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Liposomes: A Review In Cancer Therapy.

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ABSTRACT

Liposomes are most promising and broadly applicable of all novel drug delivery systems, that can encapsulate both hydrophilic and hydrophobic drugs. They are used as therapy vectors for drug delivery. Liposomes have been widely investigated since 1970 as drug carriers for improving the delivery of therapeutic agents. In the past decade, liposomal formulations have been extensively used to enhance the efficiency of drug delivery via several routes. Liposomal drug formulations have been shown to be markedly superior to conventional dosage forms. The success of liposomes as drug carriers have been reflected in a number of liposome based formulations, which are commercially available or are currently undergoing clinical trials. Although liposomes can carry a wide variety of drugs, this review paper emphasizes the usage of liposomes in cancer therapy.

Keywords: Liposomes, Therapeutic, Drug delivery, Formulation

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INTRODUCTION

Cancer is one of the most common illness today; that has third place in causes of mortality in human population throughout the world. There are more than 10 million cases of this disease annually [1,2]. Cancer impedes with any part of the human body, creating benign and also malignant tumours able to suppress or invade the surrounding tissue and metastasize. The efficacy of treatment is directly related to drug's quality to target and kill cancer cells while leaving healthy cells undamaged [3]. Thus, one of the most outstanding characteristic of novel anticancer drugs should be the high degree of cancer cell selectivity. Thus, nanotechnology in aggregation with medicine symbolises promising approach to enhance cancer therapy. Nanotechnology is the science which deals with processes that occur at molecular and supramolecular level with aim to understand new properties resulting from size of nanoparticles.

One of the prima disadvantage of antineoplastic drugs is their low therapeutic index (TI), i.e. the dose needed to produce anti-tumor effect is lethal to normal tissues. The low TI of such drugs may be due to: (i) their inefficiency to achieve therapeutic concentrations at the target site (solid tumors); (ii) nonspecific cytotoxicity to critical normal tissues such as bone marrow, renal, GI tract and cardiac tissue; and/or (iii) difficulties related with formulation of the drug, for example, low solubility in pharmaceutically suitable vehicles, leading to the use of surfactants or organic co-solvents which have their own unwanted outcomes. Thus, there is a demand for efficient delivery systems that not only act as a formulation aid but change the biodistribution of drugs in such a way that a large portion of the dose get through the target site [4].

Cancer therapeutics

To get by the difficulties of cancer chemotherapy, nanotechnological targeted cancer chemotherapy has been suggested. Such nanotechnological targeted system includes nanocapsules, nanoparticles, nanorods, nanofibers, nanocrystals, nanotubes, stealth nanoparticles, liposomes, stealth liposomes, pHsensitive liposomes, temperature sensitive liposomes etc. Such delivery implies for selective and effective localization of pharmacological active moiety at pre-identified (eg. over expressed receptors in cancer) target in therapeutic concentration while limiting its approach to non target sites thus minifying toxicity, increasing therapeutic index as well as enhance the biodistribution of drug which is a leading cause in success of cancer chemotherapy. Targeting to cancer cells by nanotechnological devices can be attained by reckoning the peculiarity of both i.e. the cancer which includes highly disordered leaky vasculature, high hydrostatic pressure, high requirements for nutrition, angiogenesis, RGD based strategy, EPR effect and the presence of over-expressed receptors. The formulation factor, which includes particle size, surface charge, hydrophilicity, hydrophobicity (determine RES uptake) and covalent attachment of ligands to carrier systems specific for over expressed receptors also plays an important role in targeting of nanodevices [5].

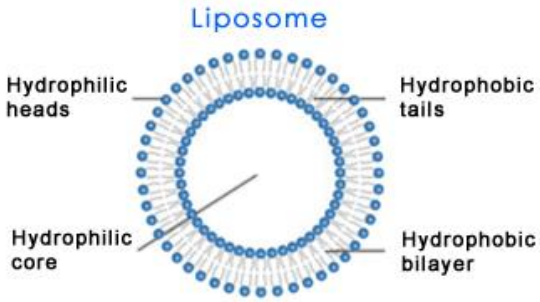

Figure 1: Structure of liposomes

Liposomes are spherical vesicles with concentric phospholipid bilayers [6] formed spontaneously in aqueous solution [7]. The word liposome is derived from two Greek words, lipos (fat) and soma (body or structure) [8,9]. Lipid bilayered membrane encloses an aqueous core and hydrophilic drugs may get entrapped in the central aqueous core of the vesicles while lipophilic drugs are entrapped within the bilayered membrane [10]. A schematic structure of a liposome is shown in fig (1). Liposomes are nonionic that can carry both water and lipid soluble drugs. They can be administered through various routes and can incorporate micro and macro molecules. They enhance protein stabilization, control hydration and alter pharmacokinetics and

pharmacodynamics of drug. Liposomes promote site specific drug delivery, helps in the direct interaction of drug with cell and act as reservoir of drugs [11]. Liposomes were first described by British haematologist Dr Alec D Bangham FRS in 1961 (published 1964), at the Babraham institute, Cambridge, when Bangham and R. W. Horne were testing the institute's new electron microscope by adding negative stain to dry phospholipids. The resemblance to the plasmalemma was obvious, and the microscope pictures served as the first real evidence for the cell membrane being a bilayer lipid structure [12].

The history of liposomes can be divided into three periods: genesis, middle age and modern era [13].

Genesis (1968-75): The physiochemical characterizations of liposomes have been explored. Liposomes were used to study the nature of biological membrane and thin lipid film hydration method was developed to prepare liposomes.

Middle age (1975 – 85): In this period, advantages, stability and interaction characteristic, liposomes, physico-chemical properties of liposomes, their interaction with the cells and their behavior within the body were studied and various methods for the preparation of liposomes were also discovered.

Modern era (1985 onwards): Today, liposomes are used in several scientific fields such as biophysics (properties of cell membranes and channels), mathematics, biochemistry (function of membrane proteins), theoretical physics (topology of two-dimensional surfaces floating in a three dimensional continuum) and biology (excretion, cell function, signaling, gene delivery and function).

Generally, cancer therapy requires three steps, namely

1) encapsulation of drug; either in the liposome interior (hydrophilic drug doxorubicin) or with in the lipid bilayer (hydrophobic drug paclitaxel)
2) targeting the liposomes to tumour tissue or circulating cancer cells;
3) drug delivery to cancer cells. For hydrophobic drugs liposomes could serve just as biocompatible carrier preventing precipitation of drug in blood stream.

