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A Review on Surface Modified Sterically Stabilized Liposomes

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Abstract:- Liposomes are microvesicles made out of a bilayer of lipid amphipathic molecules, encasing a fluid compartment. The principle constituent of liposomes is phospholipid which contains a hydrophobic tail and hydrophilic head groups which empowers the liposomes to sort out into round bilayer direction in watery media. The hydrophobic tail and hydrophilic head group of the phospholipids is the reason for entrapping both water dissolvable and lipid solvent substances, while staying scattered in the fluid condition. Besides its various points of interest the real restriction in the helpful utilization of customary liposomes upon intravenous organization lies in its quick disposal from the blood and acknowledgment by the reticuloendothelial system (RES). This prompts the improvement of surface changed sterically stabilized liposomes or the stealth liposomes. The nearness of polymers on the outside of liposomes has been appeared to enhance the blood flow time without being effectively perceived by the intrinsic insusceptible framework. This review centers around the development of stealth liposomes, summarizes the generally utilized polymers for the development and finally the applications of this promising innovation.

Keywords:- *PEG, Stealth Liposomes, Reticulo Endothelial System, Drug Delivery.*

I. INTRODUCTION

Over the past few decades lipid based formulations are the widely accepted choice of drug delivery system. Lipid-based drug delivery system can act as a promising tool for the purposes of site specific as well as time controlled delivery of drugs. The ability of the lipid formulations to be modified according to the disease conditions, route of administration, stability etc.. enhanced their application as a major drug delivery system. There are different types of lipid-based drug delivery system of which liposomes have gained importance nowadays [1]. Liposomes are nanosized lipid formulation composed of mainly phospholipids. The phospholipids have both a hydrophobic tail and hydrophilic head group (Fig.1), enabling the liposomal delivery systems to encapsulate both water-soluble and lipid soluble substances while remaining dispersed in the aqueous environment [2]. Stealth liposomes are the category of second generation of liposomes which are surface modified to enhance the utility of conventional liposomes.

II. LIPOSOMES AS DRUG DELIVERY VEHICLE

In 1965, liposomes were described as the first closed bilayer phospholipid drug delivery systems[3]. Liposomes were developed to conquer the issues related with regular medication conveyance like, inefficient biodistribution, absence of tissue targeting, lack of specific delivery etc.. These macromolecules have an alternate biodistribution profile with a drawn out plasma half-life and decreased digestion of the exemplified medication. The real explanation behind the regular utilization of nanomedicine is the ability of the macromolecular compounds to exploit the enhanced permeability and retention (EPR) effect to specifically target tumor and inflamed tissues.

Besides its numerous advantages the major limitation in the therapeutic use of conventional liposomes upon intravenous administration lies in its fast elimination from the blood and recognition by the reticuloendothelial system (RES). The certain circulating proteins(like laminin, fibronectin, C-reactive proteins, immunoglubulins) in the blood, binds specifically to the surface of conventional liposomes as a result of innate immune response through the process of opsonization resulting into a cascade of inflammatory and complex adverse reactions (Complement Activation- Related Pseudo Allergy or CARPA). These interactions result in destabilization and rapid clearance of the conventional liposomes from the circulation. Moreover, the rapid release of the encapsulated drug into the plasma without even reaching the targeted site due to the interaction of liposomes with high and low density lipoproteins (HDL and LDL) is another limitation.Upon various studies inorder to circumvent the low-systemic circulation time of conventional liposomes, surface engineered long circulating stealth liposomes has been developed by coating the outer liposome surface with polymers like polyethylene glycol (PEG), polyvinyl pyrrolidine (PVP), polyacryl amide (PAA) etc.. These stealth liposomes resulted with increased liposome stability, increased blood circulation times and improved biodistribution after systemic administration [4].

III. STEALTH LIPOSOMES

Despite the fact that liposomes are biomembranes, they are as yet remote articles to the body and are in this way effectively perceived and cleared from the systemic circulation rapidly by the mononuclear phagocytic system (MPS). In order to defeat these constraints the idea of stealth conduct similar to the stealth bombers designed by the Germans to destroy British command centers during

