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A Review on Liposome: The Cancer Targeting Aspects and Effective Upgraded Vesicular Systems

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ABSTRACT

Liposome are the concentric bilayer means core of center in which aqueous volume entirely envelope by the phospholipids 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 Paul Ehrlich 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. Drugs would be targeted by virtue of groups having affinity for specific cells, tissues or organs. Liposome having also its modifications or upgraded versions likes enzymosomes, hemosomes, virosomes, and erythrosomes. Liposome has emerged as a dynamic mode for targeted drug delivery. Ligands confer specificity on a non specific reagent. Although controlled and sustained drug delivery can be considered as the magic bullet concept. We can look forward to many more clinical products in the future.

Keyword: Liposome, Magic bullet, Controlled drug delivery system, Cancer target, Bio-carrier.

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INTRODUCTION

Liposome are basically consisting of lecithin and cholesterol, hence the classic nano-vesicles to treat disease clinically. However liposomes non-specifically accumulate in the (RES)-Reticulo-endoplasmic system. The uninvolved organ such as liver, spleen, and bone marrow for achieves of targeting the liposome surface engineering concept used for controlled drug delivery system [1]. Cancer therapy targets the traits of cancer: invasion and metastasis, deregulated cell growth, evasion and apoptosis, tissue, sustained angiogenesis. Liposomes are the first delivery system carrier by which action towards the target organ and improvement of pharmacokinetics of anticancer drugs with 2000 papers and 200 reviews. The stealth liposome concept also called as long circulatory liposome hence which are effective cancer cells [2]. The most of the anticancer drug targeted by the ligands like antibody, protein, peptide, small molecules, sugars. The targeted drug delivery achieve the carrier mediated drug delivery system of new generation of drug delivery system like emulsome, phytosome, pharmacosome, aquasome, ethosome, discosome and cubosome. In advancement of the cochleate can encapsulate hydrophobic, amphiphilic, negatively charged or positively charged drug. Nanochochleate are more stable than liposome and others vesicular system [28].

Structure of Liposome

The most important advantages of liposome are both hydrophilic and hydrophobic drug get transfer through the region in Figure 1 as follows: In the hydrophobic region the water insoluble drug are transfers. In the hydrophilic region the water soluble drug get transfer by particle engineering concept. Protein bonded on to surface can targets liposome by action towards targets organ and to cancer cell.

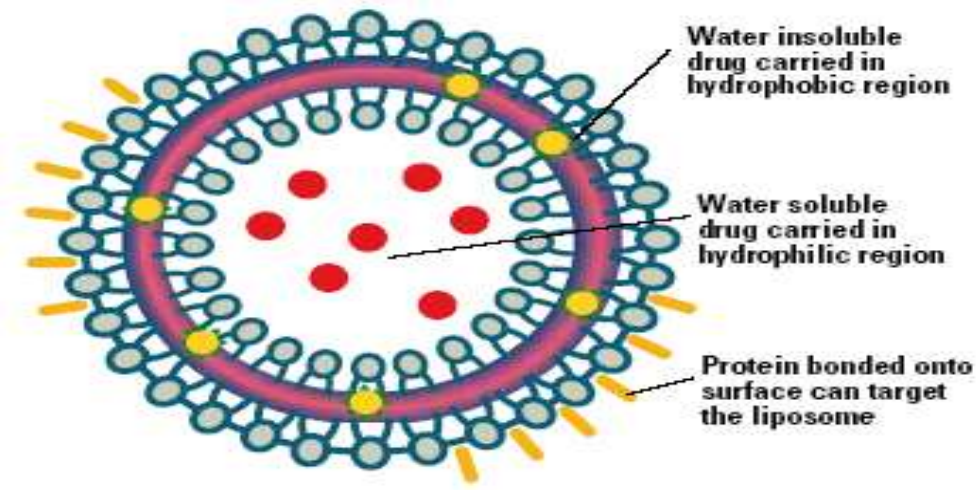

Figure 1: Structure of Liposome (jpsionline.com)

Rational for Targeted Drug Delivery System [36-37]

The rationale behind of targeted drug delivery system is as to supply drug selectively to its site of action to provide maximum therapeutic activity, To Preventing degradation or inactivation of drug, Prevention of inappropriate deposition of the drug and to improving drugs that have low therapeutic index.

