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Trends in Nanotechnology for the Treatment of Breast Cancer

Sonali B. Diwate[1*], Ziyaurrahmam Ataurrahman[1] and Kiran S. Bhise[1]

[1]Department of Pharmacology, M.C.E. Society's Allana College of Pharmacy, Camp, Pune, Maharashtra, India.

Authors' contributions

This work was carried out in collaboration among all authors. Author SBD designed the study, managed the literature searches, performed the summarization of data and wrote the first draft of the manuscript. Authors ZA and KSB reviewed and corrected the manuscript. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Breast cancer is the most common and progressively increased form of cancer mostly among women. Various therapies have been tried to cure this cancer but none of them is without side effect. These might be attributed to the indiscriminate destruction of normal cells along with cancer cells or other systemic effects of the chemotherapeutic agent. These difficulties initiate the urge to develop targeted drug delivery systems. Nanotechnology deals with formulation of nanostructures for innovative drug delivery. Nanodrug delivery systems are being used for targeting in the treatment of various diseases, hence this concept is also applicable to the treatment of breast cancer. Nanoparticles have an additional effect of improvement in the solubility of drugs such as paclitaxel, reduction in dose and toxicity, increased cellular uptake etc. Owing to smaller size these are easily taken by tumor cells and effectively encapsulate the hydrophobic drugs. This review is aimed to summarize the various management therapies majorly focusing on the recent nanodrug delivery systems to target chemotherapeutic agents in the breast cancer cells. Various nanodrug systems are in clinical trials and few of them are already in the market. These are promising tools for future cancer treatment and research.

**Corresponding author: E-mail: sonalirchintamani@rediffmail.com;*

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1. INTRODUCTION

Breast cancer is a group of diseases in which cells in the breast tissue undergo modification and uncontrolled multiplication leads to the formation of mass or lump. Most breast cancers initiate in the milk glands (lobules) or in the ducts that attach the lobules to the nipple. The most prevalent physical observation is the formation of a hard painless lump which might be enlarged. Sometimes symptoms such as heaviness or pain in the breast change in shape, ulceration, erythema, thickening and swelling of the breast might be seen. Nipple modulations, retraction or scaliness and spontaneous discharge from the nipple especially bloody discharge might be observed. Occasionally breast cancer spreads to lymph nodes of the underarm resulting in swelling or lump formation [1]. The major causes of breast cancer are previous history, significant family history, Genetic predisposition (Abnormal inherited genes *BRCA1* and *BRCA2*), hormonal causes, lifestyle and dietary causes (alcohol consumption), anthropometry (higher weight, weight gain during adulthood and body fat distribution) and environmental reasons (exposure to X-rays) [2].

Majorly breast cancer is divided as Non-invasive and Invasive based on site. Briefly, non-Invasive cancer is limited to ducts; does not spread to surrounding connective and fatty tissue. It is further categorized as ductal carcinoma *in-situ* (DCIS) and lobular carcinoma in-situ (LCIS). The former is most common while the latter is rare and lethal. In the case of lobular carcinoma *in-situ*, the uncontrolled growth of cells within breast lobules takes place. Invasive breast cancer spreads through ducts, lobular walls and invades nearby connective and fatty tissue [3]. Stages of breast cancer have been grouped into different levels starting from stage 0 to IV based on tumor, node and metastasis [4].

Breast cancer is the leading cancer death in women all over 100 countries, impacting 2.1 million women per year in 2018. 571000 women died because of breast cancer in 2015. It is the most widely diagnosed cancer in the majority of countries. Survival rates of breast cancer differ greatly world-wide. Survival rates ranged around 80% in Sweden, Japan and North America, 60% in middle-income countries and 40% in low-income countries. These variations might be attributed to delayed detection, inadequate diagnosis and treatment facilities [5]. Recently numerous approaches were developed for the treatment of breast cancer. This review majorly focused on the different nanotechnology based drug delivery systems for the treatment of breast cancer.

2. BREAST CANCER MANAGEMENT STRATEGIES

Depending on the various stages various strategies could be deployed for the treatment of breast cancer. A few of them are summarized below:

2.1 Surgery

Surgery might be recommended for removal of cancer as much as possible (mastectomy), to check whether cancer has propagated to the lymph nodes under the arm (axillary lymph node dissection), to restore the breast's shape after the cancer is removed (breast reconstruction).

