Available online at http://www.journalijdr.com

ISSN: 2230-9926

IJDR

International Journal of DEVELOPMENT RESEARCH

International Journal of Development Research
Vol. 4, Issue, 12, pp. 2676-2680, December, 2014

Full Length Research Article

THE POTENTIAL ABILITY OF LIPOSOME TO TREAT CANCER DISEASE

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ARTICLE INFO

Article History:

Received 15th September, 2014
Received in revised form
09th October, 2014
Accepted 23rd November, 2014
Published online 27th December, 2014

Key words:

Liposome; Ligands;
Nanomedicine;
Drug Carrier;
Stimuli

ABSTRACT

Since 1965s when the scientists discovered liposome, the nanomedicine world became more innovative, progressive and more researches have been done to develop liposomes. Therefore, one of the most important aim of liposome is to reduce the toxicity and side effects which is caused by traditional cancer treatments. As a result to manipulating the liposome during formulation, it can result a less toxicity of the healthy tissue to diseased tissues, Because of the features of the liposome such as the targeting tissue, small size, and biodegradability. On the other hand, we can load different kinds of drugs and combinations inside the liposome to provide good quality of treatments to diseased tissue.

INTRODUCTION

The liposome is a kind of nanomedicine and this is the reason to focus on the ability of the liposome to treat diseases. the advantages of liposome such as fast mobility as a reason to its nano size, and targets diseased tissues by attaching some antibodies to the surface by manipulating, or change the charge of the liposome (Franzen and Østergaard, 2012). In addition, liposome has a physical sensitivity to temperature and to pH. Until now the FDA approved 12 kinds of liposomes such as doxorubicin. Describing the liposome as an artificial cell, looks like a biological cell which is surrounded by a phospholipid membrane consisted of lipid bilayer (Allen and Cullis, 2013), encapsulated by a self-assembly method (Franzen and Østergaard, 2012), contains an aqueous material. Due to the lipid bilayer in liposomes membrane the permeability is low to hydrophilic drugs (Allen and Cullis, 2013). Liposome is considered now as the most promising nanomedicine treatment for many diseases including cancer diseases. It can reach the cancer cell, by manipulating the surface of liposome itself, and we can load the drug within the liposome and change their lipidity to increase the stability (Slingerland *et al*., 2013). A lot of investigations have been done in liposome, because they are aiming to reach the stability of liposome during the circulation (Badiee *et al*., 2012). By attaching PEGylation we can decrease opsonization of liposomes which it can enhance the circulation half-life and reduce the clearance. Liposome can fight the multidrug resistance which is an important feature for cancer cells that can treat cancer cells with less efficacy (Malam *et al*., 2009). PEG protects the surface of liposome from the interaction with opsonizing proteins (Yang *et al*., 2011). Liposome Therapeutics impact can be more affected by the accumulation at tumor which increase the permeability and the retention effect (Malam *et al*., 2009). Moreover, To increase the circulation time for liposome, we can attach antibodies to liposome's surface or to the remote tale termini of the liposome's-grafted PEG chains, and the last method is better because there will be no interaction between the antibodies and the PEG chines. Liposomes can provide the most important aims for scientist which are decreasing the toxicity, increasing the pharmacokinetic features of the drug, and controlling the drug release. Liposomes have the potential advantages as an innovative nano drug delivery in nanomedicine world, because of their ability to treat most of the diseases, and they can solve the diagnosis limitation. Depending on the size of the carrier the exertion is done, if the size is <30 nm it will be exerted by the renal excretion, while

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if the size over 30 nm the mononuclear phagocytic system will exert the carrier which consist in the in Kupffer cells in to the liver and spleen. The rate of excretion changes depending on the age, sex and genetic affects which makes controlling the toxicity of nanomedicines hard because of the different permeability between people (Malam *et al*., 2009).

RESULTS AND DISCUSSION

To ensure that liposomes can reach tumor cells, I think if we develop a liposome with two stimuli-responsive chemical stimuli (pH) and physical stimuli (temperature). Liposomes are a smart molecule and by modifying the Liposome we can get the most of our aim which is targeting cancer cell to release the drug. Modifying the liposome with different ligands will enhance the liposome's ability to target tumor cells, release the drug, and decrease the side effects. Creating a liposome with PH-sensitive fusogenic peptides and thermo sensitive will affect the therapeutics for these reasons: using a thermal sensitivity strategy leads to accumulating the drug at the tumor site because of the vascular permeability which it can be increased by thermal sensitivity. The drug released in the tumor vasculature and interstitium because of the promoting of the temperature-sensitive formulations which release the drug. The pH sensitive enhance the fusion between the liposome membrane, and tumor cell due to the acidic microenvironment of cancer cells. Use the pH property of cancer cells where is an acidic microenvironments is a powerful tool to increase the efficacy of targeting tumor cells and the accumulation.

