



Vesicular and Stealth Vesicular Drug Delivery – A Review

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Authors' contributions

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ABSTRACT

Vesicular systems (liposomes), one of several potential novel drug delivery systems, provide an advanced technology for delivering active compounds to the site of action, and numerous formulations are currently in clinical use. Liposome technology has developed from typical vesicles to sterically stabilised vesicles, which produce long-circulating liposomes by varying the lipid content, size, and charge of the vesicle. Several compounds, such as glycolipids, have been used to create liposomes with changed surfaces. The addition of the synthetic polymer poly-(ethylene glycol) (PEG) in liposome composition was a crucial milestone in the creation of long-circulating liposomes. PEG on the liposomal carrier's surface has been found to increase blood circulation time while decreasing mononuclear phagocyte system uptake (Stealth Liposomes). As a consequence of this technique, a vast variety of liposome formulations encapsulating active compounds have been developed, all of which have excellent target efficiency and activity. Stealth liposomes can also be actively targeted with monoclonal antibodies or ligands thanks to a synthetic alteration of the terminal PEG molecule. This article focuses on vesicular drug delivery as well as stealth technology and presents preclinical and clinical data for the most common liposome formulations, as well as discussing developing developments in this promising technology.

Keywords: *Stealth Liposomes; poly ethylene glycol; mononuclear phagocyte system; PEGylation.*

1. INTRODUCTION

The development of a novel drug delivery system has received a lot of interest in recent decades. The novel drug delivery systems are designed to meet two requirements: they release the drug at a rate determined by the body's demands during the course of therapy, and they deliver the drug directly to inflamed tissues and/or organs. None of these can be met by conventional delivery strategies, including extended release dose forms. Novel drug delivery system maintains drug action at a specified rate, sustains a relatively constant (zero-order kinetics) and efficient drug level in the body, and reduces undesired side effects at the same time. It can also target drug delivery utilising carriers or chemical derivatization to localise drug activity in the affected tissue or organ. A variety of pharmaceutical carriers, including polymeric micelles, particulate systems, macro and micromolecules, are offered as novel drug delivery methods for targeted drug delivery. Lipid particles, micro- and nanoparticles, micro- and nanospheres, polymeric micelles, and vesicular systems such as liposomes, sphingosomes, niosomes, transfersomes, aquasomes, and ufasomes are examples of particulate type carriers, also known as colloidal carrier systems.

Traditional drug delivery techniques such as tablets, capsules, and intravascular injections have significant limitations, which led to the development of the vesicular system. The fundamental disadvantage of the traditional system is that the medicine is released from the dosage forms at the application site rather than at the action site. Furthermore, the medicine is distributed throughout the body by systemic blood circulation after absorption. As a result, only a small amount of the medicine in most therapeutic drugs reaches the diseased section of the body. To achieve the desired amount of medicine at the diseased portion of the body, greater dosages and frequency of administration are required. As a result, additional dosages and administration frequency are necessary to get the appropriate amount of medicine at the diseased part of the body, which might be a particular organ or cell. Overall, traditional dosage forms had fewer beneficial effects and greater adverse effects, as we can see. Clinical research and modern drug delivery in the modern era are largely focused on decreasing toxicological behaviour and increasing a medicine's therapeutic usefulness. Site-specific drug delivery in the form of sterically protected

liposomes was invented specifically for this purpose. Liposomes made of natural phospholipids are physiologically inert, have a low inherent toxicity, and are weakly immunogenic. Drugs with varying lipophilicity can also be encapsulated in liposomes. Liposomes can be packed with drugs and utilised to distribute them to patients suffering from cancer and other disorders. Since the invention of liposomes, the related technology has improved significantly, and numerous major formulations for the treatment of various diseases are now commercially available or in advanced clinical studies. The present review can in short outlines about vesicular drug delivery systems and the characteristics regarding stealth liposomes, methods of preparation, modes of action, pharmacokinetics and their field of application.

2. VESICULAR DRUG DELIVERY SYSTEM

Vesicular drug delivery systems are highly organised assemblies made up of one or more concentric bilayers that arise when amphiphilic building blocks self-assemble in the presence of water. Bingham originally described the biologic origin of lipid-based vesicles in 1965, and the Bingham Bodies were named after him. Because of their potential to localise drug activity at the site or organ of action while reducing its concentration at other places in the body, vesicular drug delivery systems are particularly significant for targeted drug delivery.