2.2 Radiation

To destroy cancer cells high energy rays or particles are used, known as radiation therapy. This strategy is used in several situations especially after breast surgery to avoid the recurrence of cancer and when cancer is propagated in many organs such as bone or brain. Side effects of the radiation include fatigue, swelling of the breast, redness, darkening of skin and skin peeling. Long term side effect includes firmer and smaller breast, the problem in breastfeeding, damage to nerves of the arm resulting in pain, numbness, weakness in shoulder and arm.

2.3 Hormone therapy

Estrogen and progesterone help the cancer cell to grow as cancer cell have the receptor for attachment of these hormones. Treatment in which attachment of hormones to cancerous cells is prevented is referred to as endocrine or hormone therapy. Tamoxifen drugs block the estrogen receptor present on breast cancer tissue. It can be used in different ways such as a preventive drug for women at high risk of breast cancer and after the surgery. It slower or stop cancer that has spread in body parts and having the potential to shrink a few tumors. The most

prevalent side effects include hot flash and vaginal drying or discharge. Rare side effects include the risk of development of uterine cancer, blood clots and stroke.

2.4 Immunotherapy

To stimulate the immune system for the identification and destruction of cancer cells is denoted as immunotherapy. The immune response against breast cancer cells could be boosted by blocking the PD-L1 protein that is present in a few immune and tumor cells. Atezolizumab is a PD-L1 inhibitor; it has the ability to shrink the tumors. Side effects of atezolizumab include cough, fatigue, loss of appetite, diarrhea and constipation. The most serious side effect includes removing the restriction on the immune system resulting in life-threatening problems.

2.5 Chemotherapy

Treating breast cancer with the anticancer drug is called chemotherapy. This therapy can be used before and after the surgery to avoid recurrence and shrinkage of the tumor. It also plays a role when cancer is spread outside the breast. The duration of treatment depends on the tolerance and action of chemo. Numerous drugs either alone or in combination are explored as a chemotherapeutic agent. Possible side effects of chemotherapy include mouth sores, hair loss, nail changes, nausea, vomiting, loss of appetite and diarrhea. Other common side effects are menstrual changes and fertility issues, cardiomyopathy, neuropathy etc.

2.6 Targeted Therapy

The drug is directed to target the specific genes, proteins or tissue environment other than normal cells is represented as target therapy. Breast cancer cells have diverse genes; change in a gene is a trigger for uncontrolled multiplication or spread of cancer. Target therapy restricts the growth and spread of cancer cells and reduces the damage to normal cells. Different types of breast cancers can be treated by using a specific approach to target therapy. Few of them are summarized as follows:

2.6.1 HER2-targeted therapy

Breast cancer cells have overexpressed growth-promoting protein called HER2 which promotes the uncontrolled growth and spread of cancer cells. Various types of drugs are developed for the treatment of HER2 positive breast cancers.

3. MONOCLONAL ANTIBODIES

These antibodies bind to HER2 protein on cancer cells and hinder them from multiplying and propagating. Some examples of monoclonal antibodies were summarized below:

Pertuzumab- This monoclonal antibody can be used in combination with trastuzumab and chemotherapy.

Trastuzumab- It is used for early-stage and advanced breast cancer.

Antibody-drug conjugates- These are a combination of monoclonal antibodies and chemotherapeutic agents. Few examples of these are quoted below:

Fam-trastuzumab deruxtecan: This is mainly used to treat metastatic breast cancer or cases in which surgical procedures are not advisable.

Ado-trastuzumab emtansine: When chemo and trastuzumab were administered prior to surgery and cancer still exists at the time of surgery then this therapy is used.

Kinase inhibitors: HER2 is belonging to the kinase type of protein. These proteins are responsible for transmitting signals to cells. Drugs that inhibit kinases activity are known as kinase inhibitors. Examples of kinase inhibitors are as follows:

Lapatinib: It is used in combination with certain hormone therapy drugs or capecitabine for the treatment of advanced breast cancer.

Neratinib: After one year of therapy with trastuzumab; neratinib is given for the next subsequent year for the treatment of early-stage breast cancer.

4. SIDE EFFECTS HER2 TARGETED THERAPY

The antibody-drug conjugates and monoclonal antibodies treatment may result in severe diarrhea, trouble breathing, coughing, wheezing, fever, heart problems and liver problem.

4.1 Targeted Therapy for Hormone Receptor-Positive Breast Cancer

For hormone receptor-positive cancers, treatment with hormone therapy is often helpful. Few treatments of this therapy are summarized below.

