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Liposomes and current developments in anti-cancer drug delivery: An overview

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Abstract
The novel drug delivery approaches towards plant based drugs have been emerging as attractive research field and tremendous success have been achieved in making phytoconstituent more bioavailable and stable. Phytoconstituent of flavonoid class have been known for centuries possessing diverse health giving properties but not extensively formulated to modern dosage forms due the problems related to physicochemical and biopharmaceutic properties. Liposomes are simple microscopic vesicles in which an aqueous volume is entirely enclosed by a membrane composed of a lipid moiety and are well known to alter the bio distribution of entrapped substances by protecting the enclosed materials. They are widely used as vehicles or carriers to target the specific molecule to a specific organ especially in cancer. Due to extensive developments in liposome technology, a number of liposome-based drug formulations are available for human use and many products are under different clinical trials. The present review summarizes the developments in liposomal drug delivery and especially the anti-cancer drugs as liposomes along with the current literature reports on natural flavonoids based anticancer remedies.

Keywords: Liposome, cancer

1. Introduction
There have been a range of comprehensive strategies explored in the last few decades for effective treatment of cancer which are essentially under developmental stage and includes chemotherapy, surgery, radiotherapy and immunotherapy. The combination therapy plays a crucial role to enhance the recovery rate and quality of life of cancer patients, as because the surgery and radiation treatment are unable to remove all cancer cells. On the other hand, there exist a few scientific and technical issues during treatment like relapse, metastasis, broken immunity, etc. In case of immunotherapy, a limited efficacy is shown in improving the immune system of patients for a short term. There have been a number of obstacles to acquire a successful chemotherapy, yet chemotherapy plays an important role in eliminating cancer cells [1].

Consequently, the development of suitable drug delivery systems is a pressing mission and the significance for studying new drug delivery strategies are no less favorable than that for hunting high performance of new drug chemical entities. As drug carriers, liposomes have been demonstrated to be the useful delivery systems in improving unfavorable pharmacokinetics, enhancing efficacy for removing cancer and cancer stem cells, and reducing systemic side effects [2].

Conventional cytostatics used in cancer treatment are small molecular weight molecules [3]. Such molecules distribute non-specifically to both healthy and tumour tissue resulting in unwanted toxicities. To increase the therapeutic-to-toxicity ratio cytostatics can be encapsulated into small liposomes (~100 nm), which accumulate in tumours due to the enhanced permeability and retention effect. Here, leaky tumour vessels allow macromolecules to extravasate into tumour tissue, whilst reduced lymphatic tumour drainage results in particle accumulation [4].

First generation liposomes used for drug delivery suffered from fast clearance by cells of the monocyte phagocyte system (MPS). By coating liposomes with polyethylene glycol (PEG), i.e. pegylated liposomes reduce the adhesion of plasma proteins and opsonins to liposomes. Consequently, immune system recognition is reduced, decreasing MPS uptake and prolongs circulation time [5]. Today, most liposomes used for drug delivery are pegylated [6].

Upon liposome tumour accumulation encapsulated drug has to become bioavailable and prior to exerting cytotoxic actions [7].

Liposome is derived from two Greek words, *lipos* means fat and *soma* means body. Structurally liposomes are defind as concentric bilayered vesicles in which an aqueous volume is enclosed by a lipid bilayer. It can be loaded with hydrophobic and hydrophilic molecules [8]. The lipid bilayer of liposome can fuse with the cell membrane present in the site of action and thus the delivery of the liposomal content occurs [9]. Liposome properties contrast impressively with lipid creation, surface charge, size, and the strategy for arrangement [10]. Due to extensive developments in liposome technology, a number of liposome-based drug formulations are available for human use and many products are under different clinical trials. Encapsulation of drugs in liposomes enhanced the therapeutic indices of various agents, mainly through alterations in their pharmacokinetics and pharmacodynamics [11]. Liposomes characterize an advanced technology to deliver active molecules to the site of action, and at present, several formulations are in clinical use**.** Moreover, modifiability of liposomes makes the more dynamic and exact focusing on conceivable. Attributable to these favorable circumstances, liposomes turns into the best medication conveyance framework with routine clinical use, a large portion of them are for cancer treatment [12].

2. Advantages and disadvantages of liposomal drug delivery [9, 12]

Some of the advantages of liposome are as follows-

a. Liposomes are biocompatible, completely biodegradable, non-toxic in nature.
b. Liposomes are able to increase the *in vivo* drug stability and bioavailability, by preventing interactions of the transported drug with unwanted molecules, and reducing toxic side effects.
c. They are suitable for delivery of hydrophobic, amphipathic and hydrophilic drugs.
d. They protect the encapsulated drug from external environment.
e. It reduces exposure of sensitive tissue to toxic drugs.
f. Provides selective passive targeting to tumor tissues.
g. Increased efficacy and therapeutic index.
h. Increased stability via encapsulation.
i. Reduction in toxicity of the encapsulated agents.
j. Site avoidance effect.
k. Improved pharmacokinetic effects (reduced elimination, increased circulation life times).
l. Flexibility to couple with site specific ligands.
m. To achieve active targeting.

