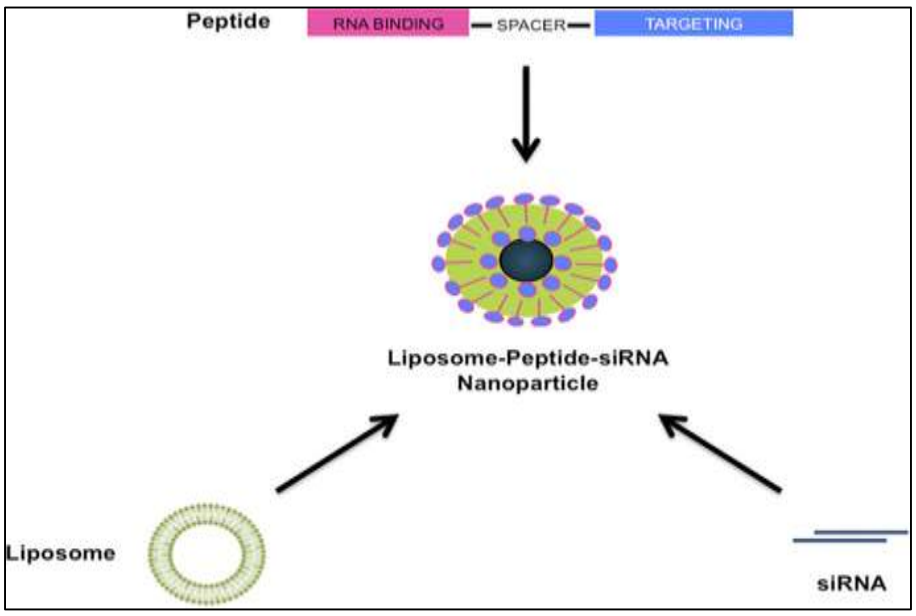

Figure 2: Si-RNA induces RNA degradation through a natural gene silencing pathway RNA

The cationic liposomes, lipolexes, stabilized by (PEG and other polymers) plasmid-lipid particles and various lipid-based nanoparticles were extensively tested for gene delivery in the1990s, but with limited success. In recent years systemic delivery of Si-RNA (small interfering double-stranded

RNA molecules) has been a very attractive field. Si- RNA induces RNA degradation through a natural gene-silencing pathway called RNA interference (RNAi), which has rapidly become the most widely used approach for gene knock down because of its potency in Figure 2.

Targeting Ligand Mechanism and Targeting [6, 33]

In the case of cancer unorganized growth of the cells takes place hence we need to targeting ligand to receptor is necessary towards target organ.

Internalization

In this mechanism in which the ligand binding to the receptor site and called receptor mediated internalization in figure 3 for the getting of optimal result the immune-liposome therapy are used. The antibody directed enzyme prodrug therapy are used in the internalization. This mechanism occurs receptor- mediated endosome in which the binding of drug to receptor and enveloping the endosome figure 3.

Receptor expression

The receptor expression in that antigen or receptor in high density to the cell surface for targeting in figure 3 shows the receptor expression.