5. CDK4/6 INHIBITORS

Cyclin-dependent kinases (CDKs), mainly CDK4 and CDK6 promote the cancer cell division. Inhibition of these proteins can slow cancer growth. Drugs used as CDK4/6 inhibitors include palbociclib, ribociclib, and abemaciclib. Side effects of these drugs are fatigue, mouth sores, hair loss, headache, diarrhea, nausea, vomiting and low blood cell counts.

5.1 Targeted Therapy for Women with BRCA Gene Mutations

Both poly ADP ribose polymerase and breast cancer genes (BRCA1 and BRCA2) are responsible to repair damaged DNA by a slightly different mechanism. Mutation in these genes prevents the repairing process. PARP inhibitors act by blocking the PARP proteins. Drugs Olaparib and talazoparib are drugs known as PARP inhibitors. These can be used to treat metastatic, HER2-negative breast cancer. Side effects of these drugs are loss of appetite, taste changes, diarrhea, nausea, vomiting, fatigue, low blood cell counts, low platelet counts, low white blood cell, muscle and joint pain.

5.2 Targeted therapy for triple-negative breast cancer

In case of triple-negative breast cancer the expression of estrogen or progesterone receptors are suppressed and HER2 protein is lacking. Approaches for treatment triple negative breast cancer comprise of antibody-drug conjugate.

Sacituzumab govitecan: Some cancer cells make excess Trop-2 protein. The monoclonal antibody links to the Trop-2 protein on breast cancer cells and carries the chemo directly to them. Some side effects of this drug include hair loss, fatigue, loss of appetite, diarrhea, constipation, nausea, vomiting, rash and low red blood cell counts [6].

6. NANOTECHNOLOGY IN THE TREATMENT OF BREAST CANCER

Nanotechnology is a new field of science and technology. Nanomolecules can interact with biological molecules at nanometric scale, hence achieved wide scope in the field of pharmaceutical research. An important area of nanotechnology is nanomedicine, it deals with the highly specific involvement of medicine at the molecular level for prevention, diagnosis and treatment of diseases. Drug delivery systems developed in the field of nanomedicine range from truly nanosystems to microparticles in the range of 100 μm. Nano and microscale drug delivery systems have been crucially useful in the development of clinically useful formulations. For the treatment of various diseases, especially cancer; nanodrug delivery systems are emerging in the market [7]. Cancer nanotechnology is a branch of nanotechnology dealing with the application of nanomaterials and nanotechnology approaches for the diagnosis and treatment of cancer. Owing to specific tumor microenvironment and vasculature; targeting of the drug through nanotechnology is favourable. Various advantages of nanotechnology in cancer treatment are specific targeting of the drug through active or passive targeting and reduction in systemic toxicity, provides controlled release drug delivery, multiple agents could be combined for effective therapy etc. [8]. Targeting can be done through an active or passive way. Passive targeting is the accumulation of the drug in the tumor attributed to enhanced permeability and retention effect due to impaired lymphatic function and leaky vasculature [9]. Active targeting refers to the interaction of nanomolecule on the surface of the cancer cell through bio-engineering that enables the recognition and interaction of nanomolecules with affected cells [10]. Nanomaterials have been approved by the U.S. Food and Drug Administration (FDA) for the diagnosis and treatment of breast cancer. Nanotechnology based on various approaches are summarized below:

7. NANOPARTICLES

7.1 Metallic Nanoparticles

Gold nanoparticles have been studied for biomedical imaging, diagnosis and treatment of breast tumors. Gold nanoparticles exhibit physicochemical properties such as the capability to bind with amine and thiol group,

flexibility in surface modification and surface plasma resonance [11]. Radiopharmaceuticals can be developed by radiolabeled gold nanoparticles. Peptides can be conjugated with gold nanoparticles for better biocompatibility, stability and targeting [12]. Surface modification of Paclitaxel-bound gold nanoparticles by functionalized groups like PEG and biotin could be effective in the diagnosis and treatment of breast cancer [13]. Platinum nanoparticles and palladium nanoparticles composed of *Gloriosa superba* tuber extract were investigated against triple-negative breast cancer. Resulting nanoparticles showed potent cytotoxicity against MCF-7 cells *in-vitro* [14]. The extract of *Clerodendrum inerme* was entrapped in cobalt-doped tinoxide nanoparticles. A study demonstrated considerable *in-vivo* antitumor and *in-vitro* anticancer activity on breast carcinoma cells (MCF-7) [15]. Nanoparticulate formulation encapsulating vitamin E, catechol and silver nanoparticles synthesized from *Hibiscus rosa-sinensis* (HRS) petal extracts within a chitosan matrix were investigated. Formulation exhibited better hemocompatibility and encapsulation efficiency [16]. Disulfiram containing metal nanoparticles formulated with the 3D printed nanofluidic device was investigated. Disulfiram combines with copper to form the diethyldithiocarbamate copper complex. Formulation exhibited strong antitumor potential [17].