Mechanism of Targeted Drug Delivery System [6]

The simple mechanism of action of liposomal targeted drug delivery like endocytosis, adsorption, fusion and transfer of liposomal contents to cell membrane these are four steps by which the drug gets transfer through targeted cell or tumor cell as follows:

Endocytosis:

The endocytosis by phagocytic cell of the Reticulo-endoplasmic system such as macrophages and neutrophils in Figure 2

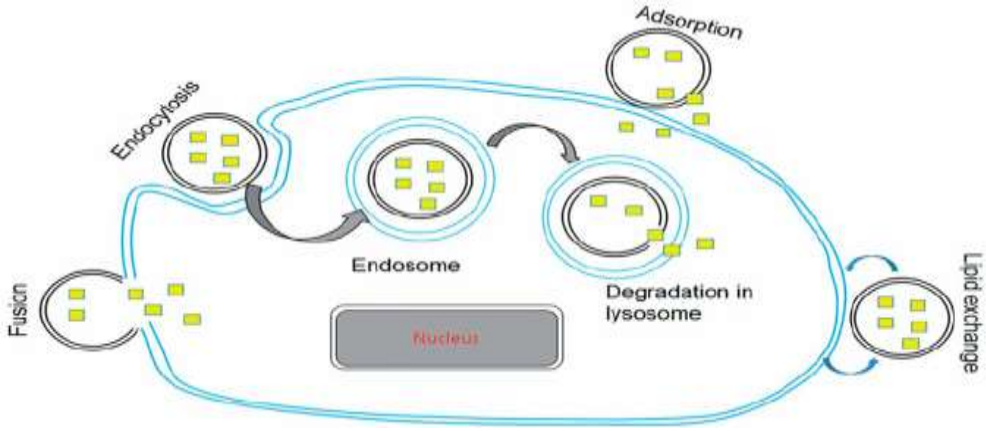

Figure 2: Mechanism of Targeted Drug Delivery System

Adsorption to cell surface

The adsorption to cell surface either nonspecific hydrophobic or Electrostatic forces or by specific interaction with cell surface component.

Fusion with plasma cell membrane

The fusion with plasma cell membrane by insertion of lipid bilayer of the liposome into the plasma membrane, with simultaneous release of liposomal content into the cytoplasm in Figure 2

Transfer of liposomal content

The transfer of liposomal lipid to cellular or sub cellular membrane, or *vice versa*, without any association of liposome content in Figure 2

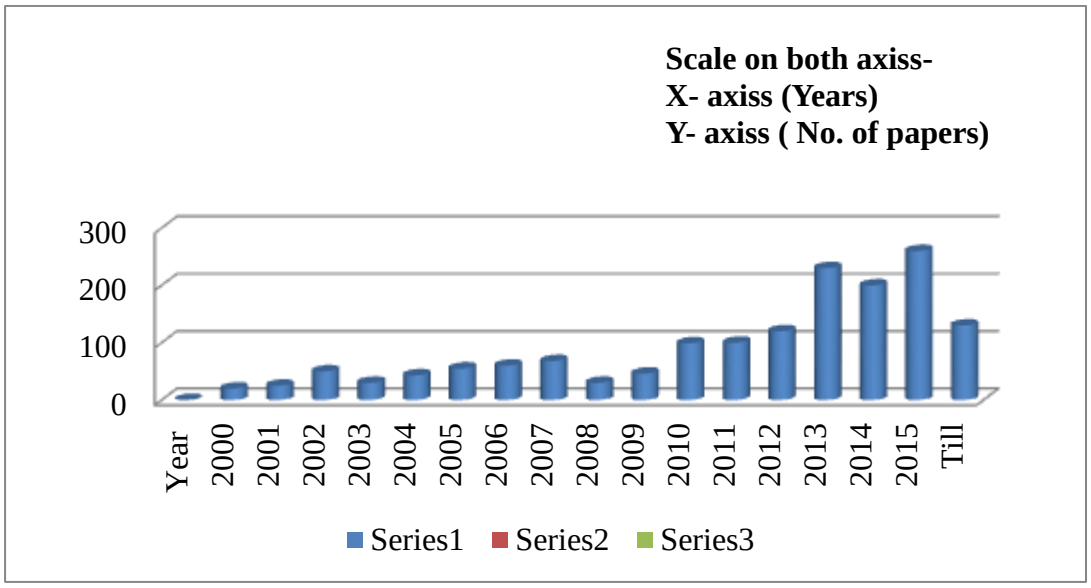

Figure 3: Trends in Liposomal Drug Delivery Research

What is Stealth Liposome?

The long circulatory liposome shows prolong release with the help of synthetic polymer (PEG) poly ethylene glycol in liposome composition. The presence of PEG surface of liposome to extend the blood circulation time while preventing phagocyte uptake. Stealth liposomes give an achievements and development new drug delivery and controlled release [3] 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 [37].

