Available online on 15.04.2019 at http://ajprd.com

Asian Journal of Pharmaceutical Research and Development

Open Access to Pharmaceutical and Medical Research

© 2013-18, publisher and licensee AJPRD, This is an Open Access article which permits unrestricted non-commercial use, provided the original work is properly cited

Open Access

Review Article

Liposomal Formulations in Cancer Therapy: Passive Versus Active Targeting

Pandya Tosha *, Patel Kaushika, Pathak Rudree, Shah Shreeraj

Department of Pharmaceutics, LJ Institute of Pharmacy, LJ Campus, Sanand circle-382210, Ahmedabad, Gujarat, India

A B S T R A C T

In Cancer therapy, Nano drug delivery system comprising of Liposomes, are the most successful mode of treatment in present scenario which also has real time clinical application. Recently it is found that the closed bilayer phospholipid vesicles have many technical advantages over the initially used liposomal formulations. The delivery of therapeutics encapsulated in liposomes changes the biological distribution profile and improves the drug therapeutic indices of various drugs. This review article throws light onto many clinical liposomal drug delivery products. The liposome Nano drug delivery by the active and passive targeting is a boon as it can reduce the off-targeting effects. The current development is more focused on the diagnostic and clinical applications. Receptor targeted delivery systems are extensively explored for active targeting. However, these delivery systems are rarely seen in the clinical application because of conjugation chemistry and other implicit hurdles to develop this system.The development of nanocarriers in the cancer treatment have enormous potential in the medical field. Moreover, Immuno liposomes have been used in cancer treatment as attractive drug targeting vehicles. On the other hand, there are many other liposomal drug delivery systems having passive targeting mechanism for cancer treatment which are widely used due to enhanced retention and permeability of formulation. This review majorly focuses on the current challenges encountered in development of liposomal Nano drug delivery systems and its effective development for cancer treatment.

Key words: Liposomes, Targeting, Nano drug delivery systems, active targeting

A R T I C L E I N F O: Received 4 March 2019; Review Completed 30 March 2019; Accepted 9 April 2019; Available online 15 April 2019

Cite this article as:

Pandya Tosha *, Patel Kaushika, Pathak Rudree, Shah Shreeraj, Liposomal Formulations in Cancer Therapy: Passive Versus Active Targeting, Asian Journal of Pharmaceutical Research and Development.**2019; 7(2):35-38**

DOI: http://dx.doi.org/10.22270/ajprd.v7i2.489

***Address for Correspondence:**

Tosha Pandya, Department of Pharmaceutics, LJ Institute of Pharmacy, LJ Campus, Sanand circle-382210, Ahmedabad, Gujarat, India

INTRODUCTION

In pharmaceutical field the development of the liposomes drug delivery plays significant role. The first-time liposomes were described by Alec Bangham, in 1961[1]. The development and research in liposomes leads to real time clinical application in various medical area like gene delivery, biomolecules and drug delivery[2]. The structural components of the liposomes include phospholipids incorporated with cholesterol sterols. For preparation of liposomes Thin-film hydration is the most commonly used method. In this method, liposome lipid components with or without drug are dissolved in organic components like chloroform. There are several techniques such as sonication, extrusion, ethanol injection and freeze-drying used to obtain desired sized liposomes. However, liposomes are processed and formulated in different size, charge, lamellarity and composition. Therefore, in the current market research the clinical development is booming and many market products are available for human use. The Encapsulation of drugs in liposomes improve the therapeutic indices of various agents through changes in their pharmacodynamics and pharmacokinetics which is shown in **Figure 1**.

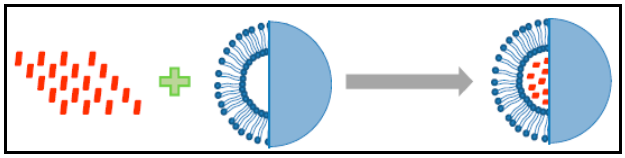

Figure 1: Liposomes with formulating the drug (32)

Observing the current world scenario every year 10 million new cases of cancer have been registered[3]. The potential of the cancer therapy depends on site specific drug delivery systems. Therefore, passive and active targeting approaches are used for targeting liposomal Nano formulations to cancerous cells[4,5]. In addition to this different gene and drug delivery systems cure cancer more effectively by reduced toxicity, improved biocompatibility and altering the pharmacokinetic profile of therapeutic agent[6]. The coating of polyethylene glycol on the liposomes enhances the blood circulation half-life, permeability and retention time. This phenomenon is known as the passive targeting. However, passive targeting has many challenges and improvement in design strategy is required for enhanced targeting. Therefore, liposomes can be developed with targeting ligand conjugated with formulation[7-9]and target the cancer cell to improve overall tumor accumulation. The selection of the receptor and targeting ligand is important parameter in drug delivery for cancer treatment[10]. Therefore, numerous research and studies have been carried out for immunoliposomes for the cancer treatment by targeted drug delivery for various types of cancer disease such as breast cancer, colorectal cancer, lung cancer, etc.[11,12]. The function of immunoliposomes in cancer treatment is to reduce the accumulation of drug in healthy tissues and increase the drug delivery to tumour by antibody-mediated guiding of the liposomes[13,14]. The following section briefly discusses about the liposomes in the cancer treatment.