7.2 Polymeric Nanoparticles

Polymeric nanoparticles are formulated from biodegradable natural and synthetic polymers. These are suitable for both hydrophilic and hydrophobic drugs. Biodegradable polymers are beneficial in terms of higher solubility and permeability, better encapsulation and controlled release property. The release of chemotherapeutics agent is initiated by the degradation of the polymeric membrane. Commonly used polymers in the fabrication of polymeric nanoparticles are albumin, polylactic-co-glycolic acid, polylactic acid, poly-alkyl-cyanoacrylates polycaprolactone, chitosan and gelatin [18]. Albumin-bound paclitaxel suspension injectable Abraxane® has been approved by the FDA in 2005 [19,20]. Doxorubicin loaded polymeric nanoparticles in PEG and hyaluronic acid-ceramide polymer were proved for better cytotoxicity and shelf life in comparison with conventional formulations [21]. pH-sensitive polymeric nanoparticles had applications in the delivery of paclitaxel for better therapeutic efficiency. pH-responsive polymers are soluble in acidic pH hence the drug was rapidly distributed and released in the acidic microenvironment of solid breast tumors [22]. Despite advantages, polymeric nanoparticles have drawbacks such as difficulty in scale-up, polymer cytotoxicity and residual solvent in the formulation [23]. Curcumin embedded albumin nanoparticles were developed to improve solubility, sustained release and targeting. Serum bioavailability of curcumin was demonstrated superior antiproliferative potential, longer circulation and slow-release as compared to free drug. [24]. Folate-conjugated pluronic F127/chitosan nanoparticles was developed for targeting. Nanoparticles taken up by the cells through endocytosis and release the drug intracellularly. Rate of uptake for folate conjugated nanoparticles were greater than chitosan nanoparticles [25].

7.3 Magnetic Nanoparticles

The target specificity of anticancer drugs could be achieved by the application of an external magnetic field. These are prepared by magnetic material such as iron. In the presence of an external magnetic field, nanoparticles are activated and showed a cytotoxic effect [26]. Curcumin loaded magnetic nanoparticles were developed by chemical precipitation. The resulting product indicated a concentration-dependent internalization in MDA-MB-231 cells and confirmed throughout accumulation in the cell. Besides particles possessed better magnetic resonance imaging properties. [27]. Antibody-conjugated magnetic nanoparticles were investigated for HER2 breast cancer. Conjugated anti-HER2 antibody and superparamagnetic iron oxide nanoparticles were developed by employing the carbodiimide method. These were found to exhibit superior breast cancer detection specificity and sensitivity [28].

7.4 Mesoporous Silica Nanoparticles

These are multifunctional particles used for diagnosis, imaging and therapeutic application. Mesoporous silica nanoparticles have a defined structure of internal mesopores with an enormous volume of pores and more surface area. High drug loading capacity, inhibition of premature drug release, overcome multidrug resistance, both active and passive targeting, site-specificity, stimuli-responsive drug release and multifunctional abilities are added advantages of mesoporous nanoparticles [29].

Nanoparticle surface charge and size are variable to determine the cytotoxicity; cationic nanoparticles exhibit more cytotoxicity and rapid cellular uptake as compared to neutral and anionic particles [30]. Lactoferrin coupled mesoporous silica nanoparticles were developed for pemetrexed and the phytomedicine ellagic acid delivery. These indicated the faster release of the phytomedicine ellagic acid and the sustained release of pemetrexed. The formulation showed maximum cytotoxicity [31]. Folic acid (FA) mesoporous silica nanoparticles containing quercetin mesoporous nanoparticles were synthesized; these were reported to initiate cell apoptosis and cell arrest. These also ensure improved bioavailability and targeted drug delivery [32].