Contains of Stealth Liposome [4]

The stealth liposome includes Polyhydroxyethyl L-asparagines coated, PEG-coating, H-PG-PEG-coated, Dope-coated liposome are prepared. 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 [4]. In most of the case hence the long chain of the PEG gives the better improvements in blood residence time [37].

Why Use Liposome in Drug Delivery?

The liposome is concentric bilayer in which aqueous volume is entirely enveloped by the lipid or phospholipids bilayer which can be used to transfer drug, vaccine and enzymes for the targeting the cancer cells or organs. Depends on the drug and liposome properties liposome composition, PH

and osmotic gradients and environmental controls are very important for the liposomal drug delivery act as bomber or killer bomber for the cancer cell [4]. The release-affects time in which drug is released and prolong time-increase duration of action and decrease administration very important in this drug delivery system.

Pharmacokinetics

The liposomal drug delivery improves or increases the efficacy and decreases the toxicity, changes the bio distribution and absorbance, deliver drug in desire form**,** multidrug resistance.

Protection

The decrease harmful side effects hence change where drug accumulate in the body. Liposome helps to improves therapeutic index, rapid metabolism and irritation, lack of stability, low solubility and unfavorable pharmacokinetics.

Drug Targeting [6, 29]

The drug targeting takes place in inactive, acti.ve, protects the drug and physical in which various strategies of drug targeting are design to promote the drug for the targeting of sites and shows the site specific and site avoidance effect. In Inactive targeting unmodified liposome gathers in specific tissue reticulo-endothelial system., in Active targeting alter liposome surface with ligands (e.g., antibodies, enzymes, protein, sugars) can targets achievements takes place, In Protects drug ensures protect the drug from the bio environments due to maintaining fluidity and rigidity and in Physical targeting temperature or pH sensitive liposome liposome are very sensitive to the condition of temperature according to the phase transition temperature. Various strategies are use to target the tumor cell which gives a liposomal functionalization to the recognized biomarkers and triggered release of therapeutic payload [29]. The drug binds or conjugated with special markers to target the site, passive or active manners. The size, surface characteristics in liposome key role in bio-distribution study [31]. The particle less than 5nm are rapidly cleared from circulation through renal clearance. The long circulatory liposome stable delivery system in which sterically stable in longer period of time. The process of protein adsorption called as apsonisation. The surface modifications are important to the conjugated drug targeting receptor. The cellular internalization influence phagocytosis, macropinocytosis, caveolar-mediated endocytosis or clathrin mediated endocytosis. The nano-particles are potentially useful for carrier of active drug and coupled with targeting legends [30]. Surface modifications is the incorporation of polyethylene glycol (PEG) preventing interaction with plasma protein and recognition by Reticulo-endothelial system (RES) the PEG effect is transients eventually to opsonization and macrophage clearance occurs [31]. 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 [29]. 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 Circulating nano-particle passively extravasates in solid tumor tissue and enhances permeability of blood vessels [38]. The drug released to extracellular matrix and diffuses through targeted tissue or cells 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 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 [38]. 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 [39]. The conjugation of polymeric carrier to low molecular weight drugs changes its pharmacokinetic disposition at both cellular level and body [44.]. Polymeric micelles are 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.

Drug Targeting Consideration [25]

The drug targeting are most important aspect by which drug administered systemically (intravenous or bolus) by blood stream and distributed through body selective to the site of action. Liposomal drug delivery system in which the increase the drug solubility, Reduce kidney clearance, increase stability and serum half life then enhance the therapeutic efficacy by PEGylated therapeutics [27] The benefit of drug targeting includes reduce drug wastage, it is possible to deliver drug to the cell or tissue region by not accessible to the free or untargeted drug. In the drug targeting approach by using ligands to action towards targeted tagged on lipid vesicles as like using ligands antibody, sugar, hormone, protein [25]. The ligands are use to recognize the specific receptor sites. In the cancer treatments dug targeted to the unorganized cells by which production of the antigens and antibodies by the defense mechanism, the ligands used to the specific attachments. The oligosaccharides often used for the ligands by direction.

Loaded Drugs, Free Drug and Receptor Mechanism [26]

The drug targeted to the specific sites of the tumor cell or organs hence the in the cytoplasm in the cell. Endocytosis mechanism internalization by transcytosis and receptor recycling takes place.