2.1 Advantages of Vesicular Drug Delivery System

- i. Drugs that are both hydrophilic and hydrophobic can be encapsulated readily.
- ii. Drug bioavailability can also be increased.
- iii. Drug's circulation life in the body can be extended.
- iv. Drug distribution that is targeted can often be accomplished.
- v. Liability drug stability issues can be overcome.
- vi. Toxicity problems with certain drugs are often resolved.
- vii. Rapidly metabolizable drugs can be delayed in their elimination.

2.2 Liposomes as Vesicular Drug Delivery System

Liposomes are colloidal, concentric bilayered vesicles in which the aqueous compartment is completely surrounded by a bilayer membrane

made primarily of natural or synthetic lipids. Fig. 1 depicts a typical liposome. Phospholipids (mostly phosphatidylcholine) and cholesterol are important components of the liposomal drug delivery system, with cholesterol acting as a fluidity buffer. Despite the fact that cholesterol does not contribute in bilayer formation, it can be added to phosphatidylcholine in a 1:1 or even 2:1 molar ratio. Liposomes have gained a lot of traction as a promising drug carrier system for precise drug delivery [1].

2.2.1 Advantages of Liposomes as Vesicular Drug Delivery System [2]:

- i. Liposomes can deliver both hydrophilic and lipophilic medicines.
- ii. Increased stability, which protects the encapsulated drug from the environment.
- iii. Less toxicity.
- iv. Less exposure to toxic drugs and their metabolites in sensitive tissues.
- v. Liposomes can be used to transport both small and large molecular weight drugs.
- vi. Targeted delivery can be achieved.
- vii. Improved pharmacokinetic features, such as decreased elimination and a longer stay in circulation.

2.2.2 Disadvantages of Liposomes as Vesicular Drug Delivery System:

- i. Liposomes are leaky by nature, resulting in drug release prematurely.

- ii. Hydrophilic drug encapsulation efficiency is poor.
- iii. Liposomes are costly.
- iv. Liposomes have a very short half-life.

3. NEW ERAS OF VESICULAR DRUG DELIVERY SYSTEMS

3.1 Niosomes

The use of nonionic surfactants in the development of vesicular drug delivery systems has been prompted by the requirement of a cryogenic environment for the handling of liposomes. This recently introduced vesicular drug delivery system, which consists of unilamellar or multilamellar vesicles, was named niosome. Non-ionic surfactant vesicles, also known as niosomes, are microscopic lamellar vesicles generated when nonionic surfactants (often of the alkyl or dialkyl polyglycerol ether class) are added to cholesterol and then hydrated in aqueous medium. The addition of cholesterol tightens the bilayer, resulting in the creation of niosomes that are less permeable. The addition of nonionic surfactants to niosomes increases the size of vesicles and gives them a charge, improving niosome entrapment efficiency. Because niosomes have a structure comparable to liposomes, they could be a promising drug delivery module. On the basis of parameters such as cost, stability, entrapment efficiency, bioavailability, and so on, niosomes are considered to be a better drug carrier system than liposomes [3].

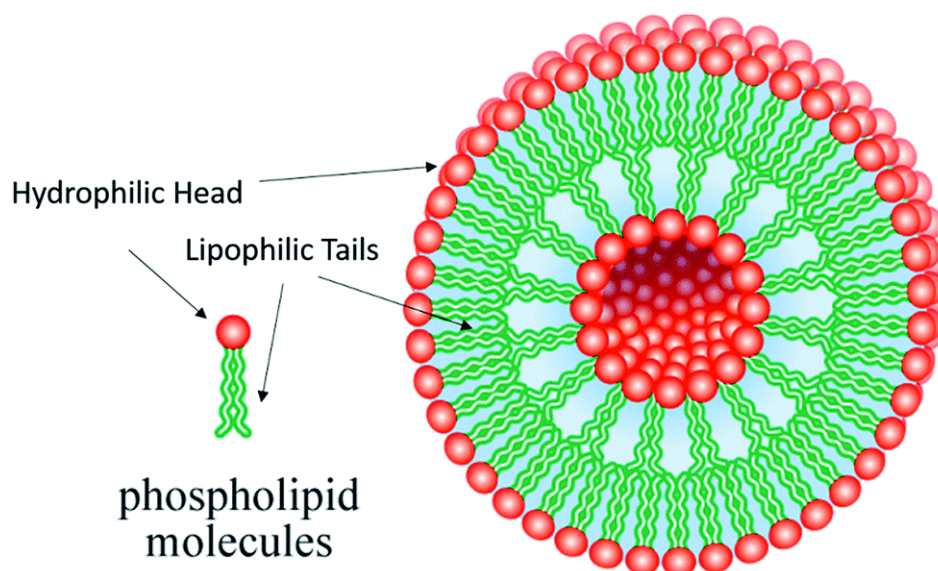


Fig. 1. Basic liposome structure

3.1.1 Advantages of Niosomes [4]:

- i. Niosomes are more stable than other proteins.
- ii. They don't necessitate any specific handling or storage.
- iii. Niosomes are osmotically active.
- iv. Niosomes have the ability to entrap drugs that have a wide range of solubility.
- v. They can be used as a depot system to slowly release the drug as required.
- vi. Niosomes have more design and structural flexibility than liposomes.
- vii. They can improve medication bioavailability in the oral, topical, and parenteral routes.
- viii. They simply improve the therapeutic performance of an encapsulated drug by limiting its action to the target cells and lowering the drug's clearance.