LIPOSOMES IN CANCER THERAPY

Liposomes are nothing but small artificial vesicles with spherical shape created by natural non-toxic phospholipids and cholesterol. The liposomes have hydrophobic and hydrophilic characteristics due to which it is widely used in the drug delivery systems[15-17]. However, liposomes have different properties because of various size, methods of preparation, lipid composition and surface properties. There is wide application of liposomes in pharmaceutical and cosmetic industry as carriers for numerous molecules because of its high potential in many treatments. The liposomes can avoid decomposition of the entrapped combinations, release the entrapped at designated targets and trapped hydrophilic and hydrophobic compounds[18,19]. The size of the liposomes are vary from 0.025 µm to 2.5 µm vesicles. As we have discussed in the previous section the liposomes have one or more bilayer membranes and the vesicle size is the important parameter to decide the circulation half-life of liposomes.

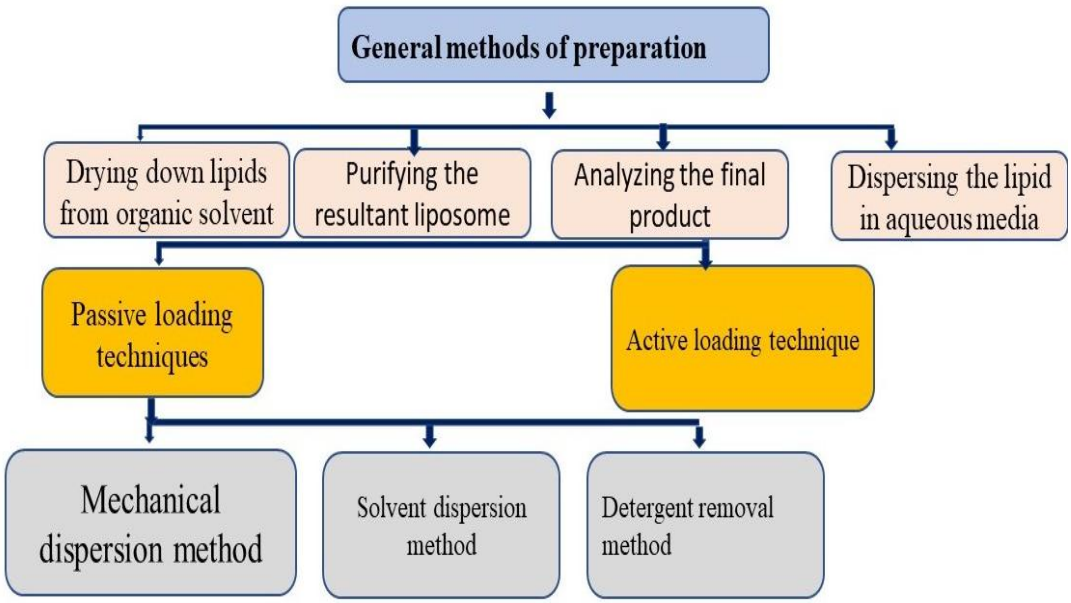

Figure 2: Various Methods of Liposome

Based on the liposomes size and the bilayers it can be classified as multilamellar vesicles and unilamellar vesicles. The further classification of the unilamellar vesicles are large unilamellar vesicles and small unilamellar vesicles[20].In the multilamellar and unilamellar liposomes the vesicle has onion structure and single phospholipid bilayer sphere respectively[21]. The methods of liposome preparations are shown in **Figure 2** There are several advantages of the liposomes such as increased stability of therapeutics via encapsulation, reduced exposure of sensitive tissues to toxic drugs, flexibility to couple with site-specific ligands to achieve active targeting, increased efficacy and therapeutic index of drug[22]. There are other several benefits of drug loaded in liposomes such as Passive targeting to the cells of the immune system, especially cells of the mononuclear phagocytic system, improved transfer of hydrophilic, charged molecules, Site-avoidance mechanism and specific targeting[23].