Classification of liposomes [14]:

Classification based on structural parameters: Table:1

Type 1	Specification
Based on Structure Parameter	
Small Unilamellar Vesicles (SUV)	Size range from 20-40nm
Medium Unilamellar Vesicles (MUV)	Size range from 40-80nm
Large Unilamellar Vesicles (LUV)	Size range from 100-1000nm
Oligo Lamellar Vesicles (OLV)	Made up of 2-10 bilayers of lipids
Multi Lamellar Vesicles (MLV)	Made up of several bilayers
Type 2	
Based on Liposome Preparation	
REV	Single or oligolamellar vesicles made by Reverse-Phase Evaporation Method
MLV-REV	Multilamellar vesicles made by Reverse-Phase Evaporation Method
SPLV	Stable Plurilamellar vesicles
FATMLV	Frozen and Thawed MLV
VET	Vesicles prepared by extrusion technique
DRV	Dehydration-rehydration Method
Type 3	
Based on Composition & Application	
Conventional Liposomes	Neutral or negatively charged phospholipids
Ph Sensitive Liposomes	Phospholipid like Phosphatidyl ethanolamine
Immuno Liposomes	Long circulatory liposome with attached monoclonal antibody
Cationic liposomes	Cationic lipid

Raw materials [15]:

Liposomes that are used as drug carriers or diagnostic agents should be made from components that are nontoxic to humans. Phosphatidylcholines and phosphatidylglycerols from natural sources, semisynthetically or fully synthetically produced and cholestrol and PEG-ylated phophatidyletanolamine, are frequently assembled in liposomes designed as drug carriers for parentral administration or for in vivo diagnostic purposes. Phosphatidylcholine (PC) is often used as a bulk neutral phospholipid. Phosphatidylglycerol (PC) is used as it is negatively charged lipid. Cholesterol is added to bilayer structure if it is desirable to reduce the permeability of "fluid crystalline state" bilayers. Sometimes lipids with a special affinity for certain target cells in the body are introduced in bilayer for eg. when hepatocytic delivery was targeted for and lactosylceramide, a ligand with a special affinity for hepatocytes, was enclosed in the liposomal bilayer.

For the liposomal preparation, phospholipids can be divided into five groups for the preparation of liposomes:

- Phospholipids from natural soures
- Modified natural phospholipids
- Semisyntheyic phospholipids
- Phospholipids with nonnatural head groups

Phospholipids from Natural sources

The natural sources for phospholipids, mainly PC, also phosphatidylethanolamine(PE), phsphotidylinositol (PI), and sphingomyelin(SPM); are egg yolks and soyabeans. The PC's are mixed acyl ester phospholipids. Considerable interbatch variation has been obsereved for egg PC, apart from source dependent differences in acyl chain type. The esterified acyl chains of egg PC are diffrent from those of soybean PC.

Modified Natural Phospholipids

Natural phospholipids can be modified. They are sensitive to oxidation because of degree of unsaturation. PC from natural sources can be catalytically hydrogenated. Partially or fully hydrogenated natural PCs are easily available. As the number of unsaturated C=C bonds drops, the iodine value of these lipids is decreased. Dependent on the degree of unsaturation left after the hydrogenation process, phase transition temperatures can be identified for liposomal dispersions of the partially hydrogenated PCs. Head group modifications can be done by using enzyme phospholipase and can convert PC into PG, PE or phosphatidylyserine (PS).

Semisyntheyic Phospholipids

These are acyl chains that are linked to phospholipids from natural sources and are often unsaturated. This are susceptible to oxidation reactions, which may limit liposome shelf life. Reproducibilty of the suitability in terms of acyl chains may be poor, which may cause alteration in stability or liposome properties. Removal of the original acyl chain, replacement by a chosen acyl chain is feasible.

Phospholipids with Nonnatural (Head) Groups

The idea of maintaining the fate of liposomes in the body by choosing the apropos bilayer characteristics has led to modified phospholipids. When polyethleneglycol chains are linked to bilayer constituents, the circulation time of liposomes in the blood compartment can be substantially prolonged. For active targeting, ligands for cell surface receptors can be attached. These ligands are chemically and physically varied structures, such as monoclonal antibodies or just a simple peptide. PEG has been linked to PE for the preparation of long circulating liposomes. Various reactions schemes have been developed. Molecular weights fractions for maximum prolongation of circulation times for PEG vary between 1900 and 5000.

Preparation of liposomes [16]

Hand shaken method: By this method, large multilamellar liposomes can be prepared. Lipid molecules must be injected into an aqueous environment. When dry lipid layer is hydrated, the lamellae swell and grow into myelin figures. Mechanical agitation provided by vortexing, shaking, swirling or pipetting causes myelin figures to break and reseal the exposed hydrophobic edges resulting in the formation of liposomes.

Sonication method: This method is widely used for the preparation of small unilamellar vesicles. There are two types sonication techniques:

Probe sonication

The tip of the sonicator is plunged into the liposome dispersion. The energy input into the lipid dispersion is very high. The dissipation of energy at the tip results in local overheating and therefore the vessel must be immersed into an ice/water bath. During the sonication upto one hour more than 5% of the lipids can be de-esterify. However, with probe sonicator, titanium will slough off and contaminate the solution.

Bath sonication

The liposome dispersion in a tube is placed into a bath sonicator. In this method, the temperature control of the lipid dispersion is easier. The tip material being sonicated can be kept in a sterile container, unlike the probe units, or under an inert atmosphere.The lipid bilayer of the liposome can fuse with other bilayers, thus delivering the liposome contents. By making liposomes in a solution of DNA or drugs, they can be delivered past the lipid bilayer.

Reverse phase evaporation method

This method provides an insight to liposome technology as the liposomes are prepared with a high aqueous space to lipid ratio and can entrap the large portion of aqueous material. It is based on the formation of inverted micelles which are formed upon sonication of a mixture of a buffered aqueous phase, which contains the water soluble molecules to be encapsulated into liposomes and an organic phase in which the amphiphilic molecules are solubilized. The slow removal of the organic solvent leads to the transformation of these inverted micelles into a gel like and viscous state. At a critical point, the gel state collapses and some inverted micelles disintegrate. The redundant of phospholipids in the environment leads to the formation of a complete bilayer around the remaining micelles, which result in the formation of liposomes. Liposomes made by reverse phase evaporation method can be made from various lipid formulations and have aqueous volume to lipid ratio that are four times higher than multilamellar liposomes or hand shaken liposomes.

Freeze dried rehydration method

Freezed dried liposomes are formed from preformed liposomes. Very high encapsulation efficiencies even for macromolecules can be achieved by this method. During the dehydration the lipid bilayers and the materials to be encapsulated into the liposomes are brought into close contact. Upon reswellig the chances for encapsulation of adhered molecules are much higher. The rehydration is very important step. The aqueous phase should be added in very small portions with a micropipette to the dried materials. After each addition the tube should be vortexed thoroughly. The total volume used for rehydration must be smaller than the starting volume of liposome dispersion.

Detergent depletion method

The detergent depletion method is used for preparation of variety of liposomes and proteoliposome formulations. Detergents can be depleted from a mixed detergent lipid micelles by various techniques which leads to the formation of very homogenous liposomes. Not all but only some detergents can be used for this method. The most popular detergents sodium cholate, alkyl thio glucoside and alkyloxypolyethylenes. Mixed micelles are prepared by adding the concentrated detergent solution to multilamellar liposomes. Equilibrium of the mixed micelles in the aqueous phase takes some. The use of different detergents results in different size distributions of the vesicles formed. Faster depletion rates produces smaller size liposomes. The use of

different detergents also results in different ratios of large unilamellar vesicles oligolamellar vesicles multilamellar vesicles.