3.2 Transfersomes

Liposomes and niosomes are not appropriate for transdermal drug delivery because to their poor skin permeability, permeable nature, aggregation and fusion in skin tissues, which led to the development of a new form of carrier termed transfersomes in 1991 by Gregor Cevc. Transfersomes is derived from the Latin word "Transfere" (which means "to carry across") and the Greek word "some" (meaning body). Thus, transfersomes are complex vesicles with an aqueous core surrounded by a complex bilayer of lipids that are ultra-deformable and stress responsive. These artificial vesicles are made up of one natural amphiphilic lipid (e.g., phosphatidylcholine, dipalmitoyl phosphatidylcholine) and a bilayer softener (biocompatible surfactant) (e.g., sodium cholate, span 80, and tween 80). Transfersomes can modify their membrane composition reversibly in the presence of amphiphilic surfactants, allowing them to pass through tiny skin pores [5].

3.2.1 Advantages of Transfersomes [6]:

Transfersomes can accommodate drugs with a wide range of solubility because they contain both hydrophilic and hydrophobic moieties.

- i. They are so deformable that they can pass through even the smallest pores in the skin without causing any damage.
- ii. Low and high molecular weight drugs can be efficiently captured.
- iii. They prevent enzymatic and metabolic degradation of the encapsulated drug.

- iv. They can be utilised for both topical and systemic drug delivery.
- v. They can serve as a depot formulation, allowing the contained drug to be released in a regulated manner.

3.2.2 Disadvantages of Transfersomes:

- i. They are expensive.
- ii. They are chemically unstable.
- iii. Purity of phospholipids is another important criterion to be considered.

3.3 Aquasomes

The pharmaceutical and biotechnology sectors have faced difficulties in administering bioactive compounds in their active state. Some potential limitations for successful formulation of these bioengineered molecules (peptides, proteins, hormones, antigens, and genes) include drug-related challenges such as appropriate route and site of drug delivery, chemical and physical instability, poor bioavailability, and potentially serious side effects of these bioengineered molecules. In the form of aquasomes, a new approach to their formulation problem has been proposed by combining biotechnology with nanotechnology (i.e., nanobiotechnology). Aquasomes are trilayered self-assembled nanostructures having a solid phase nanocrystalline core coated with an oligomeric film (made of carbohydrate) on which biochemically active molecules are adsorbed with or without modification. Ceramic nanoparticles are another term for aquasomes. The solid core provides structural rigidity while also protecting the carbohydrate coating products from dehydration and stabilising biochemically active molecules. Polymers like albumin, gelatin, or acrylate, as well as ceramics like diamond particles, brushite (calcium phosphate), and tin oxide, make the nano crystalline core. Sucrose, cellobiose, trehalose, chitosan, citrate, and other coating materials are often used. Insulin, haemoglobin, and enzymes like serratiopeptidase are all delivered through aquasomes [7].

3.3.1 Advantages of Aquasomes [8]:

- i. Aquasomes preserve bioactive molecules' structural integrity and biochemical stability.
- ii. Aquasomes avoid reticuloendothelial clearance or degradation by other environmental challenges due to their size and structure stability.

- iii. Because aquasomal suspension contains biodegradable nanoparticles in the colloidal range, they are more concentrated in the liver and muscles.
- iv. Because the drug is absorbed on the system's surface without further surface alteration, as in the case of insulin and antigen delivery, they may not have any problem recognising receptors on the active site, allowing for immediate pharmacological or biological activity.

3.4 Colloidosomes

Colloidosomes are an advanced drug delivery system that allows proteins, vitamins, and food supplements to be delivered efficiently. They're hollow shell microcapsules made up of coagulated or fused particles that form at the emulsion droplet interface. They are made by adding colloidal particles into the continuous phase of a water-in-oil emulsion, where the particles self-assemble and create a colloidal shell structure at the interface between the two immiscible liquid phases. Subsequently, the colloidal shell structures, hydrated by the water droplets dispersed in the oil phase, are transferred to an aqueous phase either by centrifugation or repeated washing. Colloidosomes with particles varying in size from 5 nm to several microns have been produced using this method [9].