7.5 Micelle Nanoparticles

Micelles are nothing but amphiphilic molecules that are assembled to form hydrophilic corona and hydrophobic core. These are beneficial to drug delivery such as structural stability, extended shelf life, prolong circulation and stability, controlled size distribution etc. [40]. Certain physicochemical characteristics such as nano dimensions, drug loading, physical stability and release kinetics must be studied prior to the incorporation of the drug in micelles.Most of the anticancer drugs are hydrophobic and could be entrapped in the hydrophobic micellar core, besides solubility of drug also improve in micellar structure [41]. Hydrophobic drug paclitaxel was found to exhibit increased tumor accumulation, delayed clearance, and ultimately enhanced *in- vivo* therapeutic activity in orthotopic human breast cancer xenografts [42]. Aminoflavone exhibits strong inhibitory effect on triple-negative breast cancer cells but it suffers from pulmonary toxicity *in-vivo*. Formulation of unimolecular micelles containing aminoflavone improved the cellular uptake and cell growth inhibition with minimum toxicity [43]. Zileuton™ -loaded polymeric micelles having anticancer and anti-metastatic effects were evaluated by the use of *in-vivo* breast cancer stem cell models. The result of the study showed a considerable decrease in cancer stem cells and a remarkable reduction in circulating cancer cells [44]. Phospholipid-Tween 80 mixed micelles were prepared for delivery of plumbagin for sustained release. About 2.1 fold enhanced antitumor activity was reported and found safe by intravenous injection [45].

7.6 Polymersome

These are artificial vesicles generated from self-assembly of amphiphilic copolymers enclosing an aqueous cavity. Polymersomes are highly flexible and biologically stable. Overall characteristics, drug encapsulation and release capabilities can be easily modulated by the application of various block copolymers. Both hydrophilic and hydrophobic drugs can be encapsulated in polymersome. Different polymers used in polymersome preparation are Polyethylene glycol, polyethyl ethylene, polylactic acid etc. [53]. An amphiphilic graft of polyphosphazene was prepared by modification of the weight ratio of methoxy-poly (ethylene glycol) chain to ethyl-p-aminobenzoate side group. Doxorubicin and doxorubicin hydrochloride could be encapsulated owing to strong intermolecular interaction with polyphosphazenes with high loading efficiency. Reduced toxicity with enhanced safety was and optimum therapeutic efficiency was reported especially doxorubicin hydrochloride [54]. Hyaluronan-polycaprolactone polymersome encapsulating doxorubicin for sustained release was investigated. The resulting product exhibited extensive bio-distribution, tissue necrosis of tumor and *in-vivo* antitumor potential [55]. The hybrid polymersomes by combining poly (ethylene glycol)-b-poly(lactic acid) di-block copolymers and phospholipids enclosing photothermal responsive porous silicon nanoparticles with gold nanorods were developed. Lipid content had a negative effect on stability. Encapsulation efficiency was above 92% and the tumor-suppressive effect was seen [56].

7.7 Liposomes

These are small, spherical shaped artificial bilayer vesicles prepared from phospholipids and cholesterol. These are some of the promising approaches for drug delivery owing to amphiphilic characteristics and tunable size. Properties of liposomes can be varied based on size, lipid composition, surface charge and formulation method [57]. Targeting of the drug to specific cells is enable, thousands of molecules can be embedded in a single liposome and targeted via ligand or few antibodies. Certain macromolecules such as antisense oligonucleotides, genes small proteins or peptides, aptamers cannot passively diffuse. Cellular uptake of these

macromolecules can be improved by trapping them into liposomes [10]. Vaccines containing P5 HER2/ neu-derived peptide conjugated to Maleimide-PEG2000-DSPE were developed and entrapped in a liposome. Expressively higher intracellular production of IFN-γ by CD8+ T cells results in shrinkage of the tumor [58]. PEGylated liposome Doxil composed of doxorubicin was the first nanomedicine approved by FDA. It was reported to achieve extended circulation for up to 55 hours. Gemcitabine (hydrophilic drug) and tamoxifen (lipophilic drug) were loaded in liposomes as a multidrug carrier, having a mean size of 150-200 nm. Both the drugs exhibited synergistic effect and tamoxifen was found tomodulate the release of gemcitabine. 10 fold reduction in dose of gemcitabine was reported in comparison with commercial GEMZAR formulation [59]. Sterically stabilized doxorubicin liposomal formulation was investigatedin the phase II trial. Mild myelosuppression was observed during the trial suggestive of use of doxorubicin in combination treatment [60]. Thermosensitive liposomes composed of indocyanine green, activated by near-infrared photodynamic therapy showed considerable retardation of cell viability, growth of the tumor and enhanced accumulation in the treatment of triple-negative breast cancer [61]. Vincristine and quercetin were encapsulated in liposomes to enhance the antitumor effect. The encapsulated formulation showed a synergistic effect ofthe drugs, prolong circulation, noteworthy antitumor activity and reduction in toxicity [62].

