

A Brief Review on Therapeutic Potential of Nanocarrier Systems Against Breast Cancer

Swarupananda M*, Saumyakanti G, Subhasis M and Bijaya G

NSHM College of Pharmaceutical Technology, NSHM Knowledge Campus, Kolkata Group of Institutions, (60) 127 BL Saha Road, Kolkata 700053, West Bengal, India

ABSTRACT

Now a day's breast cancer is one of the major type of non-cutaneous cancer occurred in female bodies. There are many approaches to treat this type of cancer, but significant treatments for breast cancer are truly limited. Not only the existing treatments are very low in number, but they have number of toxicity issues also. That is why now nano carrier based approaches are under the spot light and researchers are trying to explore this novel area of treatment for breast cancer. The success of any anticancer chemotherapy truly depends on the ability of the drug to reach their targeted body site, where the abnormal cell growth has occurred. Conventional types of treatment has no such targeting benefits. The nanocarriers based drug delivery systems are having some great advantages. These carrier systems have great specific targeting ability; they can modify the bio-distribution and pharmacokinetic profiles of the therapeutic agents. That is why nanocarriers are having lesser cytotoxic side effects than the conventional type of treatments. And these benefits make these carrier systems unique. The popular nanocarriers used for today are liposomes, carbon nanotubes, micelles, quantum dots, nanoparticles, gold nanoparticles, solid lipid nanoparticles etc. This review is a brief discussion about the nanocarriers used for breast cancer today and their advancements.

Keywords: Breast cancer; Nanocarriers; Liposomes; Nanosomes

INTRODUCTION

Breast cancer is one type of heterogeneous disease and it is having different type of subcategories. It is reported that approximately 7% of breast cancers occurred in women who are having age below than 40 years and less than 4% in women below the age of 35 years [1]. In young women breast cancer is not generally common [2]. Cancer is caused by damage or mutations. Generally surgery and radiotherapy are the primary treatments for local and non-metastatic cancers while anti-cancer drugs (chemotherapy, hormone and biological therapies) are the choice of metastatic cancers. The basic principle of the chemotherapy is the inhibition of the division of rapidly growing cancer cells. But this therapy also affects normal cells those are having fast proliferation rates, such as the hair follicles, bone marrow and gastrointestinal tract cells, generating the characteristic side effects of chemotherapy. Nanocarriers are the small carrier molecules having size range between ten to hundred nanometers. These are mainly cluster of molecules, atoms and molecular fragments. The most popular nanocarriers used for today are liposomes, carbon nanotubes, micelles, quantum dots, nanoparticles, gold nanoparticles, solid lipid nanoparticles etc.

COMMON DRUG CARRIERS USED IN BREAST CANCER

Liposome

Liposomes are one of the most common types of novel drug delivery system for breast cancer treatment (Figures 1 and 2). Liposomes can improve the pharmacological properties of the drugs by changing its distribution and pharmacokinetic profile in the body [3-5]. The liposomal-based chemotherapeutic agents have been passed the clinical trials successfully. And that is why these formulations are currently used for the treatment of the breast cancer. Doxil is one example of the approved liposomal preparations [6]. Liposomes loaded with chemotherapeutic drugs like doxorubicin (Doxil) and daunorubicin (DaunoXome) have been approved by FDA since the mid-1990s. Liposomes are also called as colloidal carriers and are made up of bio-compatible, bio-degradable, natural phospholipids. We can encapsulate water-soluble, fat-soluble, amphiphilic, biphasic insoluble drugs and cytotoxic agents into their aqueous core or their unilamellar/multilamellar membranes depending upon the solubility of the

Correspondence to: Swarupananda M, NSHM College of Pharmaceutical Technology, NSHM Knowledge Campus, Kolkata Group of Institutions, (60) 127 BL Saha Road, Kolkata 700053, West Bengal, India, E-mail: swarupananda.mukherjee@nshm.com

Received: February 01, 2019, **Accepted:** March 12, 2019, **Published:** March 20, 2019

Citation: Swarupananda M, Saumyakanti G, Subhasis M, Bijaya G (2019) A Brief Review on Therapeutic Potential of Nanocarrier Systems Against Breast Cancer. J Biomol Res Ther, 8: 174.

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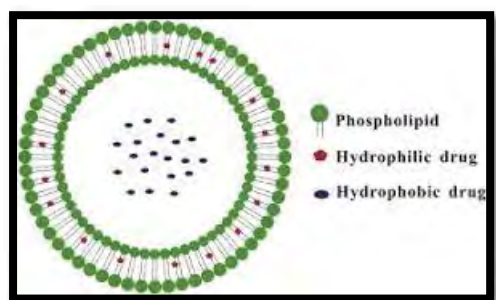


Figure 1: Principle construction of a liposome.