3.4.1 Advantages of Colloidosomes[10]:

- i. The controlled size of colloidosomes allows for a wide range of applications and encapsulated materials.
- ii. They have a better chance of controlling entrapped species' permeability and allowing selective and timed release.
- iii. Colloidosomes are simple to make.
- iv. Colloidosomes have a high mechanical strength, allowing yield stress to be adjusted to withstand mechanical loads and release at predetermined shear rates.
- v. Biomolecules and cells, which are fragile and sensitive, can be easily encapsulated.

3.4.2 Disadvantages of Colloidosomes:

- i. They give a low yield.
- ii. A considerable fraction of colloidosomes is lost when they are transferred from organic to aqueous media.
- iii. Colloidosomes agglomerate as a result of insufficient shell locking.

3.5 Cubosomes

The hydrophobic portion of amphiphilic molecules self-assembles into an array of thermodynamically stable liquid crystalline phases with lengths on the nanometer scale in the presence of polar solvents. The molecular orientation and structural symmetry of these liquid crystalline phases are sufficient. Bicontinuous cubic liquid crystalline phase is one example. Bicontinuous cubic phases are extremely viscous, optically isotropic, solid, and consist of two divided, continuous but nonintersecting hydrophilic regions divided by a lipid bilayer in to a periodic minimal surface with zero curvature, similar to liquid crystalline substance with cubic crystallographic symmetry. Such cubic phases are distinguished from micellar or discontinuous cubic phases by their bicontinuous nature, which contain micelles packed in cubic symmetry. One of the most essential aspects of these cubic phases is their tendency to disperse into cubosomes, which are small particles. High energy dispersion of bulk cubic phase, followed by colloidal stabilisation using polymeric surfactants, is how they're made. The dispersion can then be manufactured as a product and applied to a biological tissue once the cubosomes have formed. Larsson coined the term "cubosomes," which refers to the cubic molecular crystallography and similarities to liposomes [11].

3.5.1 Advantages of Cubosomes [12]:

- i. Cubosomes have the ability to deliver bioactive substances in a targeted and controlled manner.
- ii. Drugs that are hydrophilic, hydrophobic, or amphiphilic can be easily encapsulated in cubosomes.
- iii. Cubosomes are simple to make.
- iv. Cubosomes are biodegradable since the lipids utilised in their formation are biodegradable in nature.
- v. High drug payloads are possible due to the cubic crystalline structure and high internal surface area.
- vi. Cubic phases are more bioadhesive, making them more suitable for drug delivery via topical and mucosal routes.

3.6 Sphingosomes

Oxidation, hydrolysis, degradation, leaching, sedimentation, drug aggregation, and other issues with liposomes all have impact on their

stability. Sphingosomes were developed as a result of the researchers' efforts to increase stability [13][14]. Sphingosomes are colloidal, concentric bilayered vesicles with an aqueous compartment completely enclosed by a bilayer membrane made primarily of natural or synthetic sphingolipids; in other words, sphingosomes are sphingolipid-based liposomes. Sphingosomes are made up of sphingolipids (sphingomyelin) and cholesterol with an acidic intraliposomal pH ratio of sphingomyelin and cholesterol ranging from 75 to 25 %mol/%mol (most preferably 55/45 %mol/%mol).

Sphinganine, Hexadecaspheganine, Lysosphingomyelins, and lysoglycosphingolipids, N-Acylsphingosines, Gangliosides, Glucuronosphingolipids, Phosphoglycosphingolipids, and other sphingolipids have all been employed in the formation of sphingosomes.

3.6.1 Advantages of Sphingosomes [15]:

- i. Sphingosomes have greater drug retention properties.
- ii. They can be delivered through subcutaneous, intravenous, intra-arterial, intramuscular, oral, and transdermal methods.
- iii. They deliver drug to tumour tissue with selective passive targeting.
- iv. Sphingosomes boost the encapsulated drug's effectiveness and therapeutic index.
- v. Encapsulation improves the stability of the system.
- vi. The encapsulated drug's toxicity is lowered.
- vii. Sphingosomes improve encapsulated drug pharmacokinetics simply by increasing circulation time.
- viii. Sphingosomes are designed in such a way that they can be coupled with site-specific ligands to accomplish active targeting.

3.6.2 Disadvantages of Sphingosomes:

- i. Sphingosomes are not cost-effective.
- ii. Sphingosomes have a low efficiency of entrapment.