Second World War were adopted. The British officials failed to tackle the killer bombers they were helpless and destroyed to its bits. Similarly, stealth liposomes are used to fool the phagocytes and thus they fail in recognition, enhancing the blood circulation time [5]. Various methods were introduced for the stealth behavior of liposomes like the development of cholesterol-rich liposomes [6], incorporation of polyvinyl-pyrrolidine [7], polyacrylamide lipids [8], glucoronic acid lipids into the liposomes [9], also coating of liposomes with proteins, polysaccharides, glycolipids of red blood cells ganglioside G_{M1} and hydrogenated phosphatidyl inositol (HPI). Among this some success has been achieved with ganglioside G_{MI} but only in mouse model and not in a rat and rabbit models because the serum of the rat and rabbit models contains anti-G_{MI} antibodies which enhance rapid clearance of G_{MI} containing liposomes [10]. After different methodologies because of the one of a kind physical properties like boundless water dissolvability, large excluded volume and high degree of conformational entropy, polyethylene glycol (PEG) was utilized to improve the solidness and organic execution of colloidal transporter (Fig.2). PEG of certain molecular weight and graft density forestalls the adsorption of explicit proteins as well the steric behaviour of PEG prevents the aggregation of colloidal carriers and thus enhancing their stability. The ability of PEG coated liposomes to increase the blood circulation time depends on the amount of PEG incorporated and also the length or molecular weight of the polymer. The longer the PEG chain, the greater the blood residence time [11]. The PEG on surface of liposomes builds up a very hydrated layer or film of water which sterically avoids the opsonization of liposomes and their debasement by the mononuclear phagocyte system[12]. Even the PEG has several limitations like in various studies it was found out that PEG can accumulate in the body, the *invivo* behaviour is altered by the PEG's polydispersity index etc..Some other alternative polymers used for the preparation of stealth liposomes are as follows [2]:

- *Zwitterionic polypeptides:*

The zwitterionic polymers are neutral polymers that contain both positive and negative charges having similar stealth properties as PEG. In various studies in comparison with the uncharged polypeptide control it was found out that the zwitterionic polypeptides resulted in improved pharmacokinetics, polypeptide half-life and longer circulation times [13]. The major challenge in using zwitterionic polymer for stealth behaviour is due to the lack in the availability of solvents that can dissolve both hydrophilic and hydrophobic blocks.

- *Poly aminoacid-based polymers:*

Poly(amino acids)'s (PAA) can also be used for coating liposomes for prolonged blood circulation. PAAs such as polyglutamic acid (PGA), poly(hydroxyethyl-L-asparagine)(PHEA) and poly(hydroxyl ethyl-L-glutamine)(PHEG) are commonly used in drug delivery applications. In a comparative study with polyethylene glycol the prolonged circulation were comparable to those reported for polyethylene glycol coated liposomes. Also, PAAs in free just as liposome related structure are degradable by proteases protein which is advantageous in decreasing the dangers of amassing invivo [14].

- *Poly(2-Oxazoline)-based polymers:*

This water-soluble polymer is synthesized by cationic ring-opening polymerization reactions in controlled manner. 5mol% polyoxazoline containing liposomes showed circulation times similar to that of PEG linked phospholipids. In spite of the fact that polyoxazolines are with various chemical functionalities their biological and stability studies are not rapidly known.

- *Vinyl based polymers:*

Polyvinyl pyrrolidine or PVP is a water soluble, chemically stable, non-toxic and biocompatible polymer. Compared to PEG, PVP is more stable and can be synthesized by free-radical or controlled radical polymerization. Even though these polymers have the capability of showing prolonged blood circulation than other polymers they are not widely used because of their non-biodegradable nature.

IV. PREPARATION TECHNIQUES OF STEALTH LIPOSOMES

Generally there are three different ways to adjust the liposome surface with polymers to improve the blood flow time and are as per the following [2]:

- *Pre-Insertion technique:*

In this procedure the polymer is added to the lipid stage before the liposomes are shaped. Despite the fact that this is the most ordinarily utilized strategy for the arrangement of stealth liposomes, there are a few disadvantages to this technique. To start with, it requires overabundance measure of polymer. Second, both the internal and external side of the lipid bilayer film is changed. In addition, the pre-insertion technique is not an ideal method for the preparation of target-specific stealth liposomes.

- *Post-Insertion technique:*

In this method the polymers are slowly added to the dilute suspensions of the preformed liposomes at a temperature close to the transition temperature (T_m) of the constituent lipids. Critical micellar concentration (CMC) of the polymer is to be maintained during this process inorder to avoid the self-assembly of the amphiphilic polymer. In comparison with the pre-insertion technique this technique just changes the external surface of the liposomes, consequently keeping the inner space accessible for the convenience of medications.

- *Post-Modification by Chemical reaction:*

This method of preparation of liposomes is commonly used for the purpose of targeted drug delivery and not so much for the long-circulating liposomes. In this method a chemical reaction occurs between the polymer and the liposome surface. Some milder chemical reactions like photoactivated conjugation of polymers or oxime

formation reactions are used for the development of modified lipids which are then used for the preparation of liposomes.