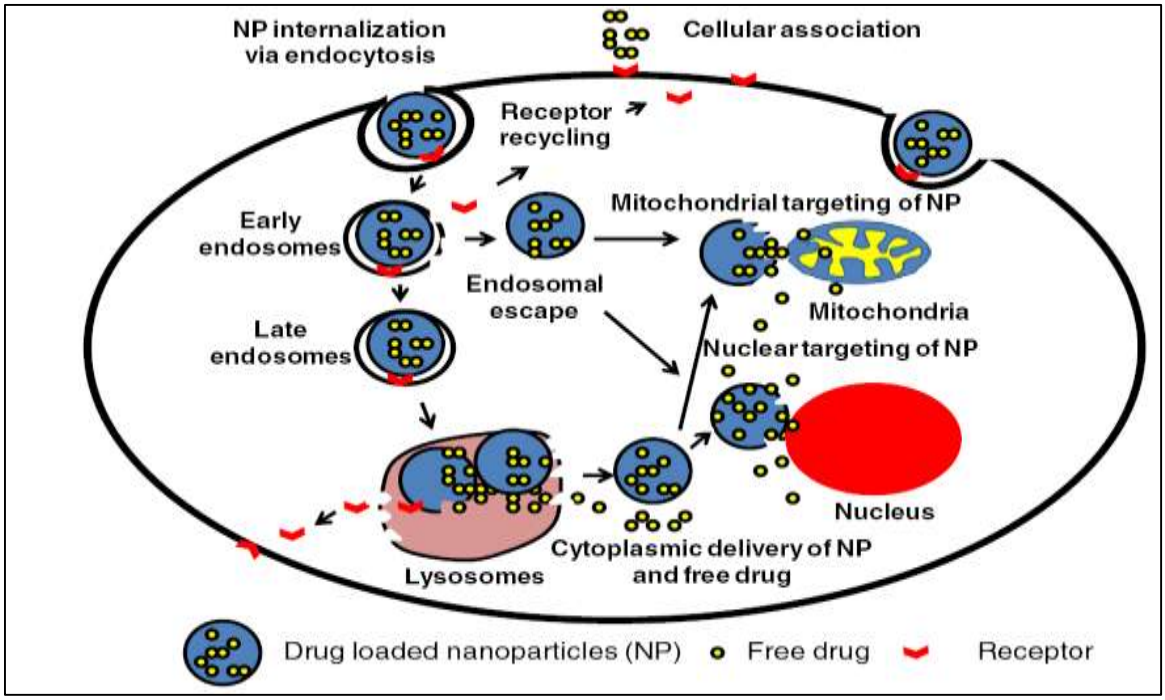

Figure 3: Drug Loaded (I) Nano-particle, (II) Free drug and (III) Receptor mechanism in cell

Binding affinity and ligand density

When binding affinity is high then the there is some decreased penetration of solid tumor since 'Binding- site barriers' high density on liposome and polymer use in to increase the desirable site to achieve the targeting of cell [6].

Antibody versus non-antibody ligands

For the achievement of goal for cancer targeting which adhesion of cellular mechanism and also folate and transferrin targets growth factor receptors [6]

Immune response to antibodies

The hybridoma technology mAb production results in murin- origin, injected in to humans the production of the anti-mouse antibodies hence evolution of immune response link to the mAbs [33].

The process of internalization of RGD ligand greatly enhanced internalizing affinity of micelle in tumor endothelial cells that over express integrin 'av β3' through receptor mediated endocytosis in **figure 4** the peptide ligands containing the arginin-glycin-aspartic acid (RGD) shows affinity and selectivity to interin generally in 'av β3'. The surface charged RGD variation in different pH to the tumor cells recognized by interin RGD- peptide [7].

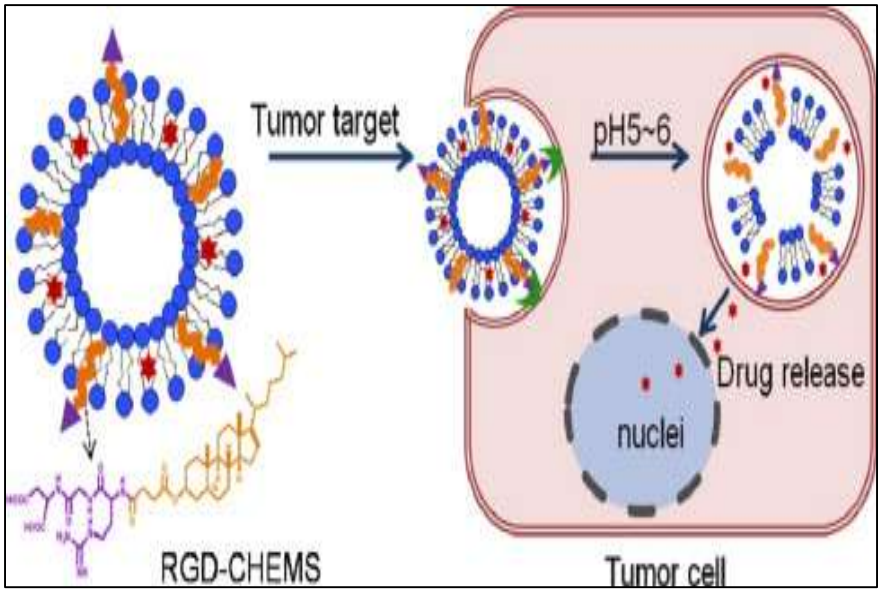

Figure 4: Liposome shows action towards target organ, tissue or tumor cell

Drug Targeting Consideration [8, 9]