Significant disadvantages to mention are-

a. The production cost is high.
b. Leakage and fusion of encapsulated drug molecules can occur.
c. It has short half life.

3. Clinical goals of liposomal drug delivery

Theoretically, liposomes have some clinically relevant benefits over noncapsulated drugs, first of which is their improved pharmacokinetics and drug release [13]. In a meta-analysis, Sidone *et al*., (2010) demonstrated that the pharmacokinetic (PK) variability of liposomal agents is 2.7 fold or 16.7 fold greater than non-liposomal agents, measured by ratio of the coefficient of variation (CV) to AUC, AUC to CV% and ratio of AUC_{max} to AUC_{min} [14]. Several studies advocated that liposomal drugs offer enhanced cellular penetration, for which there exist different mechanisms, such as fusion of the liposomal membrane with the cellular plasma membrane [14, 15]. Another clinically important fact about liposomal drugs is the ability to include several active ingredients in one complex liposomal drug delivery system. Clinical evidence supports the hypothesis of Goldie and Coldman: that treating cancers with all the available effective agents simultaneously provides the greatest chance of eliciting a cure [16]. Combination chemotherapy carried out with synergistic drugs is considered as a basis for improving its effectiveness. The ultimate goal of research is to prepare a product that encompasses traditional cytotoxic agents and new molecularly targeted modalities with optimum therapeutic effects and acceptable toxicity for healthy tissues, although this is difficult to achieve [16].

4. Applications of liposomes in cancer treatment

Liposomes have been extensively applied in the management of cancer. Some of the successful applications of liposomes in cancer therapeutics are discussed here. A number of different liposomal formulations of anti-cancer agents have been shown to deliver the drug at the site of solid tumors with minimum toxicity as compared to free drug [17, 18, 19]. Currently, there are as many products in the market and in clinical development for use as anti-cancer drug delivery vehicle [18]. Doxil, a PEGylated liposomal formulation, is the first liposomal product that was approved by the FDA for the treatment of kaposi's sarcoma in AIDS patients [20, 21]. Doxil (US), or Caelyx (outside-US) is a PEGylated liposomal formulation encapsulating anticancer drug doxorubicin commercialized by Johnson & Johnson. In 2011, an imbalance between the demand and supply of Doxil was observed as the manufacturing unit was shut down temporarily due to some quality control issues [22]. To address the Doxil shortage in USA, FDA allowed temporary importation of LipoDox. LipoDox is the same liposomal formulation as Doxil in USA and made in India by Sun Pharma and in 2013, FDA approved the first generic version of Doxil, made by Sun Pharma [22, 23]. In a study, it was observed that Doxil was also active against refractory ovarian cancer, and later approved by the FDA for the treatment of recurrent ovarian cancer also [21, 24]. Recently, it has been approved for the treatment of breast cancer [21] in USA and for the treatment of multiple myeloma in combination with velcade in Europe and Canada [21, 25]. DaunoXome, the registered trademark of Galen, is the liposomal formulation of daunorubicin approved by the FDA for the treatment of AIDS related kaposi's sarcoma [26].

The Sopherion Therapeutics in the United States and Canada is conducting a pivotal phase III global registrational trial of Myocet in combination with Herceptin (trastuzumab) and Taxol (paclitaxel) for the treatment of highly aggressive HER2-positive metastatic breast cancer [27]. The liposomal formulation of vincristine made by Talon was registered under trade name of Marqibo. Marqibo was approved in 2012 by the FDA for the treatment of acute lymphoblastic leukemia [28, 29]. Celator Pharmaceuticals Inc developed CPX-351, a liposomal formulation of cytarabine and daunorubicin. The CPX-351 showed promising results in phase III clinical trial on the patients with secondary acute myeloid leukemia (AML) by improving the induction response over 40% [30, 31]. Myocet, the registered trade mark of Cephalon, is a non-PEGylated liposomal formulation of doxorubicin. Myocet in combination with cyclophosphamide was approved for the treatment of metastatic breast cancer in Europe but was not