Using the PEGylated liposomes which have been used for cancer treatments. To increase the circulation times and stability they used the PEGylated liposomes (stealth liposomes) which can decrease macrophage. By combining two techniques of liposome targeting which are the thermo sensitive liposomes and pH-sensitive fusogenic peptides. Then, applying the thin-film hydration method (Tan *et al*., 2010 and Kim *et al*., 2014) the Pegylated (PEG) liposomes consists 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) and a lysolipid such as 1-palmitoyl-sn-glycero-3-phosphocholine or 1-stearoyl-sn-glycero-3-phosphocholine.

During the preparation of the liposome with ELP elastin-like polypeptide which is known as A responsive to high temperature during the peptide transition into dipalmitoylphosphatidylcholine (DPPC)-based liposome surface-bind with a cyclic arginine-glycine-aspartic acid cRGD modified nanocarrier which have been approved the small size of it will increase the accumulation on the αvβ3 integrin (Kim *et al*., 2014). The second peptide is GALA which can enhance the membrane fusion in acidic pH between the liposomes and endosomes (Liu *et al*., 2014). And DOX was loaded by the gradient method for ammonium sulfate. Create a liposome has two stimuli can be done to ensure the efficacy of the drug delivery. Liposome which consists1, 2-dipalmitoyl-sn-glycero-3-phosphocholine, and a lysolipid such as 1-palmitoyl-sn-glycero-3-phosphocholine or 1-stearoyl-sn-glycero-3-phosphocholine lead to achieve the Thermal triggering (Kim *et al*., 2014). Lysolipid-containing thermo sensitive liposomes control the drug release by the heating from outside device. Using two kinds of peptides in liposome will develop the nano carrier ability to be the perfect liposome. The benefits of therapeutics after applying a new techniques of nano drug delivery: (i) increase the peptides solubility, (ii) mange the release of drug, that will avoid the healthy tissue, (iii) maintain the amount of the drug until reach diseased tissue (Tan *et al*., 2010).

PH-sensitive fusogenic peptides

PH-sensitive liposomes are the most feature of the liposome that has many researches and attracted scientist. Scientists exploited the lower pH of endosome than extracellular feature of cancer cells to develop liposome. Scientists have been discovering many kinds of fusogenic peptide sequences because many trials and research have been done on the fusion of the membrane of animal tissue (Wagner, 1999). The first peptide discovered was GALA which can fuse easily with lipid bilayers at acidic PH (Subbarao *et al*., 1987). GALA can destabilize the lipid bilayer at low pH due to the Existence of amino acid sequence which is a stable α-helix. They used this feature to develop drug delivery trails in lab and biological tissue. Liposomes with GALA can reach the mitochondria of tumor cells and destroy the tumor cell therefore the liposomes