In **figure 2** polymeric micelles is novel carrier system since increase loading capacity, stability in physiological system. A polymer-drug conjugates targeting of tumor on the basis of EPR effect; polymer-drug conjugate bearing ligand targeting. The drug released to extracellular matrix and diffuses through targeted tissue or cells in figure 5 as like passive targeting in active targeting once the nano-particle passively targeted or extravasate gives an EPR effect hence the presence of ligands grafted on to nano-particle, uptake to get an enhances the internalization via receptor- mediated endocytosis in figure 5 on the basis of physicochemical properties including polymer type, size, surface charge, ligand type and density important for the drug- polymer conjugate potentiate the action to binding affinity [10]. Polymer-coated liposome are used to creates sterically stabilization of

liposome which are stabilize d by different ways of adsorption or grafting of polymer on the liposome surface, in polymer surface the repulsive interaction takes place [12]. The conjugation of polymeric carrier to low molecular weight drugs changes its pharmacokinetic disposition at both cellular level and body [11]. PEG most be added surface of liposome to stabilize or the sterically stabilization effect. On surface of liposome PEG like polymer grafted since reduces uptake by the macrophages of mononuclear phagocytic system hence to prolong circulation longer period of time in blood. In passive targeting **figure 2** circulating nano-particle passively extravasate in solid tumor tissue and enhances permeability of blood vessels [11]. Surface modification is the incorporation of polyethylene glycol (PEG) preventing interaction with plasma protein and recognition by Reticulo-endothelial system (RES) in **figure 2** the PEG effect is transients eventually to opsonization and macrophage clearance occurs [13]. Liposome and other nano-particles, low molecular weight drug are not retained in tumor sites longer period of time because which is re-enters via diffusion, this phenomenon called as passive targeting [14]. Nano-particles are potentially useful for carrier of active drug and coupled with targeting legends [15].