3.7 Ufasomes

Although the stratum corneum reduces drug penetration into living skin, topical therapy appears to be the most beneficial method of administration because it has a lower chance of systemic side effects. Ufasomes were developed to improve drug penetration into the skin via the

stratum corneum. Ufasomes are lipid carriers that bind to the skin's surface and allow for lipid exchange between the stratum corneum's outer layers. This carrier system has effective drug delivery. Ufasomes, like liposomes and niosomes, have been produced for topical/transdermal delivery of medicines, proteins, peptides, hormones, and other substances. Gebicki and Hicks first described the creation of fatty acid vesicles in 1973, and the vesicles were initially termed "ufasomes," referring to unsaturated fatty acid liposomes. Unsaturated fatty acid vesicles, or ufasomes, are suspensions of closed lipid bilayers made up of fatty acids and ionic surfactants. The pH of ufasomal suspension ranges between 7 and 9. Fatty acid molecules in ufasomes organise themselves so that their hydrocarbon tails point toward the inner side of the membrane and the carboxyl groups stay in contact with water [16].

3.7.1 Advantages of Ufasomes:

- i. Ufasomes are more stable than liposomes.
- ii. They are more effective in entrapping both hydrophilic and hydrophobic pharmaceuticals.
- iii. Ufasomes are less expensive than liposomes.

4. FIRST GENERATION LIPOSOMES

Preclinical and clinical trials of liposomal formulations of several drug ingredients are currently ongoing in a variety of fields, with promising results. The use of liposomal formulations can solve two major problems in drug therapy: biodistribution throughout the body and targeting to specific receptors. Liposomes protect encapsulated molecules from degradation and can target tissues or organs with a discontinuous endothelium, such as the liver, spleen, and bone marrow, in a passive manner. Liposomes are quickly captured by the mononuclear phagocyte system (MPS) and removed from the blood circulation after intravenous administration [17]. This behaviour has been used to deliver anti-parasitic and antimicrobial drugs to infections in the mononuclear phagocytic system [18], as well as to encapsulate immunomodulators in activated macrophages in cancer models, resulting in tumoricidal agents. When the target site is outside of the MPS, however, efficient liposome uptake by macrophages and subsequent removal from circulation is one of the major drawbacks of using liposomes as a drug delivery system.

Liposome technology has progressed from first-generation liposomes to second-generation liposomes, which are created by varying the lipid composition, size, and charge of the vesicle. The "Stealth liposome" is a spherical vesicle with a phospholipid bilayer membrane that is used to deliver drugs or genetic material into cells. Poly Ethylene Glycol was widely used as a polymeric stabiliser to improve liposome blood circulation time. PEG is a linear polyether-diol with a number of properties that are beneficial to biocompatibility and solubility in both aqueous and organic media. Liposomes have a stealth behaviour or a long circulatory action due to this property [19].

PEG on the liposomal carrier's surface has been shown to increase blood circulation time while decreasing mono nuclear phagocyte system uptake. As a result of this technology, a large number of liposome formulations encapsulating active molecules have been developed, all of which have high target efficiency and activity. Stealth liposomes can also be actively targeted with monoclonal antibodies or legends by synthetic modification of the terminal PEG molecule. Table 1 summarises the liposomal-based drugs that have been approved by the FDA or are currently in clinical trials.

4.1 Mechanism of Transportation through Stealth Liposomes [20]:

1. Liposomes interact with cells through a variety of mechanisms. endocytosis by reticuloendothelial system phagocytic cells such as macrophages and neutrophils
2. Adsorption to the cell surface via nonspecific weak hydrophobic or electrostatic forces, or through specialised interactions with cell-surface components.
3. Fusion with the plasma cell membrane via insertion of the liposome's lipid bilayer into the plasma membrane, followed by release of the liposomal cargo into the cytoplasm.
4. Liposomal lipids are transferred to cellular or subcellular membranes, or vice versa, without the liposome contents being associated.
5. Determining which mechanism is active can be challenging, and multiple mechanisms may be active at the same time.

4.2 Characteristics of Stealth Liposomes [21]

1. Stealth Liposome, which is made up of cholesterol and phospholipids such phosphatidylcholine and dicetylphosphate, with the same structure, content, and proportions as the host cell.
2. The stealth liposome can be injected into the body without causing immunological rejection.
3. Phospholipids, sphingolipids, glycolipids, and sterols are the most frequent lipids found in liposomes.
4. The Stealth liposome is a stable, colloidal, and homogeneous liposome.
5. Bipolar fatty acids, Antibody directed, Methyl/methylene X-linked, Lipoprotein coated, Carbohydrate coated, multiple encapsulated, Emulsion compatible
6. Drugs encapsulated in liposomes are distributed to various tissues and cells and can be released when the liposome is damaged, allowing enabling site-specific drug delivery.
7. Liposomes can be employed without chemical modification for both hydrophilic and lipophilic drugs.
8. The drug is protected from other body tissues and cells until it is released by the liposome, minimizing toxicity.
9. Depending on the drug and the intended use of the product, the size, charge, and other characteristics can be changed.
10. They are too small to be taken up by the reticular endothelial system, resulting in slow drug release.