PASSIVE TARGETING IN CANCER

The passive targeting in the cancer is the process of accumulating the drug at the site of action or around the tumour tissues. Such process is known as the Enhanced Permeability Retention effect (EPR)[24]. It is very difficult to say it is a form of selective targeting as per the research data. However, Enhanced Permeability Retention effect considered for the nanoparticle drug delivery system and

more than 95% of the nanoparticles were found accumulate in organs indicating the delivery of drug through blood[25]. The retention and compromised vasculature permeability can be helpful in the macromolecules accumulations and it would increase the tumour concentration by70-folds[26]. The leaky vasculature present in the cancerous tissues will be advantageous for such type of targeted drug delivery systems. The development of the leaky vasculature because of the vascularization and Enhanced Permeability Retention effect to poor lymphatic drainage. The nanoparticle size, surface area and shape are very important for the effectiveness in the tumour targeting, as they affect the circulation time and targeting efficiency. Normally, the nanoparticle size of around 10nm is most favourable to avoid the renal filtration[27]. Such characteristics of the particles in the passive targeting is one of the solutions to overcome problems as size tailored particles can follow diffusion-mediated transport. In such transportation the size of the particles is the key factor. The size of the molecules in drug loaded dextran particles was larger, due to which it accumulated in the interstitium and fond very less effect in the vascular surface. The homogenous distribution of the small particles and upper maximum limit of 400 nm is essential for enhanced transport efficiency[28]. It was observed that 40-200 nm sized nanoparticles have longer circulating time, low renal clearance rate and accumulate at tumour site specifically[29]. Another important factor is aspect ratio of the nanoparticles. The aspect ratio is dealing with the uptake of the particles. It was observed that uptake of 450nm height and 150nm diameter particles was four times faster than the symmetrical particles having aspect ratio of 200nm30.

The internalization of nanoparticles into cells is possible by good surface characteristics of the particles. The nanoparticle surface can be modified using polymer composition in order to overcome extra amount of hydrophobicity of the nanoparticles. One such surface modification approach is PEGylation in which surface of particles is coated with Polyethylene Glycol which helps Nano system escape the Reticulo-endothelial system clearance[4,28]. The passive targeting for the drug delivery system can be effective by controlling the shape, size and surface modification of the nanoparticles. On the other side the main disadvantage of such system is their detrimental effect on healthy tissues of the body just like the chemotherapeutic regimen.

ACTIVE TARGETING IN CANCER TREATMENT

The active targeting is described as the ligand and receptor interactions. The interaction between the receptor and the ligand is possible when the propinquity may be lesser than 0.5mm.The recently developed drug delivery systems are delivered by active targeting through extravasation and blood circulation[31].

Basically, active targeting is divided into three order targeting such as First, second and third order targeting. In the first order targeting the drug is delivered to the capillary beds, to the organ or to targeted tissue such as pleural cavity, lymphatic tissue, cerebral ventricles, joints peritoneal cavity etc. In second order active targeting the drug is targeting to the specific tumour cells like the kupffer cells in liver. In the third order active targeting the drug is delivered by the receptor-based ligand mediated entry and endocytosis to the site of action. The selection of the targeting agent is the significant factor in active targeted drug delivery system in order to deliver drug to cancer tissue without affecting the surrounding healthy tissue. The drug delivery system mostly depends on the capacity of ligands or the targeting agent to bind with tumour cell surface. In general, active targeting approach has the benefit of certain receptors being over expressed on the tumour surface. Polymeric micelles based Nano systems gave efficient results because of their surface chemistry[32]. However, the targeted nanocarriers have potential in comparison to the non-targeted ones in the site specific drug delivery by reducing toxicity. Float targeted drug delivery is the typical example of targeted drug delivery which is proven delivery since many years. In breast cancer, ovarian cancer[33,34] and osteocarcinomas the float receptors are over expressed. Therefore, the float receptor conjugated particles have chances to be internalized when highly over expressed float receptors are present. Polyethylene glycol particles enhance the circulating time in comparison to plain Doxorubicin particles in folate-receptor[35].

The conventional techniques are the most popular for targeted drug delivery to cancerous tissues and this strategy should be applied to target the imaging agents of concern organelles. This practice will improve the target delivery system effectiveness. Any formulation is to be examined on any patient with the imaging agent to get conformation of targeting of the delivered drug. The excessive expression of vasoactive intestinal peptide receptor in breast cancer can be used as targeting agent and the results state that active as well as passive targeting takes place to the treat breast cancer in *in vivo* settings[36,37].