Review of Literature

The main focus of this article is the use of liposomes as carriers in cancer therapy. The data has been collected from pubmed, the various liposomal formuations that has been used in anticancer drugs. The drugs encapsulated with liposomes enter tumor site easily but are restricted from healthy tissues by endothelial wall. Thus liposomes have been used as novel drug delivery systems for improving the delivery of therapeutic agents to specific sites in the body. PEGylated liposomes of epirubicin and chrysophsin-1 significantly increase the mRNA expressions of p53, Bax, and Bcl-2. Chrysophsin-1 function as a new generation of MDR-reversing agent to potentiate the activity of cancer chemotherapeutics [17]. Brucea javanica oil-loaded liposomes inhibits proliferation of human hepatocellular cancer cell line HepG2 [18]. Long-circulating Arg-Gly-Asp (RGD)-modified aclacinomycin A (ACM) liposomes supress the growth of human lung adenocarcinoma (A549) cells and decreased tumor size [19]. Stealth PLGA/Liposome nanoparticles (NPs) altered with tumor-targeting single-chain antibody fragment (scFV-P/L) for systemic delivery of recombinant methioninase (rMETase) were prepared for gastric cancer [20]. Epirubicin plus quinacrine liposomes was developed by modifying functional DSPE-PEG2000 with C(RGDfK), a cyclic peptide containing Arg-Gly-Asp that helps in the treatment of invasive breast cancer [21]. A7R-cysteine peptide (A7RC) surface modified paclitaxel liposomes (A7RC-LIPs) achieve target delivery and inhibition of tumor growth and angiogenesis [22]. c-di-GMP efficiently activates NK cells and induces antitumor effects against malignant melanomas when loaded in YSK05 lipid containing liposomes, by assisting in the efficient delivery of c-di-GMP to the cytosol [23]. RGD-modified PEGylated liposome-encapsulated ICG (RGD-PLS-ICG) system mediated by integrin was developed. RGD was conjugated covalently to the distal end of DSPE-PEG2000-NH2 lipid by amide binding, found to be a promising fluorescent dye delivery system for targeting gastric cancer cell overexpression of integrin [24]. DOX-loaded DPPC/P188 liposome formulation administered via the pulmonary route proved to be useful for lung cancer treatment [25].

Cytotoxic effect of TSL and RGD-TSL was studied on B16Bl6 melanoma, B16F10 melanoma and HUVEC. RGD-TSL have potency to increase drug efficacy due to higher uptake by tumor and angiogenic endothelial cells in combination with heat-triggered drug release [26]. Paclitaxel-loaded liposomes modified with a multifunctional tandem peptide R8-c(RGD) (R8-c(RGD)-Lip) were used for the treatment of glioma and proved to be safe and efficient antiglioma drug delivery system [27]. cMLVs (cross-linked multilamellar liposomal vesicles) represent a novel drug delivery system that serve as a potential platform for combination therapy, allowing codelivery of an anticancer agent salinomycin (Sal) and doxorubicin (Dox) and a CSC inhibitor for the removal of both breast cancer cells and cancer stem cells [28]. Targeted therapy for breast cancer stem cell (BCSC); a novel liposomal system (APTEDB -LS-siRNA(EDB)) enables simultaneous targeting and knockdown of extra domain B of fibronectin (EDB-FN) shows potent therapeutic efficacy in the BCSC-derived tumors [29]. GEMTSLnps+ mHT (GEM loaded PEGylated thermosensitive liposomal nanoparticles) significantly enhance cytotoxic effect of GEM and serve as a new chemotherapy modality for delivering GEM to pancreatic cells [30]. The combination of paclitaxel-topotecan (Pac-Top; 20:1, w/w) were loaded into folate-anchored PEGylatedliposomes (FPL-Pac-Top) for safe and effective treatment of ovarian cancer [31]. The properties of IL-4R-binding peptide-1 (IL4RPep-1), a CRKRLDRNC peptide, was investigated to target the delivery of liposomes to lung tumor. It was found that IL-4R-targeting nanocarriers may be a useful strategy to enhance drug delivery through the recognition of IL-4R in both tumor cells and tumor endothelial cells [32]. A novel surfactant Pa-Brij78 was synthesized for development of a bone targeted thermosensitive liposome formulation for treatment of tumor bone metastasis [33]. The DSPC liposomal formulation is a promising formulation for MDR tumor therapy [34].

ALA-containing liposomes (Lipo-ALA) were prepared using dipalmitoyl-phosphatidyl choline and was investigated against human cholangiocarcinoma HuCC-T1 cells. Lipo-ALA increased the uptake efficiency into tumor cells compared to ALA itself, which increased the phototoxic effect[35]. Resveratrol and 5-fluorouracil co-loaded ultradeformable liposomes could be a new nanomedicine for the treatment of squamous cell carcinoma, i.e., actinic keratosis, Bowen's disease, and keratoacanthoma [36]. A nanostructured liposome was designed and prepared for treating NSCLC. Peanut agglutinin (PNA) was modified on the liposomal surface, 3-(N-(N',N'-dimethylaminoethane)carbamoyl) cholesterol was used as cationic materials, and vinblastine was encapsulated in the aqueous core of liposomes, respectively. The chemotherapy using the PNA modified

vinblastine cationic liposomes provides a potential strategy for treating non-small cell lung cancer [37]. Combination therapy of liposomal paclitaxel and cisplatin as neoadjuvant chemotherapy (NACT) found to be efficacious and tolerable in locally advanced cervical cancer [38]. Anticancer siRNA was condensed in the presence of 9-arginine peptides (9Arg) and then complexed with cationic O,O'-dimyristyl-N-lysyl glutamate liposomes conjugated to antibodies against the epidermal growth factor receptor (EGFR). Repeated intravenous administrations of the anti-EGFR-9Arg-lipoplexes effectively inhibited tumor growth in the mouse lungs and prolonged survival of the mice compared with nontargeted lipoplexes [39]. Liposomes containing anastrozole (ANS) was developed for effective treatment of breast cancer [40]. pH-sensitive liposomes (PLPs) modified with arginine-glycine-aspartic acid (RGD) peptide was developed to enhance the effectiveness of docetaxel treatment, which confirms that RGD-modified PLPs be a potential drug delivery system to achieve controlled release and tumor targeting [41].

Liposomal drug delivery system was developed for targeted drug delivery to G- MDSCs that proves to be useful adjunct in immunotherapy in the fight against cancers [42]. Peptide D[KLAKLAK]2 (KLA) modified with 2, 3-dimethylmaleic anhydride (DMA) and combined with 1, 2-distearoyl-sn-glycero-3-phosphoethanolamine (DSPE) to yield a DSPE-KLA-DMA (DKD) lipid. In vitro anticancer efficacy of this liposome system was evaluated in human lung cancer A549 cells and drug-resistant lung cancer A549/Taxol cells. These dual-functional liposomes had the greatest efficacy for treating A549 cells and A549/Taxol cells in vitro, and in treating drug-resistant lung cancer A549/Taxol cells xenografted onto nude mice [43]. The antiproliferative activity of α-mangostin liposomes (prepared by reverse phase evaporation method) in various cancer and normal cells was found to be associated with apoptosis, with differences in sensitivity among the cell lines treated [44]. A targetable vector was developed for the targeted delivery of anticancer agents, consisting of lipid-coated poly D,L-lactic-*co*-glycolic acid nanoparticles (PLGA-NP) modified with transferrin (TF). Doxorubicin (DOX) was used as a model drug for lung cancer therapy. It was concluded that TF-LP may be an efficient targeted drug-delivery system for lung cancer therapy [45]. Liposomal encapsulation of glucocorticoid dexamethasone offers a promising new treatment option for advanced, metastatic prostate cancer which supports further clinical evaluation [46]. Cetuximab (anti-epidermal growth factor receptor - EGFR - monoclonal antibody) is a promising targeting ligand since EGFR is highly expressed in a wide range of solid tumors. EGFR-targeted immunoliposomes was developed for enhancing the delivery of CLX to cancer cells and to evaluate the functional effects of these liposomes in cancer cell lines. Selective targeting of CLX with anti-EGFR immunoliposomes appears to be a promising strategy for therapy of tumors that overexpress EGFR [47].