Table 1. Breast cancer delivery by nanoparticles

Drug	Component of drug delivery	Summary	Reference
Paclitaxel	Poly(D, L-lactide-co-glycolide) and Montmorillonite	Biphasic drug release with moderate initial burst followed by sustained release profile and higher cellular uptake.	[33]
Paclitaxel	Albumin	A phase II trial ensured antitumor activity in metastatic breast cancer. phase III study denoted superiority to standard paclitaxel overall response rate and time to progression of tumor	[20]
Paclitaxel and Ceramide	poly(beta-amino ester) and poly(D,L-lactide-co-glycolide)	Prolong retention time and increased tumor accumulation.	[34]
Doxorubicin	Hyaluronic acid, L-lysine methyl ester, Lipoic acid	Effective restriction of tumor growth, fewer side effects, biocompatibility, targetability and reversal of drug resistance	[35]
Paclitaxel	Superparamagnetic iron oxide, polyethylene glycol and folic acid	Controlled release of paclitaxel, high drug loading, better uptake by cancer cells and enhanced cytotoxicity.	[36]
Doxorubicin	Polyethylenimine, human serum albumin	Higher cell transfection percentage and cytotoxic effect on MCF-7 breast cancer cells	[37]
Silver	Bovine serum albumin	Higher cytotoxicity against cancer cells, cell death based on apoptosis and reduction of gland tumor sizes in mice.	[38]
Paclitaxel	Poly(lactic-co-glycolic acid, polyethylene glycol succinate, Folic acid	Developed for treatment of bone metastatic breast cancer. Accumulation in bone metastases in vivo and retardation of bone destruction and bone loss.	[39]

Table 2. Breast cancer delivery by micelle nanoparticles

Drug	Component of drug delivery	Summary	Reference
Paclitaxel	poly(ethylene glycol)-*b*-poly(lactide)	Increased the intracellular uptake of the drug, with enhanced cytotoxicity and restriction of tumor metastasis on 4T1 cells	[46]
Paclitaxel	Polyethylene glycol–phosphatidylethanolamine	The increased anticancer effect, enhanced apoptosis and reduction in tumor cell proliferation *in- vitro* and *in -vivo*	[47]
Doxorubicin	Biotin and retinoic acid	Cytotoxicity was found in MCF-7	[48]
Doxorubicin and Salinomycin	Polyethylene glycol and Polyacrylic acid	Micelles were effective for drug-resistant cancer cells and penetrated MCF-7 and 4T1 cells.	[49]
Paclitaxel	Polyethylene glycol Succinimidyl Succinate	Micelles were adhered to the surface of activated platelets and captured circulating tumor cells in blood circulation. These also exhibited increased metastasis, targeting and penetrating effect via binding with tumor-infiltrating platelets.	[50]
Fisetin	Pluronic127 folic acid	Bioavailability of fisetin was enhanced by 6-fold, circulation time was prolonged; plasma elimination was slower with no toxicity. The active targeting effect was noted on MCF-7 cells.	[51]
Paclitaxel	Dextran-g-indomethacin	Micelles had efficiently encapsulated and prolonged drug with cytotoxicity.	[52]

Table 3. Breast cancer delivery by Liposomes

Drug	Summary	Reference
Doxorubicin	Formulations showed a significantly increased uptake and efficient targeting in killing cancer cells in MCF-7 and SKBR-3 cells.	[63]
Resveratrol	Encapsulation of drugs within peptide liposomes significantly reduced the toxicity.	[64]
Epirubicin-hydrochloride	Greater growth inhibition and the highest percentage of cell death for the concentrations	[65]
Cisplatin	Sustained, thermo-sensitive release, and improved cellular uptake along with cytotoxic effect.	[66]
Curcumin	Enhanced uptake of liposomes compared to non-malignant cells, and higher cytotoxicity.	[67]
Paclitaxel	Increased cellular uptake and concentration dependant cytotoxicity against MDA-MB-231 and MCF-7 cells.	[68]
microRNA	microRNA can be loaded into nanometer-sized liposomes and preserved for months in a lyophilized form.	[69]
Doxorubicin and Silymarin	Only at lower concentrations, synergistic effects were observed for both the drugs	[70]