CONCLUSION

The liposomes have significant characteristics of a potential drug delivery system and therefore find application in the pharmaceutical industries for delivery of ribosomes, DNA, proteins and anti-sense molecules. In addition to these, liposomes enhance the drug delivery to the targeted location of the disease increasing their clinically acceptability. Liposomal drug reduced toxicities and improves efficiency in comparison to free complements. Moreover, the recent trend of liposome and anti-body in the technology leads to effective targeted drug delivery and enhanced development of immunoliposome formulations for cancer treatment. The highly selective anticancer developed drug discriminates the tumor and normal cells. The use of ligand conjugated liposome-encapsulated drug is very promising for cancer cell or tumor. Thus nanotechnology is beingdeveloped and explored to fulfil the unmet need for cancer treatment. Both active and passive targeting of liposomes reduces the nonspecific biodistribution of chemotherapeutics and improves effectiveness of treatment at the same time reduces the side effects. However, clinical applications of convectional, PEGylated and immunoliposomes are under research and are showing their potential as an alternative therapeutic methods.

REFERENCES

1. Bangham AD, Standish MM, Watkins JC. Diffusion of univalent ions across the lamellae of swollen phospholipids. Journal of Molecular Biology. 1965; 13(1):238-IN27.

2. Lalani R, Misra A, Amrutiya J, Patel H, Bhatt P, Patil SK. Approaches and Recent Trends in Gene Delivery for Treatment of Atherosclerosis. Recent patents on drug delivery & formulation. 2016; 10(2):141-55.
3. Jarboe J, Gupta A, Saif W. Therapeutic human monoclonal antibodies against cancer. Methods in molecular biology (Clifton, NJ). 2014; 1060:61-77.
4. Bhatt P, Lalani R, Vhora I, Patil S, Amrutiya J, Misra A, et al. Liposomes encapsulating native and cyclodextrin enclosed paclitaxel: Enhanced loading efficiency and its pharmacokinetic evaluation. Int J Pharm. 2018; 536(1):95-107.
5. Ferrari M. Cancer nanotechnology: opportunities and challenges. Nature reviews Cancer. 2005; 5(3):161-71.
6. Torchilin VP. Recent advances with liposomes as pharmaceutical carriers. Nature reviews Drug discovery. 2005; 4(2):145-60.
7. Fay F, Scott CJ. Antibody-targeted nanoparticles for cancer therapy. Immunotherapy. 2011; 3(3):381-94.
8. Mamot C, Ritschard R, Wicki A, Stehle G, Dieterle T, Bubendorf L, et al. Tolerability, safety, pharmacokinetics, and efficacy of doxorubicin-loaded anti-EGFR immunoliposomes in advanced solid tumours: a phase 1 dose-escalation study. The Lancet Oncology. 2012; 13(12):1234-41.
9. Vhora I, Patil S, Bhatt P, Gandhi R, Baradia D, Misra A. Receptor-targeted drug delivery: current perspective and challenges. Therapeutic delivery. 2014; 5(9):1007-24.
10. Chou LY, Ming K, Chan WC. Strategies for the intracellular delivery of nanoparticles. Chemical Society reviews. 2011; 40(1):233-45.
11. Bhatt P, Khatri N, Kumar M, Baradia D, Misra A. Microbeads mediated oral plasmid DNA delivery using polymethacrylate vectors: an effectual groundwork for colorectal cancer. Drug delivery. 2015; 22(6):849-61.
12. Park YS. Tumor-Directed Targeting of Liposomes. Bioscience Reports. 2002; 22(2):267-81.
13. Suthar SM, Rathva BA. Development of Liposomal Formulation: From Formulation To Sterilization. World Journal of Pharmaceutical Research. 2019; 8(3):1561-71.
14. Bhatt P, Lalani R, Mashru R, Misra A. Abstract 2065: Anti-FSHR antibody Fab' fragment conjugated immunoliposomes loaded with cyclodextrin-paclitaxel complex for improvedin vitro efficacy on ovarian cancer cells. Cancer Research. 2016; 76(14 Supplement):2065.
15. Allen TM. Liposomes. Opportunities in drug delivery. Drugs. 1997;54 Suppl 4:8-14.
16. Sahoo SK, Labhasetwar V. Nanotech approaches to drug delivery and imaging. Drug discovery today. 2003; 8(24):1112-20.
17. Gabizon A, Goren D, Cohen R, Barenholz Y. Development of liposomal anthracyclines: from basics to clinical applications. Journal of controlled release : official journal of the Controlled Release Society. 1998; 53(1-3):275-9.