The release of drug simultaneously in controlled and sustained manner called magic concept. The efficient internalization nano formulation targeted to the internalizing receptor and increases the therapeutic activity and reduces the toxicity [30]. The leading process of the cellular delivery of drug to achieve passive drug diffusion and efflux, non specific phagocytosis, non specific fluid pinocytosis and uptake by particle receptor mediated endocytosis hence drug efflux through freely through plasma membrane. Liposomal drug delivery system there many targeting aspects are studied in the formulation development. The research are done on cancer targeting, achieve the success for the breast cancer, neck cancer, glioma cell or brain tumor cancer, prostate cancer and vaginal cancer, there are tremendous work are done by using thin-film hydration method and got the result of in vivo and in vitro evaluation study. The cell line study also gives results on animals like '*mice musculous*' and *wistar* rat, '*albino'* or '*ratous verger us*'. PEGyalated and Non-PEGylated liposome are prepared approved by the FDA, Doxorubicin [24]. The Paul Ehrlich et al, 1960 called the liposome is the magic bullet for cancer targeting. Many research moving for the bone marrow targeting and glioma cell targeted or brain targeted liposome for chemotherapy. The taxane base drugs are use because of their potency and increase the efficacy and decrease the toxicity [7]. The cytosolic delivery and organelle- specific of drug loaded nano-particles most frequently liposome mechanism of transcytosis or endocytosis [26]. Long circulatory liposome are the potential drug delivery to the targeted site because shows the long stability and suitability of bio-distribution. Increase the efficacy and decrease the toxicity gives therapeutic effect in longer period of time. Generally the PEGylated liposome show the best result because of affinity of covalent binding to the drug [27]. Ligands are used for cancer cells with the help of the drug for targeting site [32]. Cellular internalization influence phagocytosis, macropinocytosis, caveolar-mediated endocytosis or clathrin mediated endocytosis. The nano-particle potentially useful for carrier of active drug and coupled with targeting legends [30]. The internalization mechanism receptor mediated endosome in which the binding of drug to receptor and enveloping the endosome.

Choice of Targeting Ligand [32]

The any condition which impairs the health with normal function of the body due to one or many reasons, disease condition of cancer the unorganized growth of the cells takes place hence we need to target ligand to receptor is necessary towards target organ.

Internalization

The ligand binding to the receptor site and called receptor mediated internalization. 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.

Receptor expression

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

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 [32].

Antibody versus non-antibody ligands

The goal for cancer targeting in which the adhesion of cellular mechanism and also folate and transferrin targets growth factor receptors is responsible [31].

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. The first approach of drug targeting RGD- peptide is used for cancer treatment [41]. The RGD-peptide derived particulate drug delivery used for the drug targeting. 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. 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 integrin RGD- peptide [42]. The terminology of integrin in 1986s the integral membrane complex involve in the transmembrane association between cytoskeleton and extracellular matrix [45].

New Ligands for Liposome Targeting [35, 40]

Transferrin mediated liposome targeting

The TF receptor are over expressed of many tumor cells so that coupling of TF on PEGylated liposome successfully used for brain targeting. Transferrin (Tf) can be conjugated to a variety of materials for cancer targeting consists of Tf-toxic protein, Tf-RNase, Tf-antibody, Tf- peptide and Tf- Chemotherapeutics [40].

Vasoactive intestinal peptide (VIP)

Target PEG liposome with radionuclide to VIP receptor on surface of tumor cell and enhance the breast cancer in rats.

Epidermal growth factor receptor (EGFR)

The EGFR-targeted liposome delivered to cancer cells that over expressed EGFR.

Galactosylated liposome

There are tremendous research works done on galactosylated to target drug to liver for the treatment of metastasis or tumor.

Cisplatin- loaded liposome

It binds to chondroitin sulphate which is over expressed in many cancer cells which can be used for suppression of tumor growth. In Table 3 various approaches are design for against the unorganized growth of cell are arrest due to presence of chemotherapy or cancer therapy hence action to get target organ. The *in vitro* and *in vivo* pharmacological results demonstrate the large amount of docetaxel released from polymeric nano prototype resulted in longer circulation time with sustained released action [38]. The second generation liposome also called as stealth liposome. The sterically stabilized liposomes are used for site- specific targeting [39].

Liposomal Drug Delivery Systems [21- 22]

The Liposomal drug delivery system are the vesicular and versatile drug delivery system by which administered by many routs for action towards target organ. These include targeting entities like proteins, peptide, and antifungal, anticancer, antibiotics and antibacterial.

Oral delivery

The uses of liposome for oral routs are very difficult due to poor stability of vesicles under the physiological condition typically in GI tract. The increase in potential for oral routs by the polymer coated liposome and microencapsulation.

Brain delivery

The brain targeting immune-liposome are used long circulating satirically stabilized liposome's minimal interaction with tissue and organs because of neutral and the carriers inert for entrapment molecules [22, 23]. The review provides the real time to the central nervous system (CNS). The real time are monitored by the infusion by which improve the real time and convection enhance delivery (CED) of clinical trial [21].