4.3 Pharmacokinetics of Stealth Liposomes

Nanocarrier-based medications are thought to be mostly eliminated from the bloodstream by phagocytosis by reticuloendothelial system elements (RES). RES is mostly found in the liver (hepatic kupffer cells), spleen, and bone marrow, where it interacts with macrophages, monocytes, and dendritic cells. As a result, factors that affect RES activity may affect Stealth liposome clearance, toxicity, and responsiveness [22]. Liposomes are promptly eliminated from the circulatory system after systemic administration by the immune system, primarily macrophages of the RES. As a result, the pharmacokinetics of liposomal systems have an impact on their delivery [23]. PEGylated liposomes

encapsulating cytotoxic medications, for example, have been shown to improve tumour delivery by altering the pharmacokinetic and distribution patterns of the encapsulated pharmaceuticals after intravenous injection. When compared to conventional cytotoxic medications, chemotherapeutic agents are shown to leak slowly from blood vessels and concentrate preferentially in tumour tissues, leading in better anticancer activity and reduced toxicity. As a result, nanocarrier medications should most likely be developed to circumvent these clearance processes and complement activation in order to prolong the half-life of anticancer treatments in the bloodstream [24]. Fig. 2 shows a comparison of the pharmacokinetics of non-pegylated and pegylated liposomes.

4.4 Preparation Techniques of Stealth Liposomes[25]

The same processes used to make conventional liposomes were used to make stealth liposomes. However, PEGylation is a critical step to include in these methods. PEGylation is the process of allowing a polymer to encase a liposome. To enhance blood flow time, there are three alternative techniques to change the liposome surface with polymers. They are as follows:

4.4.1 Pre-Insertion technique

The polymer is added to the lipid stage before the liposomes are formed in this technique.

Despite the fact that this is the most commonly used strategy for the formation of stealth liposomes, there are a few drawbacks to this method. To begin, it necessitates a large quantity of polymer. Second, the lipid bilayer film's interior and external surfaces are both altered. Furthermore, the pre-insertion procedure is not the best way to make target-specific stealth liposomes.

4.4.2 Post-Insertion technique

Polymers are slowly added to dilute suspensions of preformed liposomes at a temperature near to the constituent lipids' transition temperature (T_m) in this procedure. The polymer's critical micellar concentration (CMC) must be maintained during this process to prevent the amphiphilic polymer from self-assembling. In comparison to the pre-insertion procedure, this technique just modifies the liposomes' external surface, leaving the inside space available for drug convenience.

4.4.3 Post-Modification by chemical reaction

This method of liposome synthesis is most typically utilised for targeted drug delivery rather than for long-circulating liposomes. A chemical interaction happens between the polymer and the liposome surface in this manner. Modified lipids are developed through milder chemical reactions such as photo triggered polymer conjugation or oxime formation reactions, which are subsequently used to prepare liposomes.