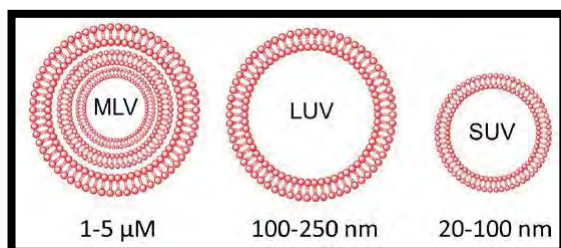


Figure 2: Different types of liposomes.

API. Liposomes have two parts, one is lipid bilayer membrane part and another is aqueous core part. Liposomes are generally classified into three types: Small Unilamellar Vesicles (SUV), Large Unilamellar Vesicles (LUV) and Multilamellar Vesicles (MLV) [7]. Liposomes are generally preferred for the following reasons. One is liposomes provide slow and sustained release, secondly they reduce cytotoxicity of the chemotherapeutic agents and thirdly they enhance the drug accumulation. New researches on liposomes are now based on modifying the drug release from liposomes. For example, drug release from liposomes can be triggered by various factors [8,9]. For example drug release can be triggered by ultrasound enzymes light, magnetism etc. [10-16]. Liposomes can also be attached with some ligands. These ligands basically act for targeting purpose. Ligand mediated liposomes are used for the targeted delivery of nucleic acids [17-20]. Doxil is one of the classic examples of nanocarriers used in breast cancer. It is constituted with cholesterol and Hydrogenated Soy Phosphatidylcholine (HSPC). HSPC is having high phase-transition temperature that leads to a stable drug delivery system with improved efficacy and reduced side effects [21]. Shahun had formulated one type of liposomes which can be loaded with Doxorubicin (DOX). This liposome can be targeted actively by using peptide ligands known as P18-4 [8]. Recently Dagar developed a vasoactive intestinal peptide receptors (VIP-R). This VIP-R is used in breast cancer for targeted imaging purpose. VIP-R is basically a mammalian neuropeptide which was attached to the surface of the Sterically stabilized Liposomes (SSL) covalently, which was further encapsulated to a radionuclide (Tc^{99m} -HMPAO). Further studies revealed that VIP-R is more expressive in case of human breast cancer by five times in comparison with other imaging probes [22].

Micellar nanoparticles

These are also highly specific nanocarriers, consist of a core and a shell in structure (Figure 3). These are basically colloidal particles, which are having size between 5 to 100 nanometers. Micelles mainly consist of surfactants. Surfactants are amphiphilic in nature. They are having a polar head portion which is hydrophilic in nature. And another portion is non-polar, hydrophobic tail portion. These surfactants exist as monomers in low concentration. But when we

increase the concentration of the surfactants gradually then above the critical micelle concentration (CMC) they form micelles. These micelles have a hydrophilic core, in which we can incorporate hydrophobic drugs. Micelles are very useful for targeting the in to the site of action. A classic example of micelles is Genexol-PM (approved by FDA in 2007) which is loaded with the anticancer drug paclitaxel [23-25]. It is composed of mPEG-PLA polymers. It showed not only greater targeting action but it showed to reduce the severe toxic effects such as hypersensitivity reactions, hyperlipidemia also.

Dendrimer

Origin of the word Dendrimer is from the Greek word "dendron". Dendron means 'tree-like structures'. Dendrimers were synthesized by Buhleier et al. and Tomalia et al. from 1970-1990 [26,27]. There are different types of dendrimers based on their shape and size. They show higher biocompatibility. Chemical modification in the structure of dendrimers could lead to a better carrier. Recently, Wang had synthesized G4 Polyamidoamine dendrimer (G4 PAMAM-D). It is conjugated with Antisense Oligodeoxynucleotides (ASODN). This conjugated carrier system shows greater stability in the body with less toxicity. It also showed increased bioavailability. Further *in vivo* studies revealed that this conjugated system has more accumulating power to inhibit tumor than naked ASODN [28].

Virus-based nanoparticles (VNPs)

Virus-Like Particles (VLPs) are self-assembled robust protein cages having uniform nanostructures and well-defined geometry. Their size is approximately less than 100 nm. Recently scientists are exploring VNPs widely. These VNPs are also used in various purposes excluding drug delivery. Viruses from different sources are used for VNPs. Recently it is found that plant viruses (Cowpea Mosaic Virus [CPMV], Red Clover Necrotic Mosaic Virus [RCNMV], Tobacco Mosaic Virus [TMV], Cowpea Chlorotic Mottle Virus [CCMV]), insect viruses (Flock House Virus), bacterial viruses or bacteriophages (MS2, M13, Q β) and animal viruses (adenovirus, polyomavirus) have the potential to act as a drug delivery carrier [29-31].