Vaccine and antigen delivery

The condition in which impairs the health with normal function of the body due to one or many reason while these are arising due to disease condition. Hence which can be avoided by the use the chemotherapy of particular disease, the oral vaccination requires an antigen delivery vehicles to protect the antigen and to enhance the translocation of the antigen to mucosa associated lymphoid tissue. In this delivery the increase the efficacy and reduce the toxicity takes place [21].

Pulmonary delivery

Targeted drug delivery system to the lung investigated the systemic and local delivery approach. The systems are most suitable because of reducing the systemic side effect and first pass metabolism [21].

Transdermal delivery

These are also the powerful approach for the transdermal drug delivery is to encapsulated drug in liposome to enhance delivery efficiency. Many liposomes are formulated variety of the drug through body by diffusion by physiological skin layer of the body. The used of transferosome and ethosome for the skin and in the alopecia diseases [21].

Upgraded Vesicular System for the Targeting-Lipoidal Bio-carrier

The carriers are the chemical entity by which transportation of loaded drug to target site. They are used in the targeted site for the optimal therapeutic index in which before the release drug.

Silent features of bio-carriers [21]

1. The carrier system should release the drug moieties inside the target organ, tissue or cell.
2. The carrier should be nontoxic, non immunogenic and biodegradable.
3. It must be cross the anatomical barriers and in case tumor chemotherapy tumor vasculature.
4. It must be recognizing specifically and selectively by the target cell.
5. The linkage of drug should be stable in Bio- fluid, interstitial and plasma. There are many carriers are used in the targeting. The different type of carrier present in pharmaceuticals which are in polymeric, macromolecular, cellular and particulates.

Types of pharmaceutical carriers

The pharmaceutical carriers are in the form of vesicle, micelles and nano-sphere. These are available in the typically functional characteristics like multifunctional and liquid crystal. These are present in either lipoidal or non-lipoidal in nature [21].

Types of some important vesicular systems [21-22]

The vesicular system are used in the site specific drug delivery for the targeting, hence the most of the vesicle are the classified on the basis of lipoidal and non-liopoidal bio-carriers in Table 4 The primary objective of the study of the vesicular system is the site specific targeting, and these are the upgraded version of the vesicular system like liposome for the action towards target organ, tissue and cell. The targeted vesicle generally tailored for site specific delivery of drug. Ideal carrier for drug-carrier property system the carrier accumulate to the required site and achieve superior drug loading, be able release at the appropriate rate at site of action. These are non immunogenic, biodegradable, non toxic to the physiological system, easy and inexpensive to

prepare and used in the sterile parenteral formulation. The advances of vesicular system give an idea about tumor targeting highly sophisticated molecule with the tumor specificity for the targeted site. 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. The process of replication starts at specific point called as origin or oric, at the origin two DNA strands break at the two hydrogen bond due to enzyme helikage, hence two strands are completely separate like Y- shaped called as replicating folk, in this manners the study of gene delivery using liposome as a magic bullet for specific sites. Gene therapies are the dynamic approach of liposomal formulation development.

Future Scope:

The Studies with insulin show that liposome may be an effective way to package proteins and peptides for use clinical trials for several liposomal formulations more studies on the manipulation of liposome. The Liposomal drug delivery system suitable for the upgraded, modification or new generation drug vesicular system for action towards target organ, tissue or cell.

Table 1: Conventional Strategies for Tumor Target [25, 29, 33]

Tumor targeting	Ligand Targeting Strategies	Special remark
Passive targeting	1. Enhance permeation and retention effects 2. Surface engineering of colloidal carriers for stealth characteristics	• Increase efficacy of cancer therapeutics. • Prolongation of long circulation half-life by PEG chain.
Active targeting	1. Albumin based targeting 2. Vitamin based targeting 3. Transferrin based targeting 4. Lectin based targeting 5. Peptide based targeting	• It binds non covalent interaction mechanism of transcytosis across endothelial cells into interstitial space. • Folate functionalised preferably absorbed receptor mediated transcytosis. • Transcytosis across BBB-Blood brain barrier using transferring as targeting ligand. • To improve hepatic delivery of lipophilic drug and achieve cytoadhesive ligand targeting. • Achievement of target by vasculature and cell surface tumor targeting.
Physical targeting	1. Endogenous- pH, temperature, redox potential. 2. Exogenous- external forces magnetic and ultrasound.	• Localise anticancer medicament to targeted tumor site. • It acts the stimuli responsive potential for colloidal drug delivery. • It acts the immense potential for colloidal drug delivery.