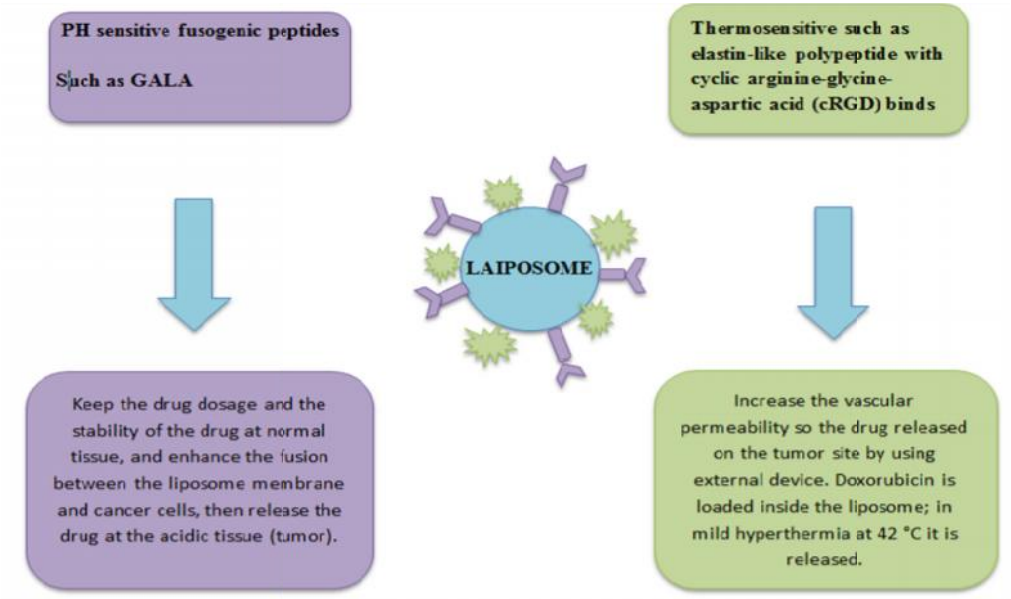

Fig. 1. Create a liposome with PH-sensitive fusogenic peptides and thermo sensitive will affect the therapeutics

caused the apoptosis in these cells because they have mastoparan a toxic peptide. GALA increase the fusion between the liposome and the membrane of the tumor cells and will release the mastoparan peptides into the cytosol on the low pH environment. PH sensitive is fusogenic peptides which happen when the membrane of endosome fused the low pH in the endosome, then the fusion happen in the organic molecules. This method of peptides have more impact in nanocarrier for drug and genes such as GALA (Glu-Ala-Leu-Ala) (Liu *et al*., 2014). Electrostatic repulsions happen at normal pH while at ph5.0 the neutralization happen due to carboxylic acid moieties of glutamic acid helical structure of the peptide which can be destabilized at natural pH and promoted at ph5 (Liu *et al*., 2014). If the pH reduces, the structure of gala changes from random coil to a α-helix so the hydrophobicity increases and the fusion with the lipid membrane happen.

Temperature-sensitive liposomes

Temperature-sensitive liposomes are a new technique used by heating the tumor by external device. The old thermo sensitive liposomes contains of a gel-to-liquid phase which can be transition at higher temperature than the physiological temperature. Lysolipids and synthetic temperature-sensitive polymers have been approved in the developed temperature-sensitization of liposomes (Ta and Porter, 2013). Mild hyperthermia playing an important role to enhance the therapeutic effect when combined with thermo sensitive liposomes by several strategies:(i) increase the accumulation of liposome on tumor cell as a result to increase the tumor permeability (ii) encourage the drug release in cancer tissue by the temperature-sensitive formulations (Ta and Porter, 2013 and Issels *et al*., 2009). Using low thermal sensitive liposome which container of 1, 2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) and a lysolipid such as 1-palmitoyl-sn-glycero-3-phosphocholine or 1-stearoyl-sn-glycero-3-phosphocholine enhance the drug accumulation at the gel-to-liquid phase transition of the liposome membrane in mild hyperthermia can target the tumor tissue (Kim *et al*., 2014).

It have proved to increase the tumor accumulation by targeting of αvβ3 integrin by the small-size peptide, cyclic arginine-glycine-aspartic acid (cRGD)-modified nanocarrier which can be used in many types of cancer. By attaching cRGD, which binds to αvβ3 integrin by Kim and his group proved the thermo sensitive liposome by a tumor-specific targeting and thermally triggered release technique. To introduce the drug carrier they used thermally triggered with a PEGylated liposome. They design liposome by incorporating a bio-inspired elastin-like polypeptide (ELP) that consists of a Val-Pro-Gly-Val-Gly (VPGVG) pentapeptide which has lower critical solution temperature (LCST) polymer. CRGD and ELP were mixed with a hydrophobic alkyl chain then fuse with the liposome membrane. When the liposome targeted tumor cells by cRGD, it released the drug by polypeptide shrinkage with hyperthermia site (Kim *et al*., 2014).

Goal of the Liposome is the perfect nanomedicine to treat cancer disease

Many modifications have been done to improve the liposome in pharmaceutical world, and because of this reasons we can get many kinds of liposomes in market. For example, by change the lipid bilayer we can get more stability in liposome, by modifying the surface with polyethylene glycol (PEG) the circulation time will increase (van der Meel *et al*., 2014). To treat cancer with a new method, the liposome with pH sensitive in nanomedicines could be an ideal method to manipulate the releasing of the drug in the acidic condition. The circulation time has a relationship with the accumulation in tumor cell, as long as the circulation time long the accumulation of the liposome will increase in tumor cells. Even the size of liposome will affect the localization, and the liposome will target the tumor cells (van der Meel *et al*., 2014). The main goal to develop liposomes is to increase the circulation time and to avoid the clearance. Liposome just interact with tumor cell due to the modification on liposomes surface which lead the liposome release the drug which can use the permeability of the membrane to transfer to tumor cells.