The study was carried to formulate breast cancer-targeted liposomal carrier by surface conjugation of transferin. Apt properties of prepared Epirubicin-HCl liposomal formulation warrant its clinical application in breast cancer treatment after further studies [48]. The anti-VEGF liposomes found to be highly specific for VEGF(+) tumor cells (in vitro and in vivo). Intravenous injection of VEGF-liposomes to rats with intracranial C6 glioma followed by their specific accumulation in the malignant tissues and engulfment by glioma cells, which attested to target delivery and selective accumulation of anti-VEGF-liposomes in the brain tumor. The use of targeting molecules significantly increase the distribution and efficiency of delivery of nanocontainers to a tumor characterized by hyperexpression of the target proteins [49]. ITGB6-targeted immunoliposomes enhanced cellular internalization in ITGB6-positive colon cancer cells compared with liposomes. ITGB6-targeted immunoliposomes provide a highly efficient approach for targeted drug delivery in colon cancer and thus offer the potential of a novel and promising anticancer strategy for clinical therapy [50]. Novel sugar-conjugated cholesterols, β-Gal-, α-Man-, β-Man-, α-Fuc-, and β-Man-6P-S-β-Ala-Chol, were incorporated into liposomes. These glyco-coated liposomes were efficiently taken up by cells expressing carbohydrate-binding receptors and are promising candidates for drug delivery vehicles [51]. PEG-dendron-phospholipid was synthesized that form super stealthliposomes (SSLs). A β-glutamic acid dendron anchor was used to attach a PEG chain to several distearoyl phosphoethanolamine lipids. This composition enhance the anticancer potency of a drug payload (doxorubicin hydrochloride) [52]. A liposomal formulation of irinotecan, Irinophore C™ (IrC™) is efficacious in a panel of tumor models, and Irinophore C™ is also effective against patient derived xenografts (PDX) of colon cancer [53]. The in vitro cytotoxicity of the optimized liposomal SIM (LCL-SIM-OPT) was evaluated on C26 murine colon carcinoma cells. LCL-SIM-OPT exerted cytotoxicity on C26 cells probably via enhancement of oxidative stress in co-culture environment [54]. Liposomal drug delivery system conjugated with cyclic arginine-glycine-aspartic acid-tyrosine-lysine peptide (cRGDyk) as αvβ3 integrin ligand was developed to improve therapeutic efficacy in a mice model of bone metastasis from prostate cancer. cRGDyk conjugated liposomes showed significantly higher cellular uptake and higher cytotoxicity of loaded cisplatin, as evidenced by in vitro cell experiments [55].

PEGylated doxorubicin-loaded liposomes(DOX-Lip) was combined with anti-metastasis Peptide S for tumor therapy. Both Peptide S and DOX-Lip inhibited the adhesion of B16F10 cells to stromal cells. Combined treatment with CXCR4 antagonist and liposomal doxorubicin was proved to be promising for antitumor and anti-metastasis therapy [56]. The effect on breast cancer cell lines and the co-delivery of liposomes containing siHIF1-α and siVEGF was investigated. The expression level of VEGF mRNA was markedly suppressed in MCF-7 and MDA-MB435 cells transfected with chitosan-coated liposomes containing HIF1-α and VEGF siRNA, The role of VEGF and HIF1-α in breast cancer, siRNA-based therapies with chitosan coated liposomes have some promises in cancer therapy [57]. The antitumor activity of long-circulating liposome-encapsulated simvastatin (LCL-SIM) was evaluated in B16.F10 murine melanoma-bearing mice. The results showed that LCL-SIM inhibits strongly the B16.F10 melanoma growth [58].

The liposomal formulation of Epigallocatechin gallate (EGCG) and anticancer drug Paclitaxel was investigated; that indicate the suitability of PTX/EGCG co-loaded liposomes for the treatment of invasive breast cancer [59]. The PEGylated VRB plus quinacrine cationic liposomes showed a potential strategy for treating NSCLC [60]. Non-cationic liposomes encapsulating si-RNA (nanocarrier-mediated silencing of EpCAM gene) is a promising strategy to treat epithelial cancers [61]. The therapeutic radionuclide (188)Re embedded in PEGylated (PEG is polyethylene glycol) liposomes suggest that the PEGylated liposome-embedded (188)Re could be used for the treatment of human lung cancers [62]. A successful conjugation of anti-CD44 aptamer to the surface of liposome and binding preference of Apt1-Lip to CD44-expressing cancer cells and conclude to a promising potency of Apt1-Lip as a specific drug delivery system [63]. A dual-targeting liposomal system modified with TAT (AYGRKKRRQRRR) and T7 (HAIYPRH) was developed, in which the specific ligand T7 could target BBB and brain glioma tumor and the nonspecific ligand TAT could enhance the effect of passing through BBB, and elevate the penetration into the tumor [64]. Nanoliposomal encapsulation improves intratumoral mitoxantrone MTO delivery over free drug. Liposome bilayer-incorporated short-chain sphingolipid SCS preferentially permeabilize tumor cell membranes enhancing intracellular MTO delivery [65]. The liposome-encapsulated ATRA may help to achieve a higher level of ATRA in comparison with free ATRA treatment and helps to enhance anticancer drug delivery in liposome-encapsulated ATRA treatment [66]. Intranasal administration of liposomal I3C has the potential to significantly improve the efficacy of I3C for lung cancer chemoprevention [67]. The antitumor activity of liposomal phospho-ibuprofen amide PIA was evaluated in a metastatic model of human NSCLC in mice. Liposomal PIA strongly inhibited lung tumorigenesis (>95%) and was significantly ($p<0.05$) more efficacious than ibuprofen. Thus liposomal PIA is a potent agent in the treatment of lungcancer and merits further evaluation [68].

A folate receptor targeted co-delivery system folate-doxorubicin/Bmi1 siRNA liposome (FA-DOX/siRNA-L) was developed. In vitro and in vivo studies showed that FA-DOX/siRNA-L inhibited tumor growth by combinatory role of Bmi1 siRNA and doxorubicin (DOX) [69]. Immunoliposomes enhanced the toxicity of 7-glucosyloxyacetylpaclitaxel in HER2-overexpressing cancer cells and showed more rapid suppression of cell growth. The immunoliposomes strongly inhibited the tumor growth of HT-29 cells xenografted in nude mice [70]. Lipoplatin exhibited a potent antitumoral activity in all ovarian cancer cell lines tested, induced apoptosis, and activated caspase-9, -8, and -3, downregulating Bcl-2 and upregulating Bax. Lipoplatin decreased both ALDH and CD133 expression, markers of ovarian cancer stem cells [71]. The effects of polyethylene glycol (PEG)-liposomal oxaliplatin (L-OHP) on the induction of apoptosis in human colorectal cancer SW480 cells was studied. The results indicate that PEG-liposomal L-OHP enhances the anticancer potency of the chemotherapeutic agent [72]. EDTA was used in a drug delivery system by adopting an NH4EDTA gradient method to load doxorubicin into liposomes with the goal of increasing therapeutic effects and decreasing drug-related cytotoxicity. The results show that use of the NH4EDTA gradient method to load doxorubicin into liposomes could significantly reduce drug toxicity without influencing antitumor activity [73]. Resveratrol and 5-fluorouracil were successfully coencapsulated in a single PEGylated nanoliposome. The nanoformulation was tested in vitro on a head and neck cancer cell line NT8e and was found to exhibit a GI50 similar to that of free 5-fluorouracil. The coencapsulation of resveratrol and 5-fluorouracil in a liposomal nanocarrier improved the cytotoxicity in comparison with the free drug combination when tested in vitro [74].