Table 2: Three Generation Vector for Magic Bullet Targeting [43]

Sr. no.	1st generation	2nd generation	3rd generation	Specification modes for target
1	Liposomal capsule	PEGylated capsule	PEGylated liposome with specific ligands	Structure
2	(Indirect targeting) The capsule is phagocyte by kuffer cell	(Passive targeting) PEG coating invisibility to kuffer cells	(Active targeting) Molecular recognition	Addressing mode
3	Liver(Hepatic tropism)	Non specific cancer cells	Specific cancer cells	Target

Table 3: Liposomal Drug Delivery for Cancer Targeting

Drugs	Method	Outcomes	References
Docetaxel	Thin Film Hydration	Semi-synthetic taxane exerts antitumor activity against prostate cancer cells.	7
Doxorubicin Hydrochloride	Extrusion Method	Super stealth liposome for anticancer therapy.	8
Doxorubicin	Thin Film Hydration	Remote loading of doxorubicin into liposome by trans membrane pH gradient to reduce toxicity toward *H9c2 cells*.	9
Hylauranic Acid, Paclitaxel	Thin Film Hydration	Hyaluronic acid-coated liposome for targeted delivery of paclitaxel.	10
Doxorubicin	Reverse Phase Evaporation	Ehrlich tumor inhibition using doxorubicin containing liposome	11
Doxorubicin	Extrusion Method	Doxorubicin encapsulated in stealth liposome conferred with light-triggered drug release.	12
Antibody-OX26/CTX.	Reverse phase Evaporation	*OX26/CTX*-conjugated PEGylated liposome as a dual-targeting gene delivery system for brain glioma.	13
Doxorubicin	Thin Film Hyration / Lipid Film	Anti-cancer activity of doxorubicin loaded liposome co-modified with transferrin and folic acid.	14
Doxorubicin	Thin Film Hydration	Tumor-specific pH-responsive peptide-modified pH sensitive leptosomes containing doxorubicin for enhancing glioma targeting and anti-tumor activity.	15, 23
Docetaxel	Thin Film Hydration	Effect of ligand density on cytotoxicity and pharmacokinetic profile of docetaxel loaded liposome	16
Tamoxifen, Doxorubicin	Thin Film Hydration	Tamoxifen guided liposome for targeting encapsulated anticancer agent to estrogen receptor positive breast cancer cells.	17
Doxorubicin	Lipid Film Hydration	PH-sensitive liposome constructed by poly (2-ethyl-2-oxazoline) cholesterol hemi Succinate for doxorubicin delivery.	18

Table 4: New Generation Lipoidal and Non-lipoidal biocarriers [21, 22]

S. no.	Lipoidal biocarrier	Non-lipoidal biocarrier
1	Liposome	Niosome
2	Ethosome	Bilosome
3	Enzymosome	Aquasome
4	Emulsome	-
5	Sphingosome	-
6	Transferosome	-
7	Pharmacosome	-

8	Virosome	-

Table 6: Target allowing with Drug as Liposomal Drug Delivery [24]

S. no.	Drugs	Marketed	Type of liposome	Target	Development stage
1	Doxorubicin	Mycoset Doxil, Caelix	Non-PEGylated PEGylated	Breast cancer Caposis sarcoma, Overian cancer, Breast cancer	Phase-III
2	Daunorubicin	Daunoxome	PEGylated	Caposis sarcoma	Phase-II
3	Paclitaxel	LEP-ETU, Taxol, Abraxane, Nov-onxol	PEGylated	Breast cancer	Phase-II
4	Pemetaxel, Cisplatin	Alimta	PEGylated	Head and neck cancer	Trial
5	Bendumustine Hcl	Trenda	Long- circulating	Breast cancer	Phase-I
6	Docetaxel anhydrous	Taxotere	Long- circulating	Breast cancer	Phase-I
7	Cyclophosphamide	Cytoxan inj. (No longer in market)	-	Lung cancer	NA

CONCLUSION:

In this review article considering the advantages of this drug delivery system of liposome and also its modifications or upgraded versions like enzymosomes, hemosomes, virosomes, erythrosomes, vesosomes, ufosomes, discosomes, niosomes, pharmacosomes, transferosomes, proteosomes, herbosome, photosomes, cryptosomes, and phytosomes. Liposome has emerged as a dynamic mode for targeted drug delivery. Based on the results in this study, it is suggested that the proposed liposomal formulation could be employed to enhance the intracellular delivery of anticancer agents such as cytotoxic drugs, antisense nucleic acids and delivery of nucleic acids. Cationic liposome, lipolexes, stabilized by (PEG and other polymers) plasmid-lipid particles and various lipid-based nano-particles 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. The current concept of ligand- modified PEGylated nano-liposome as magic bullet needs to be modified.