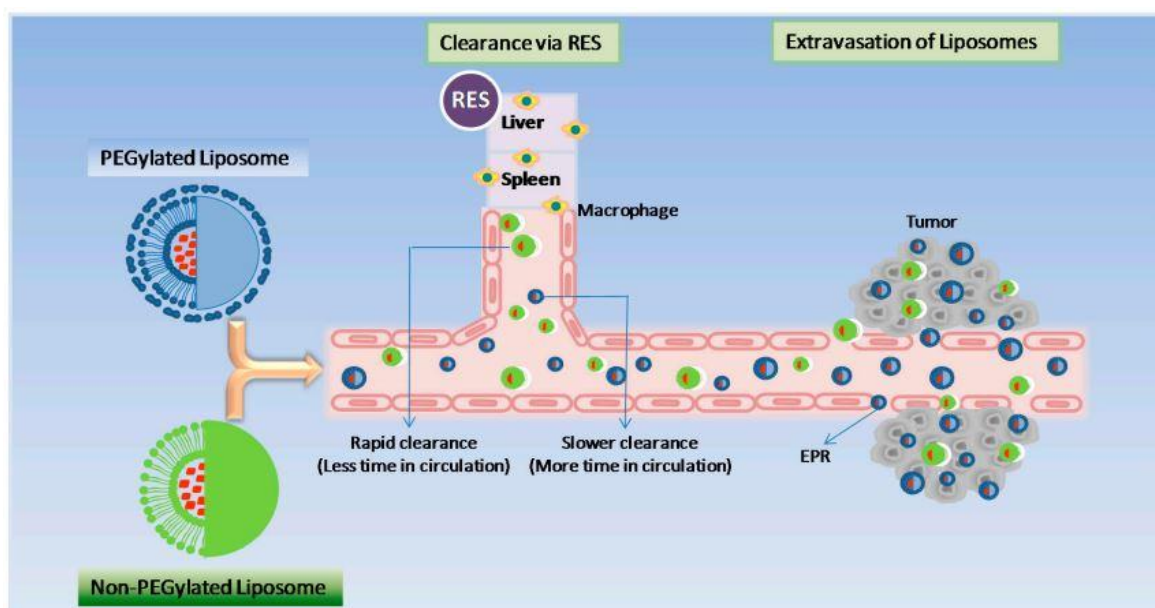


Fig. 2. Pharmacokinetics of Non-Pegylated and Pegylated Liposomes

Table 1. Marketed Liposomal based therapeutics in market and in clinical development

Drug	Disease	Status	Type of liposomal-based delivery system
Amikacin	Lung infection	Phase II/III	Conventional
Amphotericin B	Anti-fungal prophylaxis	FDA approved	Conventional
Annamycin	Acute lymphoblastic leukemia	Phase I/II	Conventional
Camptothecin analog	Ovarian cancer	Phase I	PEGylated
Cytarabine	Neoplastic meningitis and lymphomatous meningitis	FDA Approved	Conventional
Daunorubicin	Leukemia and solid tumors	FDA Approved	Conventional
Doxorubicin	Leukemia, breast cancer, bone cancer, lung cancer, brain cancer	FDA Approved	PEGylated
Doxorubicin and bortezomib	Relapsed or refractory multiple myeloma	FDA Approved	PEGylated
Irinotecan	Advanced refractory solid tumors and colorectal cancer	Phase I	PEGylated
Irinotecan SN-38	Metastatic colorectal cancer	Phase I/II	Conventional
Lurtotecan	Ovarian cancer, head, and neck cancer	Phase I/II	Conventional
Mitoxantrone LEM-ETU	Acute myeloid leukemia and prostate cancer	Phase I	Cationic
Morphine sulfate	Pain Management	FDA Approved	Conventional
Nystatin	Fungal Infections	Phase I/II	Conventional
Paclitaxel	Advanced triple-negative breast cancer	Phase II	Cationic
EndoTAG-1			
Paclitaxel	Pancreatic cancer	Phase II	Cationic
EndoTAG-1			
Paclitaxel LEP-ETU	Advanced triple-negative breast cancer	Phase I/II	siRNA
siRNA	Ovarian cancer	Phase I	DOPC neutral liposomes
Thermosensitive doxorubicin	Liver tumors	Phase III	PEGylated
Thermosensitive doxorubicin	Chest wall recurrences of breast cancer	Phase I	PEGylated
Topotecan	Advanced solid tumors	Phase I/II	Conventional
Tretinoin	Acute promyelocytic leukemia and hormone-refractory prostate cancer	Phase II	Conventional
Verteporfin	Molecular degeneration	FDA Approved	Cationic
Vincristine	Non-Hodgkin lymphoma	FDA Approved	Conventional
Vinorelbine	Newly diagnosed or relapsed solid tumors	Phase I	Conventional

4.5 Applications of Stealth Liposomes

Stealth liposomes' potential to change biodistribution profiles and accumulate at specific sites in specified porous blood capillaries, such as tumours, inflammations, and infections, has increased their use [26]. The following are some of the most important applications;

4.5.1 Cancer therapy

The ability of cytotoxic drugs to kill both normal and malignant cells is the most common disadvantage. The trapping of these medications in stealth liposomes resulted in a prolonged flow life and better deposition at the target site, lowering harmful side effects. Various cancer research utilising stealth liposomes concluded that polyethylene glycol coated immune stealth liposomes outperformed conventional immune liposomes in terms of target ability. In the case of the delivery of highly toxic anticancer medicines, the active targeting of tumour tissues by these polymer modified liposomes is important [27].