Immunoliposomal docetaxel exhibited the strongest growth inhibitory effect against CA IX-positive lung cancer cells and a promising drug delivery system for targeted killing of lung cancer cells [75]. A liposome-mediated c-myc antisense oligodeoxynucleotide and 5-fluorouracil can inhibit the proliferation and invasion of livercancer cells by reducing the expression of c-myc. A c-myc antisense oligodeoxynucleotide can increase the sensitivity of liver cancer cells to 5-fluorouracil and decrease the dosage of the agent necessary for efficacy,

providing an experimental basis for the clinical therapy of liver cancer [76]. A novel delivery system of iRGD (CRGDK/RGPD/EC)-modified sterically stabilized liposomes (SSLs) containing conjugated linoleic acid-paclitaxel (CLA-PTX) was prepared. The anti-tumor effect of iRGD-SSL-CLA-PTX was investigated on B16-F10 melanoma in vitro and in vivo. The antitumor effect of iRGD-SSL-CLA-PTX was confirmed on B16-F10 melanoma in vitro and in vivo [77]. The in vivo antitumor activity also showed that DOX-loaded C-TAT-Lipo with injection of cysteine achieved the best tumor growth inhibition [78]. The nanostructured targeting epirubicin plus celecoxib liposomes could eliminate invasive breast cancer along with the VM channels, hence providing a promising strategy for treatment of invasive breast cancer [79]. A novel liposome-silica hybrid nano-carrier for tumor combination therapy via oral route, using paclitaxel and cyclosporine as a model drug pair was formulated. The co-delivery of cyclosporine and paclitaxel significantly enhanced the oral absorption of paclitaxel with improved anti-tumor efficacy, suggesting a promising approach for multi-drug therapy against tumor and other serious diseases via oral route [80].

iRGD-modified and doxorubicin-loaded sterically stabilized liposomes (iRGD-SSL-DOX) and passive liposomes (SSL-DOX) were prepared. In conclusion, iRGD reserved its tumor-penetrating properties well when modified on the surface of liposomes at optimal density and iRGD-SSL-DOX would be a promising drug delivery system for active targeting tumor therapy [81]. Tamoxifen (TMX), an estrogen receptor (ER) antagonist, incorporated at surface of liposomes loaded with Doxorubicin (DOX), was hypothesized to serve as ligand for targeting overexpressed ERs on surface and cytosol of breast cancer cells, in addition to its synergism with DOX in killing MCF-7 cells [82]. Liposomal celastrol can decrease the viability of prostate cancer cells, while eliminating the need for toxic solubilising agents [83]. (-)-Antofine liposomes prepared by film dispersion method has high encapsulation efficiency, the water-soluble and the anti-tumor activity are improved compared with (-)-Antofine [84]. GE11-modified liposomes for targeted drug delivery to EGFR-positive NSCLC was evaluated. GE11-modified liposomes showed enhanced accumulation and prolonged retention in tumor tissue. GE11-modified liposomes may be a promising platform for targeted delivery of chemotherapeutic drugs in NSCLC [85]. Liposomally encapsulated CDC20siRNA was found to be efficient in silencing the expression of CDC20 in tumor and endothelial cells at both mRNA and protein levels under in vitro settings. Liposomal formulation of CDC20siRNA is a promising RNA interference tool for use in anti-angiogenic cancer therapy [86]. The ability of pH-sensitive liposomes in enhancing the cytotoxicity of Rapamycin was evaluated in vitro by using colon cancer cell line (HT-29) and compared with its cytotoxicity on human umbilical vein endothelial cell (HUVEC) line. pH-sensitive PEG-PMMI-CholC6-based liposomal formulation can improve the selectivity, stability and antiproliferative effect of Rapamycin [87].

PEG-coated irinotecan cationic liposomes was investigated for its efficacy and mechanism of action in the treatment of breast cancer in preclinical models. PEG-coated irinotecan cationic liposomes had significant inhibitory effect against breast cancer in vitro and in vivo, hence providing a new strategy for treating breast cancer [88]. A novel cytotoxic gas delivery system has been developed using NO-loaded echogenic liposomes (ELIP) for breast cancer treatment. This novel cytotoxic gas delivery nanomedicine using liposomal carriers, NO-ELIP, has the potential to provide improved therapeutic effect for breast cancer treatment [89]. The local perfusion of galactosylated liposomal doxorubicin had a great promise for the treatment of liver metastasis from colon cancer [90]. Dual-targeting doxorubincin (Dox) liposomes were produced by conjugating liposomes with both folate (F) and transferrin (Tf), which were proven effective in penetrating the BBB and targeting tumors, respectively. The results indicate that this dual-targeting liposome can be used as a potential carrier for glioma chemotherapy [91]. The development of liposomal formulations containing t-DCTN or t-DCTN:HP-beta-CD improves antitumor activity [92]. EGCG encapsulated chitosan-coated nanoliposomes (CSLIPO-EGCG) was synthesized, and their antiproliferative and proapoptotic effect in MCF7 breast cancer cells was evaluated [93]. The liposomal encapsulation of crocin was characterized for in vitro cytotoxicity against BALB/c mice in C26 colon carcinoma cells which indicated that liposomal encapsulation of crocin could increase antitumorigenic activity [94]. The therapeutic efficacy of a new radio-therapeutics of (188)Re-labeled pegylated liposome in a C26 murine colon carcinoma solid tumor model eas investigated. Apoptotic marker in tumor was also evaluated by the TUNEL (terminal deoxynucleotidyl transferase biotin-dUTP nick-end labeling) method after injection of (188)Re-liposome. The results evidenced the potential benefits achieved by oncological application of the radio-therapeutics (188)Re-liposome for adjuvant cancer treatment [95]. CD74-targeted liposomal dexamethasone provides a support for a potential use as a new therapy for B-cell malignancies [96]. New-type three-component cationic hybrid liposomes (HLs) composed of dimyristoylphosphatidylcholine (DMPC), polyoxyethylene(21)dodecyl ether (C(12)(EO)(21)) and O,O'-ditetradecanoyl-N-(α-trimethylammonioacetyl) diethanolamine chloride (2C(14)ECl) were produced.

Cationic HLs could remarkably inhibit the growth of human colon cancer (HCT116) cells along with apoptosis in vitro for the first time in this study [97].