REFERENCES:

1. Liu X, Peng H, Wang Q; Surface engineering of liposomal formulation for targeted Drug Delivery; Chem Eng Process Technol 2014: 2(1): 3
2. Perche F, Torchilin VP; Recent trends in multifunctional liposomal nanocarrier for enhanced tumor targeting; J Drug Dev Rev 2013: 2: 1-32.
3. Kataria S, Sandhu P, Bilandi A, Akanksha M, Kapoor B; Stealth liposomes: A review; Int J Res Ayur Pharm 2011: 2(5): 1534-1538.
4. Zhang Y et al; Stealth liposomes: The silent nanobombers; Trend Bio/Pharm Ind 2008: 19-24.
5. Sipai AB, Vandana. Y, Mamtha. Y, Prashanth VV; liposomes: An overview; J Pharm Sci Innov 2012: 1(1): 13-21.
6. Venkateswarlu L, Jayashankar R, Vishwantha R, Pravillika C, Suneetha K; A review on liposome; Res J Pharm Biological and Chem 2011: 2(3): 739-751.
7. Guangyao L, Dengjun S, Jingwen Z, Xiaoxia X, Xiaoqiong W, Weishuo F, Jingwei T, Chunhong Y, Hongbo W, Fenghua F; Lx2-32c, a novel semi-synthetic taxen, exerts antitumor activity against prostate cancer cells in vitro and in vivo; Acta Pharmaceutica Sinica B, Chinese Pharmaceutical Association, Institute of Materia Medica, Chinese Academy of Medical Science. 2016; 1-7.

8. Fresta M, Gianfranco P, Donatella P, Christian C, Mero A, Adrian SJ, Joy W, Donato C, Oddone S, Shen H; Polyethylene glycol (PEG) -Dendron phospholipids as innovative constructs for the preparation of super stealth liposomes for anticancer therapy; J Control Release 2016: 199: 106-133.
9. Alyane M, Gillian B, Mesbah L; Remote loading of doxorubicin into liposomes by transmembrane pH gradient to reduce toxicity towards H9c2 cells; Saudi Pharm J 2016: 24: 165-175.
10. Dorkoosh FA, Fatemeh R, Ebrahim S, Mehdi G, Pouya D, Mehdi M, Samira A; Hyaluronic acid- coated liposomes for targeted delivery of paclitaxel, in-vitro characterization and in-vivo evaluation; J Control Release 2016: 229: 10-22.
11. Mohsen MM, Nihal SE; Ehrlich tumor inhibition using doxorubicin containing liposomes; Saudi Pharm J 2015: 23: 182-187.
12. Jonathan FL, Dandan L, Kevin AC, Aida R, Jumin G, Shuai S, Daniel G, Ulas S, Joaquin O; Doxorubicin encapsulated in stealth liposomes conferred with light-triggered drug release; Biomaterials 2016: 75: 193-202.
13. Xie D, Peng Y, Pei-jian Y, Shu-wei Q, Yi-Li, Yi-Ji, peng L X, Yue et al; OX26/CTX-conjugated PEGylated liposome as a dual- targeted gene delivery system for brain glioma; Mol cancer 2014: 191: 1-13.
14. Vladimir T, Shravan KS, Giusseppina S, Can S; Anti-cancer activity of doxorubicin loaded liposomes co-modified with transferrin and folic acid; Eur J Pharma Biopharma 2016: 105: 40-49.
15. Zhang X, Zhao Y, Wei R, Zhang T, Zhang S, Huang D, Guo Y, Xin Y, Wang C, Zhang QW, Zhang Q; Tumor specific pH responsive peptide-modified pH sensitive Liposome Containing doxorubicin for enhancing glioma targeting and antitumor activity; J Control Release 2016: 22: 56-66.
16. Chun Chun Ping X, Xu P, Zhao H, Chen Q, Chen D, Hu H, Zhao X, Quao M; Effect of surface ligand density on cytotoxicity and pharmacokinetic profile of docetaxel loaded liposomes; Asian J Pharma Sci 2016: 366: 1-24.
17. Nagarsenkar MS, Ankitkumar S.J, Peeyush NG, Sanket MS, Vivek VD, Yuvraj N, Rajiv P G; Tamoxifen guided liposomes for targeting encapsulated anticancer agent to estrogen receptor positive breast cancer cells: *In vitro* and *in vivo* evaluation; Biomed Pharmacother 2014: 68: 429-438.