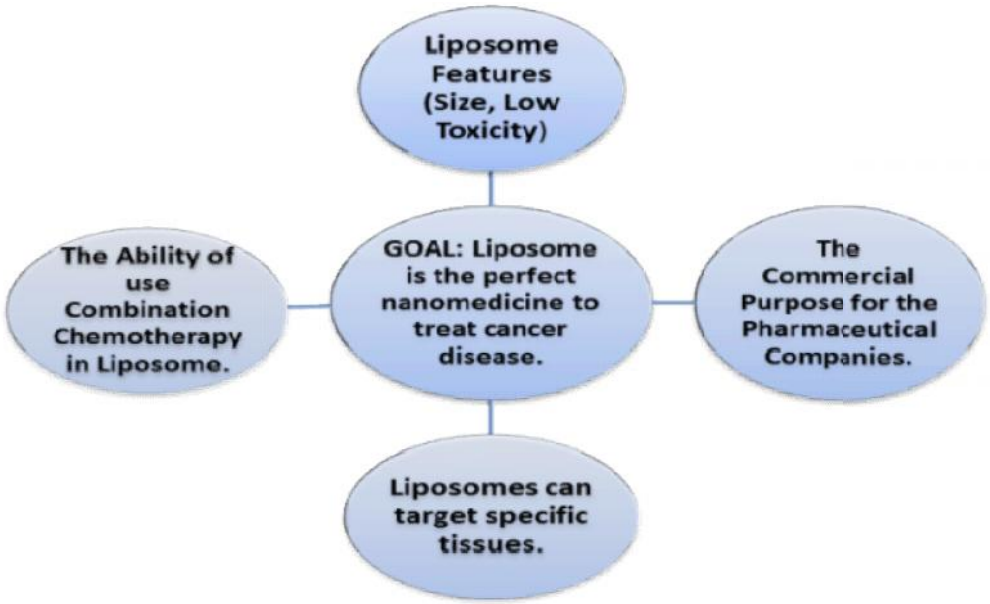

Fig. 2. The most important reasons which proved the ability of liposome to treat cancer disease

PH-sensitive liposomes are the most features of liposomes which have many researches and attracted scientist. Scientist exploited the lower pH of endosome than extracellular feature of cancer cells to develop liposome. As a result to the discovered of the pH cancer environment which is an acidic it becomes the most effective technique for nano drug delivery. They expect to develop nano drug delivery in near future for cancer therapy. They want to offer in the same time the detection of the cancer with the treatments. The developments of liposomes make scientists reach their aim to be successful in nanomedicines world, their property to encapsulate with different size from nano to micro size of drug.

Liposome Features (Size, Low Toxicity)

The nano size of liposomes can be obtained by extrusion or sonication techniques the formulation of liposome done, after transfer a large amount of energy to the membrane (van der Meel *et al*., 2014). The lowest liposome size 30 nm while between 40nm-900 nm the opalescence shown from the liposomes. The small size of liposomes can go to the space of Disse from the liver sinusoidal through the permeability of the sinusoidal wall. Liposomes size effect the uptake in the body tissue, if the liposome size large the clearance done in spleen and enhanced the uptake by the physical barriers (van der Meel *et al*., 2014). Liposome with size 400 nm can pass the hepatic sinusoid of the liver by their fenestration. The liposome which contains lager drug will involve the deformation mechanisms after they pass the membrane fenestrations (Lammers *et al*., 2012 and Romero *et al*., 1999). The drug toxicity becomes an impediment factor for cancer treatment because of the side effects which lead doctors to reduce the drug dosage to avoid the damage. The traditional cancer treatment will affect both healthy and cancer cells without identify the cancer cell. The side effects starts from nausea, losing hair, nerves, and damage of the kidney (Malam *et al*., 2009).

The Commercial Purpose for the Pharmaceutical Companies

Pharmaceutical companies want to reduce the cost and the time during developing a new drug, because of this reason they look toward encapsulate the drug and use a new delivery method to target the specific cells. Pharmaceutical companies make many researches to maintain their commercial monopoly to be in advance stage between each other. The developments on pharmaceutical research make the chance to treat different diseases such as cancer. Pharmaceuticals companies possess the tool to guide scientist toward more Innovations on drug such as nondrug (DiMasi *et al*., 2003). Innovation is the key for pharmaceutical companies to discover drugs, we can see the development in a healther life , many diseases becomes more easy to treat such as cancer (Khanna, 2012).