yet approved by the FDA for use in the United States [32]. Lipoplatin is the liposomal formulation of cisplatin designed by Regulon Inc. and currently, it is being evaluated in phase III clinical trial for the patients with non-small cell lung cancer [33]. Another liposomal formulation Stimuvax is designed as anti-MUC1 cancer vaccine by Oncothyreon to treat non-small cell lung cancer and presently is in phase III clinical trial [33, 34, 35]. The thermo sensitive liposomal formulation of doxorubicin, called ThermoDox (Celsion) is under phase III clinical trial to treat the patients with primary hepatocellular carcinoma, in phase II for refractory chest wall breast cancer and colorectal liver metastasis [36, 37]. MM-398 is a liposomal sphere encapsulating irinotecan developed by Merrimack pharma. MM-398 is being evaluated in the clinical trials for its ability to treat various cancers, which are resistant to chemotherapy such as pancreatic, colorectal, lung and glioma [38, 39, 40]. Another liposomal formulation developed by Merrimack pharma is MM-302, which encapsulates doxorubicin. MM-302 is designed for selective uptake of drug into tumor cells while sparing off healthy tissues. MM-302 contains a novel antibody-drug conjugated on the surface that specifically targets cancer cells overexpressing the HER2 receptor. Currently, MM-302 is being evaluated in phase I clinical trials for its ability to treat advanced metastatic HER2-positive breast cancer [41]. MBP-426 is transferrin receptor targeted liposomal formulation of oxaliplatin designed by Mebiopharm. MBP-426 is being evaluated in phase II clinical trial for the treatment of patients with gastric cancer [42, 43].

5. Some liposomal formulations currently used for various cancer treatments: [1, 3, 13, 44, 45]

Drug loaded liposome and their trade name	Lipid phase	Indication	Company
Doxorubicin long circulating liposome(Doxil®)	PEG-DSPE/ phospholipids	Ovarian Cancer	Janssen-Cilag
Doxorubicin liposomes (Myocet®)	Phospholipids	Metastatic Breast Cancer	Enzon Pharmaceuticals
Vincristine sulfate liposomes (Marqibo®)	Phospholipids	Acute Lymphoblastic Leukemia and Melanoma	Talon Therapeutics Inc.
Daunorubicin liposome (DaunoXome®)	Phospholipids	Breast Cancer, Lung Cancer	Galen Ltd.
Doxorubicin liposomes (MCC-465)	Mcab-GAH-phospholipids	Gastric carcinoma	Mitsubishi
P53 plasmid DNA liposomes (SGT-53)	Transferrin/ phospholipids	Solid tumors	SynerGene Therapeutics, Inc.
Cisplatin liposomes(SPI-77)	PEG-DSPE/ phospholipids	Head and neck cancer, nonsmall cell lung cancer	ALZA
Oxaliplatin analogue liposomes (Aroplatin/LNDDP)	Phospholipids	Colorectal cancer	Aronex Pharmaceuticals
Annamycin liposomes (L-annamycin)	Phospholipids	Acute lymphoblastic leukemia	Callisto Pharmaceuticals
Paclitaxel liposome (Lipusu)	Phospholipids	Ovarian cancer	Luye Pharma Group
Oxaliplatin liposomes (MBP-426)	Transferrin/ phospholipids	Various cancers	Mebiopharm Co., Ltd

6. Scope of liposomes of some flavonoids with anti-cancer property

Many anticancer drugs are either natural compounds or have been developed from naturally occurring parent compounds. Much attention is currently being paid to flavonoids, which are found in fruit, vegetables, seeds, herbs, flowers, olive oil, tea and red wine [46]. Flavonoids are one of the classes of heterocyclic natural compounds that are widely distributed in plants as glycosides or as free aglycones. They are subdivided according to their structure into flavonols, flavones, flavanones, chalcones and anthocyanidins. They exhibit several biological effects such as anti-inflammatory, antibacterial, antifungal, antiviral, antiulcer, hepatoprotective, antitumour and antioxidant activity [47]. Many of these effects are the consequence of their ability to scavenge free radicals, to inhibit enzymes and to interact with biomembranes [48]. Several flavonoids have been studied for their antitumour activity; a carbonyl group at C-4 of the flavone nucleus was found to be responsible for their activity. The flavone derivative, flavone-8-acetic acid, has been shown to have considerable antitumour effects. Another flavone, genistein, has been proposed to be responsible for the lower rate of breast cancer in Asian women and this effect may be related to the high isoflavone-containing soy content of their diet [46, 49]. Genistein has received much attention as a potent anticancer agent owing to its wide range of effects on a number of cellular processes. Polymethoxylated flavones isolated from citrus were examined for their antiproliferative activities against several human cancer cell lines. Their strong antiproliferative activities suggest that they may serve as anticancer agents in humans [50, 51]. Quercetin, which belongs to the flavonols, has been reported as an antineoplastic compound, exerting growth inhibitory activity against several cancer cell lines *in vitro* and exhibiting a synergistic cytotoxic effect with cisplatin against drug-resistant leukaemia cells *in vitro*. Catechin, quercetin and resveratrol, which are the main polyphenols in red wine, were shown to inhibit the growth of human breast cancer cells [52]. *In vitro* studies have revealed the cytotoxic activity of flavonoids belonging to the group of kaempferol glycosides [53]. *In vitro* and animal studies have demonstrated that flavonoids may inhibit cancer cell growth by binding to type II receptors, which are over expressed in a wide range of tumour tissues such as breast, ovaries, colon and lung. Interest in flavonoids has also increased because of their antioxidant activity and their ability to prevent heart disease [54]. Many biological properties of flavonoids may be related to their capacity to penetrate into cell membranes and to affect their biological activity [55]. Though flavonoids possess anticancer activity, most flavonoids lack required physichochemical properties favorable for solubility in physiological fluids, ability to cross biomembrane, biodistribution and bioavailability to meet therapeutic goal, restricted stability, manufacturability to modern dosage form, etc. All these issues associated with natural flavonoids can be satisfactorily addressed by formulating liposomes enclosing the flavonoids moieties.