Oxaliplatin is one of the agents used against colorectal cancer. Using PEG-liposome encapsulated oxaliplatin may enhance the accumulation of drugs in tumor cells, inducing apoptosis. The effect of PEG-liposomal oxaliplatin on apoptosis of SW480 human colorectal cancer cells may be through regulation of expression of Cyclin A or Cyclin D1, as well as pro-apoptotic and anti-apoptotic proteins [98]. Topotecan was encapsulated into preformed liposomes containing 300 mM copper sulfate and the divalent metal ionophore A23187. Topophore C was 2-to 3-fold more toxic than free topotecan, however showed significantly better anti-tumor activity than free topotecan administered at doses with no observable toxic effects. Topophore C is a therapeutically interesting drug candidate and we are particularly interested in developing its use in combination with liposomal doxorubicin for treatment of platinum refractory ovarian cancer [99]. E-selectin functionalized L-DXR, provides a novel approach to selectively target and deliver chemotherapeutics to CTCs in the bloodstream [100]. Anti-IGF1-R immunoliposomes have been successfully tested in vitro and in vivo in a preclinical model for ACCs and represent a promising therapeutic approach for this tumor entity. Moreover, a combination of mitotane plus liposomally encapsulated cytostatic agents could also be an interesting novel treatment option for ACC in the future [101]. Lf-PLS might be a promising drug delivery system for hepatocellular carcinoma therapy with low toxicity [102].

The PR_b-functionalized PEGylated nanoparticles offer a promising strategy to deliver their therapeutic payload directly to the breast cancer cells, in an efficient and specific manner [103]. Delivery of MLP in pegylated liposomes is more effective than conventional chemotherapy in the treatment of gastroentero-pancreatic ectopic tumor models, and may represent an effective tool for treatment of these malignancies in the clinical setting with improved safety over free MMC [104]. The RGD-PEG-LP-DCs were found to be most cytotoxic in BT-20 and MDA-MB-231 cell lines [105]. A PEGylated liposomal formulation of cromolyn, composed of dipalmitoylphosphatidylcholine (DPPC), dimyristoylphosphatidylcholine (DMPC), distearoylphosphatidylcholine (DSPC) and 1,2-distearoyl-sn-glycero-3-phospho-ethanolamine-N-[methoxy(polyethyleneglycol)-2000] (DSPE-mPEG2000), has been developed with the purpose of improving the antitumor activity of cromolyn for human pancreatic adenocarcinoma [106]. The ability of oxaliplatin long-circulating liposomes (PEG-liposomal L-oHP) was investigated to provide an improved therapeutic index of colorectal carcinoma. The PEG-liposomal L-oHP exhibited a tendency to target tumour tissue and demonstrated a significantly greater impact on apoptosis compared to free oxaliplatin [107]. The liposomes used for the treatment of glioblatoma mutiforme, a grade 4 glioma tumor for central nervous system, crosses the blood brain barrier and deliver the drug to the brain tumor tissue, can carry both hydrophilic and hydrophobic drugs, protect them from degradation and release the drug for sustained period [108]. EGF liposomes were developed for selective delivery in tumor expressing EFGR. Selective intracellular drug delivery and efficacy was tested by oxaliplatin encapsulation. LP-EGF represents an attractive nanosystem for cancer therapy or diagnosis [109]. Clinical trials of Vincristine sulfate liposomal injection have demonstrated safety, toxicity and activity leading to Food and Drug Administration approval for relapsed acute lymphoblastic leukemia [110]. Dopamine-loaded biotinylated liposomes were attached through streptavidin to biotinylated capture probes and the telomerase activity extracted from 10 cultured cancer cells was detected [111].

7-glucosyloxyacetyldocetaxel encapsulated in liposomes significantly inhibited the growth of tumour in vivo with side effects less than unencapsulated drug [112]. Systemic delivery of VISA-Claudin4-BikDD by liposome complexes significantly inhibited mammary tumor growth and slowed down residual tumor growth post cessation of therapy in MMTV-HER2/Neu transgenic mice compared to the controls [113]. In vivo studies indicated the active targeting and intratumoral diffusion capabilities of R8-dGR modified liposomes. When paclitaxel was loaded in the liposomes, PTX-R8-dGR-Lip induced the strongest anti-proliferation effect on both tumor cells and cancer stem cells [114]. iRGD conjugated doxorubicin loaded liposome (iRGD-LP-DOX), and its effect on targeting and inhibiting growth of A549 cells was evaluated. Release of doxorubicin from iRGD-LP-DOX was detected by the dialysis bag method. The anti-proliferation efficiency of iRGD-LP-DOX was evaluated by MTT assay. iRGD can enhance uptake of liposomes by A549 cells and inhibit the proliferation of tumor cells [115]. A lactoferrin-containing PEGylated liposome system (Lf-PLS) was tested in vitro as a hepatoma-targeting drug delivery system. PEGylated liposomes (PLS) were prepared using the thin film hydration method with peglipid post insertion. The results suggest that Lf-PLS has a good targeting effect on HepG2 cells in vitro and be a potential drug delivery system in targeting hepatocellular carcinoma [116]. Paclitaxel and rapamycin

liposome was evaluated for breast cancer efficacy both in vitro and in vivo. Liposomes were more cytotoxic to 4T1 breast cancer cell line than the free drugs. The co-loaded paclitaxel/rapamycin pegylated liposome better controlled tumor growth compared to the solution [117]. The anticancer drug ESC8 was used in dexamethasone (Dex)-associated liposome (DX) to form ESC8-entrapped liposome named DXE. Liposomal formulation was developed that could sensitize and kill highly aggressive and drug-resistive cancer stem-cell-like cells [118]. The PEGylatedliposomes containing l-OHP (Intravenous injection of oxaliplatin) may have the potential to treat metastatic hepatic cancer-not only via the direct killing of the cancer cells but also via a reduction in tumor-supportive Kupffer cells [119]. Tetraethylenepentamine-based polycation liposomes (TEPA-PCL) were prepared and modified with Ala-Pro-Arg-Pro-Gly peptide (APRPG) for targeted delivery of miR-499 (APRPG-miR-499) to angiogenic vessels and tumor cells. The accumulation of doxorubicin (DOX) in the tumors was increased by pre-treatment with APRPG-miR-499. The combination therapy of APRPG-miR-499 and DOX resulted in significant suppression of the tumors [120]. Liposomal coencapsulation of doxorubicin with LLO enables a significantly larger percentage of the dose to colocalize with the nucleus compared to liposomes containing doxorubicin alone. The change in intracellular distribution resulted in a significantly more potent formulation of liposomal doxorubicin as demonstrated in both the ovarian carcinoma cell line A2780 and its doxorubicin-resistant derivative A2780ADR [121].