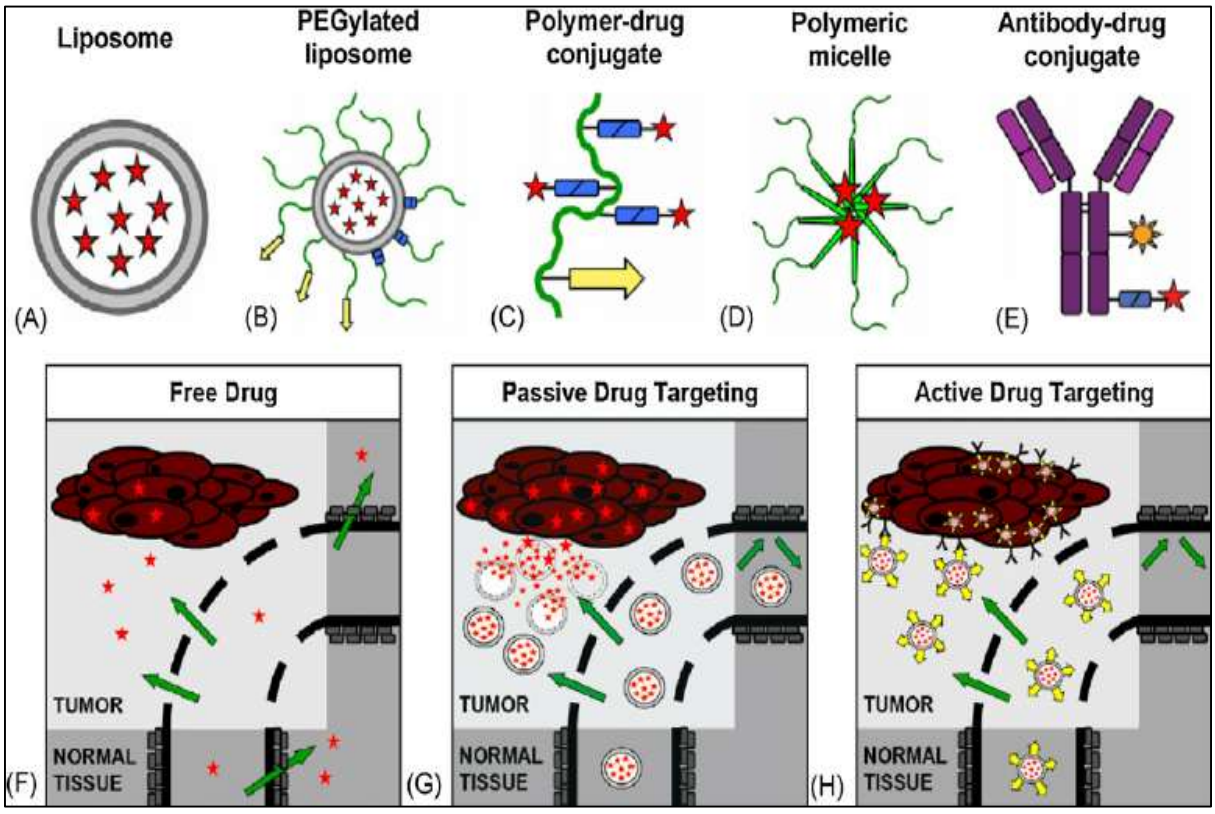

Figure 5: Drug targeting (A) Liposome, (B) PEGylated liposome, (C) Drug- polymer conjugate, (D) Polymer micelle, (E) Drug-Antibody conjugate.

Mechanisms of Drug Release from Liposome [16]

Drug encapsulated into the liposome can be release into targeted cell cytoplasm by various mechanisms that are listed below:

- Adsorption
- Fusion
- Endocytosis
- Lipid transfer

Liposome binds specifically or non-specifically to the cell membrane (a). The liposome gets adsorbed onto the cell surface and gets fused with it (b). Liposome releases their contents into cell cytoplasm by the destabilization of certain cell membrane components when adsorbed on the cell surface (c). The release drug can enter the cell via micro-pinocytosis by transport through protein-mediated exchange of lipid component with the cell membrane (d). Liposome subjected to specific or non-specific endocytosis (e). In endocytosis the endosomes deliver liposome to the lysosome (f). Through lysosome endosome destabilized occurred (g). Finally the encapsulated drug gets release into cytoplasm (h) in figure 6.

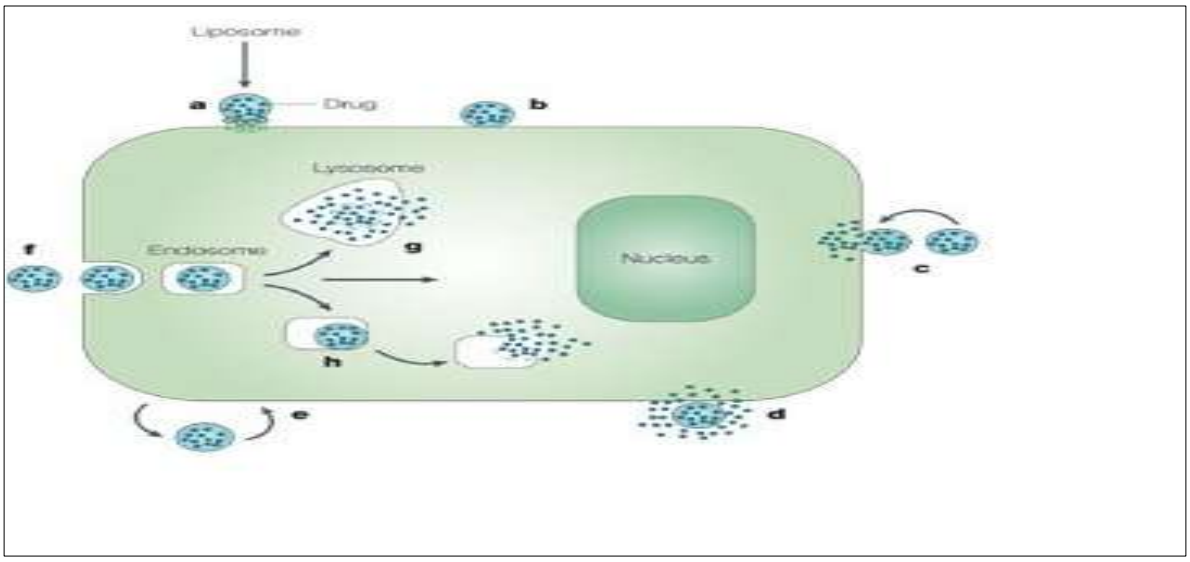

Figure 6: Mechanism of Drug release through liposome

Therapeutic Application of Liposomes [17]