18. Benech RO, Kheadr EE, Laridi R, Lacroix C, Fliss I. Inhibition of Listeria innocua in cheddar cheese by addition of nisin Z in liposomes or by in situ production in mixed culture. Applied and environmental microbiology. 2002; 68(8):3683-90.
19. Shehata T, Ogawara K, Higaki K, Kimura T. Prolongation of residence time of liposome by surface-modification with mixture of hydrophilic polymers. Int J Pharm. 2008; 359(1-2):272-9.
20. Sharma A, Sharma US. Liposomes in drug delivery: Progress and limitations. International Journal of Pharmaceutics. 1997; 154(2):123-40.
21. Riaz M. Liposomes preparation methods. Pakistan journal of pharmaceutical sciences. 1996; 9(1):65-77.
22. Lalani R, Misra A, Amrutiya J, Patel H, Bhatt P, Patel V. Challenges in Dermal Delivery of Therapeutic Antimicrobial Protein and Peptides. Current drug metabolism. 2017; 18(5):426-36.
23. Pathak Nandish PP. Applications of liposome in cancer drug delivery and treatment: A review Asian Journal of Pharmaceutical Research and Development. 2019; 7(1):62-5.
24. Yewale C, Baradia D, Patil S, Bhatt P, Amrutiya J, Gandhi R, et al. Docetaxel loaded immunonanoparticles delivery in EGFR overexpressed breast carcinoma cells. Journal of Drug Delivery Science and Technology. 2018; 45:334-45.
25. Pathak N,Pathak P. Nanoparticles and Target Drug Delivery for Cancer Treatment: A Comprehensive Review. International Journal of Drug Regulatory Affairs.2019; 7(1):53-8.
26. Duncan R. The dawning era of polymer therapeutics. Nature reviews Drug discovery. 2003; 2(5):347-60.
27. Davis ME, Chen ZG, Shin DM. Nanoparticle therapeutics: an emerging treatment modality for cancer. Nature reviews Drug discovery. 2008; 7(9):771-82.
28. Alexis F, Pridgen E, Molnar LK, Farokhzad OC. Factors affecting the clearance and biodistribution of polymeric nanoparticles. Molecular pharmaceutics. 2008; 5(4):505-15.
29. Liechty WB, Peppas NA. Expert opinion: Responsive polymer nanoparticles in cancer therapy. European journal of pharmaceutics and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik eV. 2012; 80(2):241-6.
30. Vhora I, Patil S, Bhatt P, Misra A. Protein- and Peptide-drug conjugates: an emerging drug delivery technology. Advances in protein chemistry and structural biology. 2015; 98:1-55.
31. Lalani RA, Bhatt P, Rathi M, Misra A. Abstract 2063: Improved sensitivity and in vitro efficacy of RGD grafted PEGylated gemcitabine liposomes in RRM1 siRNA pretreated cancer cells. Cancer research. 2016; 76(14):2063.
32. Wakaskar RR, Bathena SP, Tallapaka SB, Ambardekar VV, Gautam N, Thakare R, et al. Peripherally cross-linking the shell of core-shell polymer micelles decreases premature release of physically loaded combretastatin A4 in whole blood and increases its mean residence time and subsequent potency against primary murine breast tumors after IV administration. Pharmaceutical research. 2015; 32(3):1028-44.
33. Bhatt P, Vhora I, Patil S, Amrutiya J, Bhattacharya C, Misra A, et al. Role of antibodies in diagnosis and treatment of ovarian cancer: Basic approach and clinical status. Journal of Controlled Release. 2016; 226:148-67.
34. Gandhi M, Bhatt P, Chauhan G, Gupta S, Misra A, Mashru R. . IGFII-Conjugated Nanocarrier for Brain-Targeted Delivery of p11 Gene for Denhanced permeability and retention (EPR)ession. AAPS PharmSciTech. 2019; 20(2):50.
35. Ambardekar VV, Wakaskar RR, Sharma B, Bowman J, Vayaboury W, Singh RK, et al. The efficacy of nuclease-resistant Chol-siRNA in primary breast tumors following complexation with PLL-PEG(5K). Biomaterials. 2013; 34(20):4839-48.
36. Tandel H, Bhatt P, Jain K, Shahiwala A, Misra A. In-Vitro and In-Vivo Tools in Emerging Drug Delivery Scenario: Challenges and Updates. In: Misra ASA, editor. In-vitro and in-vivo tools in drug delivery research for optimum clinical outcomes. Boca Raton: CRC Press; 2018.
37. Javia A, Amrutiya J, Lalani R, Patel V, Bhatt P, Misra A. Antimicrobial peptide delivery: an emerging therapeutic for the treatment of burn and wounds. Therapeutic delivery. 2018; 9(5):375-86.
1.