V. CHARARACTERISTICS OF STEALTH LIPOSOMES

The following are the characteristics of stealth liposomes [5,15]:

a) Stealth liposomes are spherical bilayer lipid vesicles with a size ranges from 50 to 500nm.
b) It is composed of cholesterol and phospholipids such as phosphatidylcholine or diacetylphosphate.
c) They are colloidal and stable in nature.
d) They cannot be taken up by the endoplasmic reticular system and thus shows enhanced blood circulation time.
e) The size and shape of the stealth liposome depends upon the drug and the materials used.
f) Stealth liposomes can act as a small deposit encapsulating an antigen or an antibiotic or an allergen or a drug molecule or a gene for therapeutic purpose
g) Stealth liposome can be administered into the body without the triggering of any immune reactions.

VI. APPLICATIONS OF STEALTH LIPOSOMES

The ability of stealth liposomes to alter the biodistribution profile along with its site specific accumulation at characterized porous blood capillaries such as tumour, inflammations and infections enhanced their application [14]. Some of the major applications are as follows:

➢ *Cancer therapy:*

Most common disadvantage with the cytotoxic drug is their ability to cause death of normal as well as malignant cells. The entrapment of these drugs in stealth liposomes resulted in increased flow life span with improved deposition at the targeted site and thus reducing the toxic side effects. Upon various cancer studies with stealth liposomes it was concluded that polyethylene glycol coated immune stealth liposomes showed superior target ability than the conventional immune liposomes. The active targeting of tumor tissues by this polymer modified liposomes is very important in case of the administration of highly toxic anticancer drugs [16].

➢ *Vaccination, Gene therapy and Diagnostics:*

Recombinant-DNA technology and studies of gene function and gene therapy all depend on the delivery of nucleic acids into cells both *in vitro* and *in vivo.* For the *invitro* delivery there are many DNA-carrier systems but for the gene therapy that is the treatment of diseases at the molecular level by switching genes on or off the *invivo* delivery is more demanding and commonly preferred. The cationic lipid-based DNA complexes or simply the liposomes can act as an adjuvant or carrier of co-adjuvants and ultimately initiate an immune response to the vaccine antigen but there are limitations for their accessibility. A significant barrier in the development of liposomes for oral or mucosal delivery of macromolecules is the degradation of liposomes by enzymes. Mechanically or sterically stabilized (polymer coated) liposomes can survive these conditions [15].

➢ *In inflammations:*

Stealth liposomes can be used for the localization as well as targeted delivery of drug substances into the inflamed tissue. Thus, they can also be used for diagnostic purpose. Liposomes containing non-steroidal anti-inflammatory agents as well corticosteroids are injected directly into the inflammation sites mostly for a sustained release system [17].

➢ *Delivery of enzymes and hormones:*

Stealth liposomes are suitable 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 various side effects associated with the direct administration of hormones like tachycardia, arrhythmias etc.. can be reduced with the development of an effective targeting drug delivery system [18].

➢ *Antimicrobial therapy:*

Conventional liposome is a carrier of choice for the sustained release of various antimicrobial agents. But these conventional liposomes are easily recognized and degraded by the cells of mononuclear phagocyte system mostly the kupffer cells and spleen macrophages. Moreover, drugs like pencillins and cephalosporins is a very sensitive towards the degradation by β-lactamase enzymes generated by some infective agents Encapsulation of drugs mainly powerful antibiotics in sterically stabilized liposomes can protect the drug from degradation as well as improves the efficacy of the drug[6], also the lipid nature of these formulations can easily permeate cell membrane of micro-organisms and increase cellular concentrations which eventually reduces the dose and toxicity[19]. The intracytoplasmic delivery of plasmids, antisense oligonucleotides and ribozymes *in vivo* for the treatment of human immunodeficiency virus and other infections can be made possible with pH-sensitive liposomes [20].

➢ *Diagnostic imaging:*

The capacity of liposomes to convey various sorts of compound in the bilayer or in the watery compartment makes them an appropriate method for all different strategies like, gamma-scintigrapgy, attractive reverberation imaging (MRI), processed tonography imaging (CTI) and sonography. Using liposomes in diagnostic imaging leads to several advantages, owing to their capability to incorporate multiple contrast moieties, to specifically deliver them at the targeted site and thus enhancing the contrasting signal. To build the stability and half-life of liposomes as complexity operator after organization can be gotten by adjusting the outside of the liposomes with polyethylene glycol. For the blood pool imaging, Gd-Liposome (Gadolinium liposome), a long circulating liposome was successfully developed prolonging the presence of contrast agent in the body [21].