Liposomes conjugated with E-selectin adhesion protein and Apo2L/TRAIL (TNF-related apoptosis-inducing ligand) apoptosis ligand attach to the surface of leukocytes and rapidly clear viable cancer cells and; can prevent the spontaneous formation and growth of metastatic tumors in an orthotopic xenograft model of prostate cancer, by greatly reducing the number of circulating tumor cells [122]. Raloxifene-loaded liposome and cochleate formulations were used for Breast cancer cell lines (MCF-7). Highest antitumor activity was observed, and MMP-2 enzyme was also found to be inhibited with raloxifene-loaded cochleates containing DM-β-CD [123]. 6BrCaQ was loaded into (liposomes) for drug delivery to solid tumors. Liposomal 6BrCaQ showed good activity on PC-3 cell lines in vitro in terms of apoptosis induction and cell growth arrest in G2/M. Liposomal encapsulation of 6BrCaQ revealed promising anti-cancer effects [124]. Nanomedicine based combination therapy using QLPVM conjugated liposomal tamoxifen (TAM) and doxorubicin (DOX) was designed. The nanomedicine based combination therapy using QLPVM-SSL-TAM and QLPVM-SSL-DOX might provide a rational strategy for Luminal A breast cancer [125]. A novel folic acid-targeted liposomal formulation simultaneously co-loaded with C6 ceramide and doxorubicin [FA-(C6+Dox)-LP] was developed with an antiproliferative effect due to cell cycle regulation and subsequent induction of apoptosis and thus warrants its further evaluation in preclinical animal models [126]. Positively charged PEGylated liposomal formulation of GA (GAL) was developed for parenteral delivery for the treatment of triple-negative breast cancer (TNBC). Results of western blot analysis indicated that GAL significantly suppressed the expression of apoptotic markers, bcl2, cyclinD1, survivin and microvessel density marker-CD31 and increased the expression of p53 and Bax compared to GA and control [127]. 5-FU-loaded pH-sensitive liposomal nanoparticles (pHLNps-5-FU) was developed and anti-cancer effect of pHLNps-5-FU was evaluated as a potential candidate for the treatment of colorectal cancer [128].

Anti-tumor activity of Folate-tagged poloxamer-coated liposomes FDL against murine B16F10 melanoma tumor-bearing mice revealed that FDL inhibited tumor growth more efficiently than the DL. The results demonstrated the significant potential of the folate-conjugated nanoliposomal system for drug delivery to tumors [129]. TSLnps increased the delivery of gemcitabine-HCL Gem to tumor cells and also enhanced significantly the antitumor activity of Gem when combined with heat [130]. FUS introduced doxorubicin-loaded cationic liposomes (DOX-CLs) were applied to improve the efficiency of glioma-targeted delivery. Doxorubicin-loaded CLs (DOX-CLs) and quantum dot-loaded cationic liposomes (QD-CLs) were prepared using extrusion technology. FUS + DOX-CLs showed the strongest inhibition on glioma based on glioma cell in vitro and glioma model in vivo experiments [131]. Syndecan-1 tagged liposome containing fluorescent dye was developed for detection of pancreatic adenocarcinoma in vivo using multispectral optoacoustic tomography. By targeting the liposome with Syndecan-1, this nanovehicle has potential as a targeted theranostic nanoparticle for both drug and contrast agent delivery to pancreatic tumors [132]. It is shown that targeting natural killer cells with TRAIL liposomes enhances their retention time within the tumor draining lymph nodes to induce apoptosis in cancer cells. This approach can be used to kill cancer cells within the tumor draining lymph nodes to prevent the lymphatic spread of cancer [133]. Therapeutic studies in C26 mouse tumor models demonstrated dose-dependent improved efficacy of PL-MLP over MMC. Liposomal delivery of MLP confers a favorable pharmacological profile and greater therapeutic index than MMC [134].

The formulation of GX1-Ad5-AL was effective for enhancing the inhibition effect and suppressing the migration of gastric cancer vascular endothelial cells. Significantly, VCR-Lip-CD20 could selectively kill CD20+ melanoma CIC in populations of WM266-4 cells both in vitro and in vivo. VCR-Lip-CD20 has the potential to efficiently target and kill CD20+ melanoma CIC [135]. DOTAP (a liposome formulation of a mono cationic lipid N-[1-2,3-Dioleoyloxy)]-N,N,N-trimethylammonium propane methylsulfate in sterile water) cationic liposomes was prepared containing an antisense oligonucleotide (AsODN) against HIF-1α. Gene transfer of antisense HIF-1α was effective in suppressing tumor growth, angiogenesis and cell proliferation and including cell apoptosis. The results suggested that antisense HIF-1α therapy could be a therapeutic strategy for treating HCC [136]. The RGD-LP may be an efficient targeting drug delivery system for prostatic cancer [137]. The hydroxycamptothecin inclusion liposomes were successfully prepared by film evaporation method. The hydroxycamptothecin inclusion liposomes also exhibited better inhibition effect for the three kinds of cancer cell lines hepatoma (HepG-2), lung cancer (A549), and gastric cancer (SGC-7901) cell lines above, when compared to the commercially available hydroxycamptothecin the anti-cancer effect being at a dose-dependent manner [138]. A novel liposomal preparation was developed, co-loaded with NCL-240, a small-molecule inhibitor of the PI3K/mTOR pathway, along with cobimetinib, a MEK/ERK pathway inhibitor. This combination drug-loaded nanocarrier, (N+C)-LP, was able to significantly enhance the cytotoxicity of these drugs against colon carcinoma cells in vitro demonstrating a clear synergistic effect [139]. BPA-PEG-LPDOX significantly suppressed the growth of the DU145cancer cells, that suggested that BPA-PEG-LP could be a useful drug carrier for the treatment of human prostate cancers [140]. The in vivo antitumor efficacy showed that CMCS-Sf-CL inhibits tumor growth effectively when compared with free Sf solution. Therefore, co-delivering Sf with siRNA by CMCS-SiSf-CL might provide a promising approach for tumor therapy [141]. The study was designed to determine whether SVV-D53A plasmid encapsuled by DOTAP: Chol liposome would have the anti-tumor activity against SPC-A1 lung adenocarcinoma. The research results proved that the administration of SVV-D53A plasmid resulted in significant inhibition of SPC-A1 cells both in vitro and in vivo [142].

A novel type of targeted liposomes was developed by modifying a mitochondria-tropic material, D-a-tocopheryl polyethylene glycol 1000 succinate- triphenylphosphine conjugate (TPGS1000-TPP), to encapsulate sunitinib and vinorelbine separately and a combination of the two targeted drug liposomes was used to treat invasive breast cancer as well as VM channels. A combination of targeted sunitinib liposomes and targeted vinorelbine liposomes may provide an effective strategy for treating invasive breast cancer and prevent relapse arising from VM channels [143]. PMX encapsulated in cholesterol-free liposomes (PMX/Non-Chol CL) drastically inhibited the tumor growth in the pleural cavity [144]. Folic Acid conjugated liposomes encapsulating Oxaliplatin (L-OHP) were entrapped in alginate beads and further coated with Eudragit-S-100 for effective delivery to colon tumors. The results demonstrate that Eudragit coated calcium alginate beads bearing folic acid coupled liposome can be used as a prospective carrier for drug delivery to colon specific tumor [145]. Long-circulating and pH-sensitive PEG-coated (SpHL-PTX) and PEG-folate-coatedliposomes containing PTX (SpHL-FT-PTX) were prepared. The results suggest that SpHL-FT-PTX can be a promising formulation for the treatment of metastatic breast cancer [146]. The functional vincristine plus dasatinib liposomes, modified by a targeting molecule DSPE-PEG2000-c(RGDyK), were fabricated. The investigations were performed on TNBC MDA-MB-231 cells and MDA-MB-231 xenografts in nude mice. The nanostructured functional drug-loaded liposomes may provide a promising strategy for the treatment of invasive TNBC along with deletion of VM channels [147].