4.5.2 Vaccination, gene therapy and diagnostics

The delivery of nucleic acids into cells, both in vitro and in vivo, is essential for recombinant-DNA technology, gene function investigations, and gene therapy. There are several DNA-carrier systems for in vitro administration, but in vivo distribution is more demanding and often favoured for gene therapy, which is the treatment of disorders at the molecular level by switching genes on or off. The cationic lipid-based DNA complexes, or simply liposomes, can operate as an adjuvant or carrier of co-adjuvants, triggering an immune response to the vaccine antigen, but their accessibility is limited. The breakdown of liposomes by enzymes is a critical obstacle in the creation of liposomes for oral or mucosal administration of macromolecules. Liposomes that are mechanically or sterically stabilised (polymer coated) can survive these conditions [28].

4.5.3 In inflammations

Stealth liposomes can be used to localise and distribute drug substances to inflamed tissue with pinpoint accuracy. As a result, they can be employed for diagnostic purposes as well. Liposomes containing nonsteroidal anti-inflammatory drugs and corticosteroids are injected directly into inflammation sites for a sustained release mechanism [29].

4.5.4 Delivery of enzymes and hormones:

Stealth liposomes are good carriers for enzymes and hormones. They are safe, biocompatible and also reduce systemic toxicity. Many hormones like triiodothyronine can be successfully delivered to the cancerous liver cells. The many negative effects associated with the direct injection of hormones like tachycardia, arrhythmias etc. can be eliminated with the development of an effective targeted drug delivery system [30].

4.5.5 Antimicrobial therapy

The conventional liposome is the preferred carrier for the long-term release of antimicrobial drugs. These conventional liposomes, on the other hand, are easily detected and digested by mononuclear phagocyte cells, particularly kupffer cells and spleen macrophages. Furthermore, drugs like as penicillins and cephalosporins are highly susceptible to breakdown by -lactamase enzymes produced by several infectious organisms. Encapsulation of drugs, mainly powerful antibiotics, in sterically stabilised liposomes can protect the drug from degradation while also improving its efficacy [31]. Additionally, the lipid nature of these formulations can easily permeate microorganism cell membranes and increase cellular concentrations, resulting in lower doses and toxicity. pH-sensitive liposomes can transfer plasmids, antisense oligonucleotides, and ribozymes intracytoplasmically in vivo for the treatment of human immunodeficiency virus and other infections [32].

4.5.6 Liposome encapsulated haemoglobin

Liposomes' ability to transport a variety of compounds in the bilayer or in the aqueous compartment makes them a viable option for a variety of imaging techniques, including gamma-scintigraphy, magnetic resonance imaging (MRI), processed tomography imaging (CTI), and sonography. Liposomes have significant advantages in diagnostic imaging because of their ability to include multiple contrast moieties, deliver them selectively to the targeted region, and therefore enhance the contrasting signal. By modifying the exterior of the liposomes with polyethylene glycol, the stability and half-life of liposomes can be increased as a complexity operator after organisation. Gd-Liposome (Gadolinium liposome), a long circulating liposome that prolongs the presence of contrast

agent in the body, was effectively developed for body imaging [33].

4.5.7 Diagnostic imaging

Liposome encapsulated haemoglobin (LEH) is an example of a transfusable (non-allergenic) oxygen-carrying blood replacement fluid that can be utilised to give temporary life support in an emergency situation. Many studies have found that haemoglobin encapsulated in stealth liposomes can minimise harmful effects while also preventing macrophage identification, increasing blood circulation time [34].

5. CONCLUSION

Vesicular drug delivery systems are now widely used in a variety of applications. Because of their efficient qualities and functionalities, such as selective targeting, these systems have become one of the most widespread and important delivery methods in recent years. The pharmacokinetics of drugs, on the other hand, is being studied in order to make these drug delivery methods more valuable. This system's actuation mechanism is also in the last stages of development. Liposomes are a lipid-based drug delivery method that has been extensively explored. Certain surface modifications are required to overcome some of the problems with regular liposomes in terms of stability and mononuclear phagocyte system uptake. Stealth liposomes are sterically stabilised surface designed liposomes that overcome many of the challenges that traditional liposomes. MPS uptake and opsonization are reduced when the liposome surface is coated with PEG, whereas surface hydrophilicity is increased.

Furthermore, employing cell-penetrating proteins and peptides as targeting agents, PEG grafted onto the liposome surface can lead the liposome to a specific intracellular target. Liposome distribution to specific subcellular compartments is a topic of tremendous interest in a variety of domains, including gene therapy and immunisation. Although the interaction of stealth liposomes with cell membranes and drug release in the area of target tissues are still being studied, new research suggests that the use of detachable PEG may increase cell penetration and/or intracellular distribution of vesicles. Taking these factors into account, as well as the significant benefits of PEGylated liposomes in reducing specific drug toxicity and passively targeting incorporated molecules to the site of

action, new and "improved" stealth liposomal formulations for various therapeutic and diagnostic applications may be on the way soon.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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