➢ *Liposome encapsulated haemoglobin:*

The liposome encapsulated haemoglobin (LEH) is an example of a transfusable (non-allergenic) oxygen carrying blood replacement fluid which can be used in emergency situation to provide temporary life support. Many study results showed that haemoglobin encapsulated in stealth liposomes can reduce the toxic effect as well as prevents the recognition by the macrophages and thus enhancing its blood circulation time [22,23].

VII. ALTERNATIVE LIPSOMAL TECHNOLOGIES [24]

There are various technologies specifically developed for liposomes apart from stealth liposomal technology to optimize the drug delivery and effectiveness of the product. Some of them are as follows:

➢ *Non-Pegylated Liposome technology:*

The Non-PEGylated liposome (NPL) technology commonly used for the cancer therapy was developed to eliminate the side effects associated with PEGylated-liposome.The most common adverse effect associated with the PEGylated liposome is the hand-foot syndrome (HFS). With the development of non-PEGylated liposomes these side effects are reduced. The non-PEGylated liposome of Doxorubicin (NPLD) injection is a better example of the technology which showed a better safety profile over the conventional as well as PEG coated doxorubicin liposomes. Myocet®a NLPD manufactured by Elan pharmaceutical is the marketed formulation using this technology, approved in Europe and Canada [25,26].

➢ *DepoFoam™Liposome Technology;*

DepoFoam™technology the core technology behind the marketed products such as Depocyt®, DepoDur™, Exparel® is a proprietary, extended-release drug delivery technology introduced by Pacira Pharmaceuticals, Inc., Parsippany, NJ, USA. In this technology there are multivesicular liposomes encapsulating the drug particles and showing an extended release of about 1 to 30 days. The DepoFoam™ consists of microscopic spheroids (3-30μm) with drug in each non-concentric aqueous chambers covered by a single bilayer lipid membrane giving a honeycomb like structure (Fig.3). Most commonly used lipids for the technology are the analogs of naturally occurring cholesterol, triolein etc.. The DepoFoam™ technology is a remedy for the medications that require frequent multiple injections as it can release the drug over a period of hours to week. Also, this technology is a better solution for the drugs with short period of action and side effects[27].

➢ *Lysolipid Thermally Sensitive Liposome (LTSL) Technology:*

Lysolipid thermally sensitive liposomes are the lipid products used for targeting sites with elevated temperature. Mostly lipids like DPPC, MSPC with a transition temperature between 40ºC and 45ºC are used for the preparation of these liposomes. These liposomes show a temperature-dependent release of encapsulated drug. At the desired elevated temperature in the site of action (local tissue) there occurs a gel to liquid transition making it more permeable and thus releasing the drug. This technology is mostly used in tumour therapy as there develops a local hyperthermia in tumour cells resulting into increased accumulation of the thermo-sensitive liposomes. The ThermoDox® of Celsion Corporation encapsulating doxorubicin now under clinical trial phase III is developed by the lysolipid thermally sensitive liposomal technology [28,29].

VIII. MARKETED FORMULATIONS

There are various stealth liposomal or PEG-Liposome available as well under various clinical trial phase. Some of them are mentioned in the following table (**Table 1.**)[15,21]

IX. FUTURE PROSPECTIVE

When injected into the blood circulation nano-lipid carriers rapidly interact with blood components increasing their clearance rate and degradation by the mononuclear phagocyte system. In order to preserve the optimal efficiency of nano carriers various methods have been adopted. Among them many investigations evidenced that the presence of a PEG hydrophilic polymer on the outer surface of the liposomes has tended to alter the pharmacokinetics of nanoparticles as well as showed prolonged blood circulation time while reducing the uptake by mononuclear phagocytic system. Both active and passive targeting is possible with the stealth liposomes enhancing the chances of targeted delivery of drugs in both for the therapy of cancer and joint inflammatory disorders. In an anti-inflammatory study of PEG coated liposomes with Sialyl Lewis moieties it was observed that formulation inhibited the binding of circulating lymphocytes to selectins expressed on vascular epithelium is an example of a biological receptor binding events. The presence of ligands like antibody or antibody fragments, vitamins and growth factors, folates can also enhance the targeting capability of the formulation. Stealth liposomes are found to be a suitable vehicle for the delivery of plasmid genes or catalytic polynucleotide , hormones like triiodothyronine to the targeted site[5,18]