18. Xu X, Hu M, Yu X, Li Y, Fu Y, Zhou X, Zhang D, Li J; Design and evaluation of pH-sensitive liposome constructed by Poly (2-ethyl-2-oxazoline)-cholesterol hemisuccinate for doxorubicin delivery; Eur J Pharma Biopharm 2015: 91: 66-74.
19. Chandan PK, Geeta A and Harikumar SL; A comparative review on vesicular drug delivery system and stability issue; Int J Res Pharm Chem 2012: 2(3): 704-713.
20. Chundra D, Yadav KK, Kumar V; An overview: The novel carrier for vesicular drug delivery system; World J Pharma Res 2014: 3(6): 1299-1322.
21. Patel N, Panda S; Liposomal drug delivery system: A critic review; J Pharma Sci Biosci Res 2012: 2(4): 169-175.
22. Nuno M, Christiane D, Catarina PR; Recent advanced in drug delivery systems; J Biomat Nanobiotecnol 2011: 2: 510-526.
23. Schnyder A, Huwyler J; Drug transport to brain with targeted liposomes; J American Soci Experimental Neuro Ther 2015: 2: 99-107.
24. Francicullino R, Cicclini J; Encapsulated anticancer drug: Still waiting for the magic bullet; Curr Med Chem 2009: 4361-6373.
25. Thanki K, Jain S; Recent advances in tumor targeting approaches. Targeted drug delivery and design: Concept and design; Adv. Deliv Sci Technol 2015: 18: 41-111.
26. Melis C, Ali DS, Seyda B; Liposome as a potential drug carrier system for drug delivery; Application of Nanotechnol Drug Deliv System 2014; 10/5772/58459: 1-50.
27. Misra P, Nayak B, Dey RK; PEGylation in anticancer therapy; Asian J Pharm Sci 2016: 11 337-348.
28. Li J, Wang X, Zhang T, Wang C, Huang Z, Luo X, Deng Y; A review on phospholipids in drug delivery Systems; Asian J Pharma Sci 2015: 10: 81-98.
29. Torchilin VP, Deshpande PP, Biswas S; Current trend in use of liposome for tumor targeting. Nanomed (Lord) 2013: 8(9):1-32.
30. Saltzman M, Goyal A, Fong PM; Targeted for drug delivery system. Nanotoday 2005; 18 26.
31. Desimone JM, Petros RA; Strategies in the design of nanoparticles for therapeutic application. Nature Rev / Drug Discovery 2010: 9: 615-627.
32. Allen TM et al; Ligand targeted therapeutics in anticancer therapy; Nature Publishing group 2002: 2:750-763.
33. Changwa H, Chang KD, Huang CT; Targeted therapy of cancer; J Can mol 2006: 2(2): 57-66.

34. Barakat NS, Al Salchi AS; Target nanoparticle: An appealing drug delivery platform; Nanomed Nanotechnol 2012: S4:009: 1-9.
35. Torchilin VP et al; Recent advances with liposome as pharmaceutical carriers; Nature Rev Drug Discovery 2005: 4: 145-160.
36. Allen, Theresa M: Liposomal drug formulations: Rationale for development and what we can expect for the future drugs 1998; 56: 747-756.
37. Imordina ML, Dosio F, Cattle L: Stealth Liposomes: Review of basic science, rational and clinical application. Existing and potential Int J Nanomed. 2006; 1(3): 297-315.
38. Sanna V, Pala N, Sechi M: Targeted therapy using nanotechnology: Focus on cancer. Int J Nanomed 2014, 9: 467-483.
39. Nil Bergstrand: Liposome for drug delivery- from physicochemical studies to applications. Acta Univasitatis Upsaliensis UPPSALA. 2003; 25: 1-71.
40. Kumar BS, Md. Amin L: Nanotechnology in cancer drug delivery and selective targeting. ISRN Nanotechnol 2014; 1-23.
41. Chen K, Chen X: Interin targeted delivery of chemotherapeutics. Theronostics 2011; 1:189-200.
42. Zhang Q, Lu L, Zhang L, Shi K, Cun X, Yang Y, Liu Y, Gao H, Qin H: Dual functionalized liposomal drug delivery system for solid tumors based on RGD and PH-responsive antimicrobial peptide. Scientific Report 2016; 6:19800: 1-11.
43. Vincent BB, Loeve S: Metaphore in nanomedicine: The case of targeted drug delivery. Nano Ethic Springer Verlag 2014; 8(1): 1-23.
44. Khanna VK: Targeted delivery of nanomedicine. ISRN Pharmacol 2012; 1-9.
45. Gellerman G, Firer M, Giladi Y: Recent innovation in peptide based targeted drug delivery to cancer cell. Biomed 2016; 4(11): 1-24.