PTX-TR-Lip would improve the therapeutic efficacy of brain glioma in vitro and in vivo[148]. The therapeutic studies in MCF-7 nude mice exhibited CuDox-TSLs plus AuNRs in combination with NIR irradiation inhibited tumor growth to a great extent with less side effects that suggest to be a considerable potential of CuDox-TSLs combined with AuNRs for treatment of metastatic cancer [149]. The role of ceramide in ovarian cancer metastasis was examined. Ceramide liposomes had an inhibitory effect on peritoneal metastasis in a murine xenograft model of human ovarian cancer [150]. Co-delivery of protein and peptide antigens along with α-GalCer in a liposomal formulation was developed that could stimulate therapeutic anti-tumour immune responses. Enhanced production of IFN-γ, increased cytotoxic T-cell responses and tumour survival were observed when a long TRP2-peptide was delivered with α-GalCer in cationic liposomes [151]. Small molecule inhibitors against protein geranylgeranyltransferase-I such as P61A6 have been shown to inhibit proliferation of a variety of human cancer cells and exhibit antitumor activity in mouse models. Delivery of GGTI to human pancreatic cancer cells was demonstrated by the inhibition of protein geranylgeranylation inside the cell and this effect was blocked by Bafilomycin A1. In addition, GGTI delivered by pH-

liposomes induced proliferation inhibition, G1 cell cycle arrest that is associated with the expression of cell cycle regulator p21CIP1/WAF1. Proliferation inhibition was also observed with various lungcancer cell lines. Availability of nanoformulated GGTI opens up the possibility to combine with other types of inhibitors [152]. Long-circulating and pH-sensitive liposomes (SpHL) containing 99mTc-HYNIC-βAla-Bombesin(7-14) (99mTc-BBN(7-14) was prepared. SpHLG-99mTc-BBN(7-14) found to be suitable for a diagnostic agent, and is a potential tool for breast cancer tumor identification [153] .

Table 2: Liposomal Drug Formulations [154-158]

Sr. No	Liposomal Product	Application
1.	Daunorubicin	Kaposi's sarcoma
2.	Myocet (Doxorubicin)	Metastatic breast cancer
3.	Aroplatin	Colorectal cancer
4.	LEP-ETU (Paclitaxel)	Ovarian, Lung, Breast cancer
5.	Marqibo (Vincristine)	Non Hodgkins lymphoma
6.	Atragen	Acute promyelocytic leukemia
7.	Vinorelbine	Breast, Colon, Lung cancer
8.	Mitoxantrone	Leukemia, breast, stomach, liver, ovarian cancer
9.	Liposomal annamycin	Bresat cancer
10.	SPI-077 (Cisplatin)	Head & Neck cancer, Lung cancer
11.	Leutotecan	Ovarian cancer
12.	Cytarabine	Leukemia
13.	Topotecan	Relapsed solid tumors
14.	Transferrin-targeted oxaliplatin	Gastric cancer

CONCLUSION

Liposomes constitute a world in themselves as study objects in fundamental sciences and also as sophisticated tools in biotechnology. The success of liposomes in cancer therapy have made these systems promising drug delivery vehicles for future work aimed to improve their overall drug delivery efficacy. Predicting the future of nanotechnology in drug delivery system is not simple due to its fast developing technology and is changing rapidly. Additional research is required on liposomal drug delivery system to overcome the problems for effective therapy without side effects that can improve the quality of life in cancer patients. Liposomal encapsulation of anticancer drugs offers a number of benefits. Although current studies have shown that the use of these targeted nanoparticles as a drug delivery system is a promising strategy to treat human cancers, it is still in its early stage of development. Clinical data using targeted nanoparticles are limited, since most nanoparticles have not yet reached the clinical level. Only a few targeted nanoparticles are under clinical investigation. In sum, liposomes provide many targeting strategies and have shown a promising future as a new generation of cancer therapeutics. Certain critical question and many obstacles still remain, which present specific limitations to their overall efficacy. As soon as more clinical data becomes available further understanding will certainly lead to more rational design of optimized liposomes with improved selectivity, efficacy and safety in cancer treatment.

Abbreviations

1. p53: also known as TP53 or tumor protein
2. Bax: protein encoded by BAX gene.
3. Bcl-2: B-cell lymphoma-2
4. MDR: multi drug resistant
5. HepG2: human liver cancer cell line
6. RGD: Arg(R)-Gly(G)-Asp(D) motif peptide
7. ACM: aclacinomycin
8. PLGA: poly(lactic-coglycolicacid)
9. ScFv-P/L: tumor targeting single chain antibody fragment
10. rMETase: recombinant methioninase
11. DSPE-PEG-2000:1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(poyethyleneglycol)-2000
12. DPPC/p188: dipalmitoylphosphatidylcholine/poloxamer 188
13. HUVEC: human umbilical vein endothelial cells
14. TSL: thermo sensitive liposomes
15. CSC: cancer stem cells
16. BCSC: breast cancer stem cells

17. GEMTSLnps+mHT: gemcitabine thermosensitive liposomes using mild hyperthermia
18. Il-4R: inter leukin 4 receptor
19. NSCLC: non small cell lung cancer
20. NACT: neoadjuvant chemotherapy
21. ANS: anstrazole
22. pH: pH sensitive liposomes
23. G-MDSC: granulocytic myeloid derived suppressor cells
24. DMA: 2,3-dimethylmaleicanhydride
25. PLGA-NP: poly D,L-lactic-co-glycolic acid nanoparticles
26. TF: transferrin
27. EGFR: epidermal growth factor receptor
28. CLX: celecoxib
29. VEGF: vascular endothelial growth factor
30. ITGB6: integrin β6
31. PDX: patient derived xenogratfs
32. CXCR4: chemokine receptor type 4
33. MCF-7: breast cancer cell line
34. LCL-SIM: long circulating liposome-encapsulated simvastatin
35. EGCG: epigallacatechin gallate
36. MTO: mitoxantrone
37. SCS: short chain sphingolipids
38. ATRA: all-trans-retinoic-acid
39. LDH: lactate dehydrogenase
40. L-oHP: liposomes encapsulating oxaliplatin
41. CLA-PTX: conjugated linoleic acid-paclitxel
42. SSL: sterically stabilized liposomes
43. TMX: tamoxifen
44. ER: estrogen receptor
45. ELIP: echogenic liposomes
46. T-DCTN: Trans-dehydrocrotonin
47. CSLIPO: chitosan loaded liposomes
48. EGCG: epigallocatechin gallate
49. TUNEL: terminal deoxynucleotidyl transferase dUTP nick end labelling
50. HL: hybrid liposomes
51. DMPC: dimyristoyl phosphatidyl choline
52. HCT116: human colon cancer cells
53. ACC: liposomal encapsulated amorphous calcium carbonate
54. MLP: mitomycin c
55. BT20: breast cancer cells
56. MDA-MB-231: human breast cancer cell lines
57. Lf-PLS: lactoferrin pegylated liposomes
58. TEPA-PLS: tetraethylenepentamine based polycation liposomes
59. TNBC: triple negative breast cancer
60. FDL: folate tagged poloxamer coated liposomes
61. DOTAP: N-[1-2,3-dioleoyloxy]-N,N,N-tri-methyl ammonium propane methyl sulfate
62. AsODN: antisense oligonucleotide
63. BPA-PEG-LPDOX: Bauhinia purprea agglutinin modified pegylated liposomes encapsulating doxorubicin
64. CMCS: carboxymethyl chitosan modified cationic liposomes
65. CMCS-SiSf-CL: CMCS modified Si and Sf RNA codelivery cationic liposomes
66. GGTI: geranyl geranyltransferase I inhibitor

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