8. LIPID-BASED DRUG DELIVERY

8.1 Lipid-Based Nanoparticles

Lipid-based solid lipid nanoparticles increase the permeability and retention effect and can be prepared from a variety of materials. These have been predicted to provide superior drug delivery, reduced adverse effects, biodegradable, biocompatible, target-specific and reverse the multidrug resistance conditions. Solid lipid nanoparticles based on triglycerides, compritol 888 ATO containing camptothecin were found to exhibit good drug entrapment, enhanced cellular uptake, retention and cytotoxicity. [71]. Intracellular release of noclosamide in the treatment of triple-negative breast cancer by employing solid-lipid nanoparticles was investigated. Results are suggestive of enhancement of anticancer drug accumulation contributing to enhanced anticancer activity [72]. Tamoxifen loaded solid lipid nanoparticles were developed using stearic acid and Tween 80. The cytotoxicity results suggestive of enhanced the effectiveness of tamoxifen and reversal tamoxifen resistance by encouraging apoptosis without affecting controlled cells [73].

8.2 Nanostructured Lipid Carriers

These exhibit high loading potential and fewer chances of leakage for the drug. These can be manufactured by simple methods, tuned for controlled release and shields the drug from degradation [74]. Lycopene loaded lipid carriers were prepared from Precirol ATO 5 and vitamin E by probe sonication technique. Increased cytotoxicity and fourfold enhanced permeation of lycopene were noted by the oral route [75].

Nanostructured lipid carriers were explored to excel in the bioavailability of Diindolylmethane derivatives. Formulations were composed of Myglyol 812, Compritol 888, Vitamin E and Diindolylmethane 10,14 and prepared by hot-melt homogenization process. Results revealed remarkable bioavailability and anticancer activity also found to be higher than only drugs [76]. Chitosan grafted lipid nanocapsules were developed for co-delivery of docetaxel and thymoquinone, improvement in the uptake and endosomal escape effect were reported along with noteworthy cytotoxicity [77].

8.3 Dendrimers

Dendrimers are nano-sized, radially symmetric with organized homogeneous and monodisperse structures. It resembles a tree branches with a diameter ranging from 2-10 nm. [78]. Size of the dendrimers could be precisely controlled; surface functionality could be modified as per the need, low polydispersity, ability to alter the pharmacokinetics of the drug are key characteristics to develop dendrimers for breast cancer treatment. Doxorubicin was conjugated via Gly-Phe-Leu-Gly, an enzyme-responsive tetra-peptide linker to the periphery of the dendrimer. The dendrimer–DOX conjugate further these were self-assembled into a nanoparticle. Resulting nanoparticles demonstrated better antitumor activity, induced apoptosis, avoid doxorubicin toxicities and good biosafety [79]. CXCR4 and its ligand CXCL12 are responsible for metastasis of different cancer, breast tumors metastasize to vital organs secrets more CXCL12. The efficacy of CXCR4 targeted dendrimers carrying doxorubicin was studied. PAMAM dendrimers consisting of doxorubicin were surface-functionalized with CXCR4 recognizable LFC131 peptide. The complex was bound to breast cancer cells; produced enhanced *in-vitro* cytotoxicity with decreased infiltration of BT-549-Luc breast cancer cells to chemoattractant [80]. PAMAM G4.5 dendrimers derivatized with piperizine were nontoxic and readily internalized. Besides it was possible to generate the fluorescent image for *in-vivo* tumor investigation [81]. To overcome microsomal glutathione transferase-1 mediated drug resistance and increased mitochondria-mediated apoptotic cell death, hyperbranched dendritic-linear based nanoparticles composed of doxorubicin was developed. Modulation of subcellular drug distribution by specific endocytic and trafficking pathways results in alteration of enzyme levels and cellular signaling pathways result in increases in the induction of apoptosis [82].

8.4 Nanoemulsion

Nanoemulsions are an emulsion of nanosize; developed to improve drug delivery. The size of the nanoemulsion range between 10-1000 nm and thermodynamically stabilized by a mixture of surfactant and co-surfactant [83]. Nanoemulsions are having the ability to deliver a greater concentration of chemotherapeutic agents to cancerous cells without side effects. As most of the anticancer drugs are hydrophobic; nanoemulsions had proven drug solubilization. These are unique in size and enables passive targeting by increased retention effect and permeability. Controlled drug release, tumor-

specific targeting and long circulation strategies can be applied in modified nanoemulsions. Delivery of doxorubicin was carried out by o/w nanoemulsion composed of chloroaluminum phthalocyanine. The formulation exhibited good internalization; chloroaluminum phthalocyanine encapsulation generated a good photodynamic effect and contributed to the death of cells. Doxorubicin was found to be distributed in the cancer cells, resulting in cell cycle arrest and cytotoxicity [84]. *Nigella sativa* essential oil was formulated in nanoemulsion for breast cancer treatment. It may be confirmed by nucleocytoplasmic morphological features of treated cells such as cytoplasmic vacuolation, marginalization of chromatin and fragmentation of the nucleus. The nanoemulsion induced apoptosis in MCF-7 cells [85].