Polymers

Polymeric nanoparticles are also used for universal drug delivery carriers. These are formed by attaching a copolymer to a polymer matrix. Cellulose, chitosan, alginate, and gelatin are the most common polymers those are used for the preparation of polymeric nanoparticles. These polymers are having several advantages. The most important advantage is that they are biocompatible and biodegradable. They also slow down the drug degradation rate, increase the drug stability. Chemotherapeutic drugs like paclitaxel,

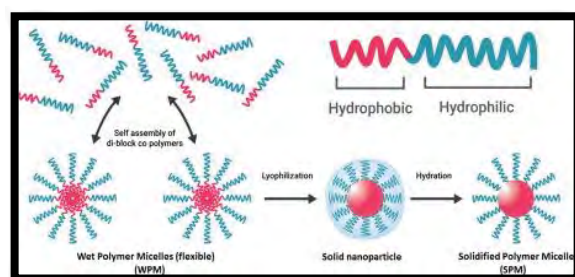


Figure 3: Different pattern of Micellar nanoparticles.

doxorubicin, camptothecins, and platinates have been successfully clinically tested through these polymeric nanocarriers.

Gold carriers

Gold carriers have a core of gold atoms. These atoms could be functionalized by the attaching of unilayer of thiol (SH)-containing groups [32,33]. These carrier molecules are synthesized with the help of thiol-containing groups. These thiol containing groups actually forms a layer around the gold atoms. The first clinical trial with gold carriers done in 2009 [34].

Magnetic carriers

These are also a type of special carriers those are used in breast cancers (Figure 4). These are generally placed into the bloodstream of the patient and a magnetic field is focused over the target site [35]. The first clinical trial report came in 1996 [36].

Albumin carriers

Body protein albumin is also widely used as a drug carrier. It is having good solubility in both water and ethanol. Albumin is an integrated part of our own human body system that makes it non-toxic, well-tolerated and higher half-life in blood circulation [37]. The first anticancer drug containing albumin carrier is Abraxane, paclitaxel is attached to this carrier [38].

Carbon carriers

Carbon Nanotubes (CNTs) are the carriers those are the members of the fullerene family. Structurally CNTs are made up of benzene rings rolled-up into the tubular structure (Figure 5). CNTs are having two classes based on their structure. One is Single-Walled (SWNTs) CNTs, and another is Multi-Walled (MWNTs) CNTs. SWNTs are made up of one layer of cylinder graphene and MWNTs contains multiple concentric graphene layers. There are some extraordinary features of CNTs. They have well organized structure, very light weight, high mechanical strength, and high surface area [39]. These

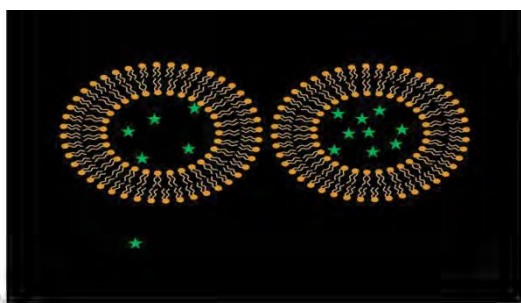


Figure 4: Magnetic nanoparticles.

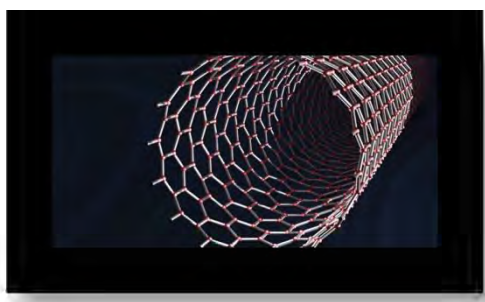


Figure 5: Carbon nanotube.

properties make CNTs a good candidate for drug delivery in case of breast cancer [40].

CONCLUSION

Nanotechnology is relatively new in cancer treatment. It has a great potential in the treatment of different types of cancer including breast cancer and from the research it is very clear that nanocarriers are now one of the promising tools for cancer treatment and drug delivery. Still there are some limitations to use these nanocarriers. The targeting mechanisms of the nanocarriers and the development of multi-drug resistances should be investigated more carefully. In spite of these limitations there are numerous benefits of these nanocarriers and these advantages make them one of the most promising treatments for breast cancer.

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