The Ability of use Combination Chemotherapy in Liposome

Liposome has the potential to treat cancer because during the formulation it encapsulate with chemotherapy drug, then can reach the tumor cells (Yang *et al*., 2011; Hollande *et al*., 2010 and Laginha *et al*., 2005). Using liposome encapsulated with chemotherapy will reduce the unwanted targets by the passive targeting technique which depends on the vascular permeability and weakness lymphatic drainage in tumor cells. Some trails done on mice to ensure that the significant result make scientists be sure that the more antibodies will lead to more destruction on cancer cells (Loi *et al*., 2010).

Liposomes can target specific tissues

During cancer therapy the permeability aim is to increase the localization and deliver of anticancer drug to diseased tissue rather than normal tissue (Kono *et al*., 2010). To achieve this aim, scientists developed many nano carrier that depends on stimuli such as (pH, Temperature, light, enzyme). Controlled release system depends on temperature has advantages by using external device such as radio frequency, microwave (Ranjan *et al*., 2012). Temperature-sensitive liposomes are a new technique used by heated the tumor from external device. The old thermo sensitive liposomes contains of a gel-to-liquid phase which can be transition at higher temperature than the physiological temperature. Lysolipids and synthetic temperature-sensitive polymers have been approved in the developed temperature-sensitization of liposomes (Ta and Porter, 2013).

The liposome can recognize the tumor cell due to the microenvironment of this cell are is highly acidic different than healthy tissues, tumor cells features such as the active metabolism (Liu *et al*., 2014). In cancer therapy they widely use the pH-sensitive because the sensitive pH in cancer cell than the healthy cells, the PH in healthy cell is 7.4 where the tumor cells are between 5.7-7.8 (Stubbs *et al*., 2000). They treat patients with the key of this factor the pH sensitive, because the pH are different from organs to anther and from healthy tissue to tissue with tumor, infection and others. PH sensitive is an important factor to develop nanomedicines because their ability to reach cancer cells.

Importance of the model

Until now most of the cancer diseases happens without any reason, and this is making cancer more a challenge for doctors and scientists. Some of cancer diseases such as breast cancer could happen due to some change or existence of one kind of gene in the human body. I believe if we make more researches on liposome based on drug delivery, we will get many benefits for cancer treatments and other diseases. Cancer cells are different than other cells, we can describe them as a hungry cell, and beside we can't use the liposome because of it is feature of sensitivity to pH and temperature to achieve the cancer cell. Doxorubicin encapsulated inside liposome, has been approved by FDA and used in chemotherapeutic to treat cancer. My goal in this paper is to prove more regulated description about liposome for cancer treatment. I want for the reader to distinguish the most important benefits in liposome. From the size of liposome, to the attachment of some antibodies to liposome's surface, the physical features of the liposome, and provide deep understanding to tumor cells that will lead us to a perfect cancer treatment. The nanomedicines can recognize the tumor cell due to the microenvironment of this cell are highly acidic different than healthy tissues, tumor cells features such as the active metabolism (Liu *et al*., 2014). By use the PH-sensitive in this tumor cell, targeted the cancer become more impossible (Liu *et al*., 2014).

Conclusion

Many researchers have been done to improve the liposomes ability to treat cancer disease. Since the discovered of liposome until now the promise advantages of liposome make these nano carriers become the ideal method to treat patients. We can avoid the side effects of chemotherapy by using liposome. Our manipulation of liposome surface will make the achievement to diseased cell easy. By modifying the liposome with different ligands it will enhance the liposome ability to target tumor cells, release the drug, and decrease the side effects. We can increase the circulation time for liposome, we can attach antibodies to liposome's surface or to the remote tale termini of the liposome's-grafted PEG chains. The two promising methods PH-sensitive and thermal sensitivity liposome can make the liposome the ideal method to treat cancer. Create a liposome with PH-sensitive and thermal sensitivity will affect the therapeutics for these reasons, using thermal sensitivity strategy leads to accumulating the drug at the tumor site because of the vascular permeability which is increased by thermal sensitivity. Using the pH property of cancer cells where is an acidic microenvironments is a powerful tool to increase the efficacy of targeting tumor cells and the accumulation.

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