7. Current research in liposomes for cancer treatment

Imanaka *et al.*, (2008) reported that the beta-sitosterol liposomes exhibited the chemopreventive effect of tumor metastasis by oral delivery. Their results showed that the amount of immune response cytokines, such as IL-12 and IL-18, were increased in the small intestine after the intake of liposomes. After administration of the liposomes for 7 days, natural killer cell activity in the mice was increased, suggesting that the immune surveillance activity of mice was enhanced by the intake of beta-sitosterol liposomes. Furthermore, daily intake of beta-sitosterol liposomes prevents the metastasis of tumor [56]. Cogswell *et al.*, (2006) investigated that the long-circulating econazole liposomes had a superior efficacy in the treatment of breast cancer by parenteral administration. In the study, long-circulating econazole liposomes were prepared by a novel micelle exchange technique in incorporating drug into the lipid bilayer of preformed liposomes using a polyethylene glycol-linked phospholipid, distearoylphosphatidyl ethanolamine (DSPE-PEG). This method allowed for stable and efficient drug incorporation. Results showed that the liposomes had a long-circulating effect and a better efficacy but did not induce significant liver toxicity, renal toxicity or weight loss in human breast cancer MCF-7 cells xenografted model in mice [57]. Zeng and his coworkers, (2015) developed a kind of functional vincristine plus dasatinib liposomes modified with a targeting molecule DSPEPEG2000- C (RGDyK) for eradicating triple-negative breast cancer (TNBC). C(RGDyK) is a cyclic peptide that has a specific affinity with integrin receptor. It is found that the integrin receptor is over expressed on many malignant cancer cells, including TNBC cells. Consequently, this cyclic peptide acts as a targeting molecule in modifying drug liposomes for binding with integrin receptor on the cancer cells [58].

Sriraman *et al.*, (2016) developed a kind of pegylated doxorubicin liposomes modified with folate (F), transferrin (Tf) or both (F+Tf). The dual-targeted liposomes (F+Tf) showed a 7-fold increase in cell association compared to either of the single-ligand targeted ones in human cervical carcinoma (HeLa) cells [59].

Fanciullino *et al.*, (2005) developed a kind of pegylated liposomes of 2'-deoxyinosine (d-Ino), which was used as a 5-fluorouracil (5-Fu) modulator, and evaluated its efficacy *in vitro* and in tumor-bearing mice and its pharmacokinetics in rats. The deoxyinosine liposomes exhibited a strong potentiation effect in a combination use of 5-Fu *in vitro*, and displayed a 7-fold longcirculating effect in animals. In tumor-bearing mice, the combination of deoxyinosine liposomes with 5-fu led to 70 % of tumor reduction with a doubling median survival time as compared to the control. In addition to the long-circulating effect, the deoxyinosine liposomes had demonstrated a capability to reverse the 5-Fu resistant colon cancer SW620 cells [60].

8. Conclusion

An area of major challenges in cancer treatment is that most of the chemotherapeutics have erratic pharmacokinetics and associated toxicity. The search for newer therapeutics for management of cancer resulted into development of drug carriers and the clinical success of various liposomes have been encouraging as promising drug delivery system capable to improve drug delivery efficacy. The passively delivering chemotherapeutics encapsulated within liposomes in cancer treatment have emerged as attractive cancer management technique. The liposomal drug delivery system improves the specificity of the drug carrier towards cancer cells and thereby healthy host cells are exempted from unwanted toxicity. The naturally occurring flavonoids with anticancer activity are not sufficiently explored due to their unfavorable physicochemical and biopharmaceutic properties. Literatures suggested that liposomal drug delivery of flavonoidal drugs have great potential in cancer treatment and consequently would serve as alternative to conventional chemotherapy without compromising the quality of life of cancer patients.

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