8.5 Carbon Nanotubes

These are carbon allotropes, tubular and made up of graphite. These are available as single and multiple walled with a wide range of characteristics [86]. These provide a large surface area and stable thermally and electrically these characteristics have added advantage to adhere to various material such as cytotoxic agents, DNA, fluorescence substance, hence could be used cancer diagnosis and treatment [87]. Single wall nanotubes are graphene-based nanosheets and rolled over into cylinder having a diameter of 1-2 nm. Various anticancer drugs can be entrapped in the inner cavity or on their surface due to large surface area. Surface modified carbon nanotubes exhibit lower toxicity and non-immunogenic [88]. These can cross the plasma membrane and enter into cancerous cells by endocytosis or penetrate like a needle [89]. Carbon nanotubes noteworthy reduce cell proliferation and cell adherence; enhance the membrane destabilization and rate of oxidative stress. Cytotoxic activity of carbon nanotubes is reliant on the length, dimension, purity, concentration and functionalization moieties. For killing cancer cells artemisinin react with iron to produce radicals but concurrent delivery of hydrophobic artemisinin and iron is major concern. Hyaluronic acid-derivatized; multi-walled carbon nanotubes containing targeting ligand transferrin and drug artemisinin was investigated. Cytotoxicity of artemisinin was seen due to intracellular accumulation. Synergistic anti-tumor effect of artemisinin and transferrin was observed *in- vitro* and *in-vivo* [90].

8.6 Arsenic Trioxide–Loaded Nanobins

Arsenic causes cellular alterations such as inhibition of proliferation, stimulation of differentiation, induction of apoptosis, stimulation of differentiation, and inhibition of angiogenesis [91]. Arsenic trioxide nanobins are nanoparticulate preparation in which arsenic trioxide is stabilized as nanoscale precipitate inside the pegylated liposome. Nanobinsare nanoparticulate core composed of extremely high densities of arsenic and Ni2+ cations that stabilize and potentiate drug activity. The release of arsenic is triggered by low environments near about 5-6.5. Hence it is possible to release arsenic trioxide inside endocytotic vesicles in a tumor, acidic tumor milieu and tumor macrophages. Nanobins enhance *in-vitro* cytotoxicity as compared to free arsenic trioxide as bioactivity is suppressed inside the vesicle. Besides these also reduce the systemic toxicity of arsenic trioxide by protecting normal cells owing to encapsulation and overcome the drawbacks of free arsenic trioxide. Nanobins are stable for at least 12 months at 4°C with less than10% leakage of free arsenic trioxide [92]. Investigation was carried out to study *in-vitro* and *in-vivo* activity of arsenic trioxide. Formulation would increase the antitumor activity of arsenic trioxide by promoting its pharmacokinetics *in-vivo* ,improving tumor accumulation of arsenic trioxide via the EPR effect and decreasing systemic toxicity by protecting healthy tissues from drug exposure [93].

8.7 Nanobubbles

These are long-lasting a gas-containing hollow structures in the aqueous solution and it exhibit low internal pressure and surface tension owing to charged gas/liquid interface [94]. Cell penetrating peptide composed of epidermal growth factor receptor- targeted small interfering RNA nanobubbles were investigated for triple negative breast cancer. Expression of EGFR mRNA and protein were effectively down regulated and breast cancer cells growthwas restricted by the treatment [95]. The effect of water containing oxygen nanobubble on breast cancer tumor growth in 4T1-bearing mice was studied. Tumor size, HIF gene expression was significantly decreased at the end of treatment [96].

9. CONCLUSION

Various advances in nanotechnologies such as nanoparticles, nanomicelles, nanoemulsion, dendrimers, carbon nanotubes, liposomes etc. have been explored and currently in use to deliver the drug with minimum side effects. The major purposes of most of these therapies are targeting and enhancement of cellular uptake of drugs without affecting healthy cells. A detailed understanding of the mechanism of nanodrug delivery systems and the biological system could effectively land up with the development of more safe, compatible and effective medicine for the treatment of breast cancer. In the future, the personalized nanomedicine based on the individual need of patients should be developed for the prevention and treatment of breast and other cancers.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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