Liposome as drug/protein delivery vehicle

- Controlled and sustained drug release in situ
- Enhanced drug solubilization
- Altered pharmacokinetic and biodistribution
- Enzyme replacement therapy and lysosomal disorders

Liposome in antimicrobial, antifungal and antiviral therapy

- Liposomal drugs
- Liposomal biological response modifier

Liposomes in tumour therapy

- Carrier of small cytotoxic molecule
- Vehicle for macromolecule as cytokines or genes

Liposome in gene therapy:

- Gene and antisence therapy
- Genetic (DNA) vaccination

Liposome in immunology:

- Immunoadjuvant
- Immunomodulator
- Immunodiagnosis

Liposome as artificial blood surrogates

Liposomes as radiopharmaceutical and radio diagnostic carrier

Liposomes in cosmetics and dermatology

Liposomes in enzyme immobilization and bioreactor technology

Table 1: Vesicular systems [26, 27]

Novel vesicles	Terminology	Advantages
Emulsome	A nano-size lipid particle consists of microscopic lipid assembly with a polar core.	Parenteral drug delivery of poor water soluble drug.
Genosome	Artificial macromolecular complexes for functional gene transfer mechanism the cationic lipid are most suitable because of stability in blood stream and biodegradability.	Cell specific gene transfer delivery system achieve
Enzymosome	Liposomal model constructs by engineered to provide a mini bioenvironmental in which enzymes are covalently coupled or immobilised liposomal surface.	Action towards target organ hence targeted drug delivery
Photosome	Photolysase entrapped liposome, release contents by photo trigger changes the membrane permeability characteristics in this system.	Therapy of photodynamic mechanism
Vesosome	Bilayer nested compartments in vitro via inter-digested bilayer phase formed by adding alcohol like ethanol to variety of saturated phospholipids.	Better protection to the interior contents in serum.
Proteosome	These are the multi-subunit enzyme and high molecular weight complexes with catalytic activity specifically due to assembly pattern of enzymes.	Better catalytic activity of enzyme which is than non associated enzyme.

Hemosome	Haemoglobin containing liposome engineered by immobilising haemoglobin with polymerizable phospholipids	Oxygen carrying in high capacity

Table 2: List of clinically approved liposomal formulations

Name	Trade Name	Company	Indications	Excipients used
Liposomal amphotericin B	Abelcet	Enzon	Fungal infections	DMPC, DMPG
Liposomal amphotericin B	Ambisome	Gilead Sciences	Fungal and protozoal infections	HSPC, Cholesterol, DSPG
Liposomal cytarabine	Depocyt	Pacira (formerly SkyePharma)	Malignant lymphomatous meningitis	DOPC, Cholesterol, DPPG
Liposomal daunorubicin	DaunoXome	Gilead	HIV-related Kaposi's sarcoma	DSPC, Cholesterol
Liposomal doxorubicin	Myocet	Zeneus	Combination therapy with cyclophosphamide in metastatic breast cancer	LIPOVA-E120, Cholesterol
Liposome-PEG doxorubicin	Doxil/Caelyx	Ortho Biotech, Merck	HIV-related Kaposi's sarcoma, metastatic breast cancer, metastatic ovarian cancer	MPEG-DSPE, HSPC, Cholesterol
Liposomal vincristine	Marqibo	Spectrum Pharmaceuticals	Acute Lymphoblastic Leukemia (ALL) and Melanoma	Cholesterol and egg sphingomyelin
Liposomal verteporfin	Visudyne	QLT, Novartis	Age-related macular degeneration pathologic myopia ocular histoplasmosis	Egg PG, DMPC
Liposomal morphine	DepoDur	Skye Pharma, Endo	Postsurgical analgesia	DOPC, Cholesterol, DPPG

CONCLUSION

Liposome offers many advantages over conventional dosage forms, like increased bioavailability, possibility of releasing drug at slower and constant rate, accurate drug release. The stealth or long circulatory liposome most play vital role in liposomal drug delivery system. More efficient and target based approach most be achieved. However patent status of these polymers makes them freely available for research in industry. The vast number of patents covering the various applications of these polymers within drug delivery area of research and development

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