X. CONCLUSION AND PERSPECTIVES

Liposomes are one of the most widely studied lipid-based drug delivery systems. To overcome some of the difficulties in the conventional liposomes with respect to the stability and the mononuclear phagocyte system uptake certain modifications in its surface are required. Stealth liposomes are sterically stabilized surface engineered liposomes which can overcome many of the difficulties with conventional liposomes. The coating of liposome surface with PEG reduces MPS uptake and opsonization while increasing the surface hydrophilicity.Many stealth liposomal formulations are available in the market nowadays. Apart from the stealth liposomes there are non-stealth liposomal formulations like Non-Pegylated

Liposome technology, DepoFoam™ Liposome Technology, Lysolipid Thermally Sensitive Liposome (LTSL) Technology which are approved for use in many applications.Designing of such surface modified liposomes is a promising drug delivery system which further leads to an effective and personalized treatment. In addition, these liposomal details give another worldview in nanotherapeutics centering towards analysis, treatment, and prevention.

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Company Name	Brand Name	Targeted disease	Position
Caely®	Doxil	Kaposi's sarcoma	Marketed
Temodal®	Temozolomide	Anti-cancer agent	Phase I/II
Neo Pharm	LF-SN38	Various solid tumors	Phase I/II
	LEM	Prostate cancer	Phase I/II
	LE-AON	Various solid tumors	Phase I/II
	LEP	Various solid tumors	Phase I/II
Celsion	ThermaDox	Prostate cancer	Phase I
Antigenics Inc.	Aroplatin ATRA-IV	Colorectal cancer, Acute promyelocytic Leukemia	Phase II
Ghead Sciences	AmBisome DaunoXome	Fungal infection Kaposi's sarcoma	Marketed
ALZA	Doxi	Ovarian cancer	Marketed

Table 1:- Stealth Liposome Formulations And Its Different Stages

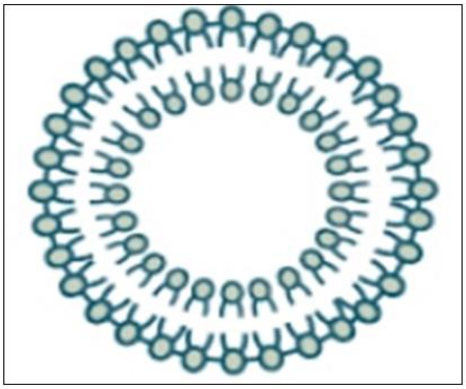

Fig.1:- Liposome

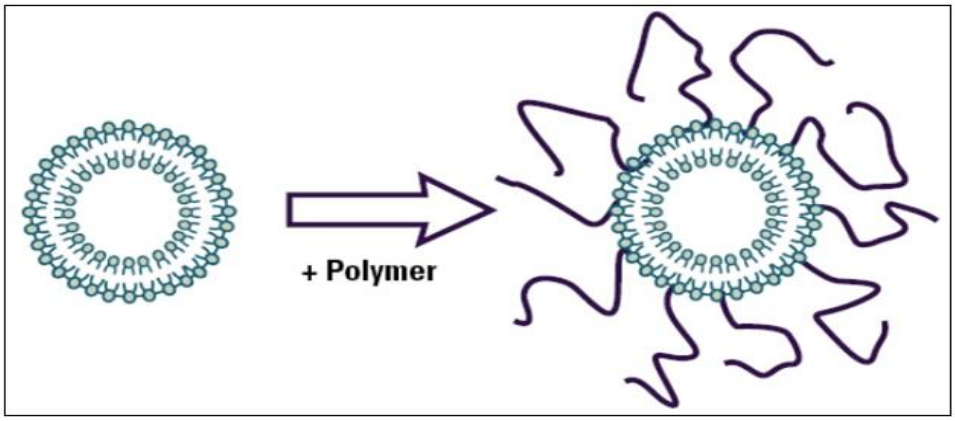

Fig.2:- Stealth Liposome

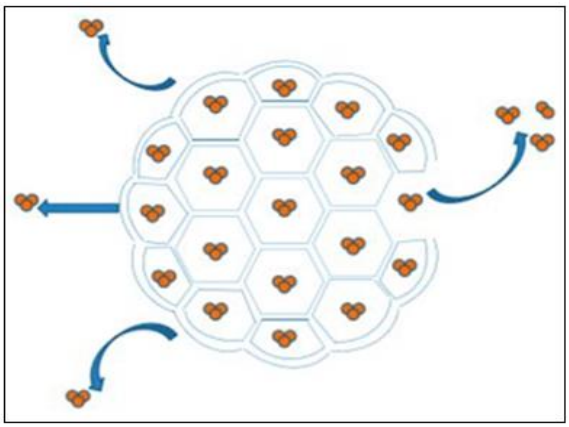

Fig.3:- Honey comb structure of DepoFoamTM liposome