IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
January 2023 Vol.:26, Issue:2

A Systematic Review of Nano-Formulations in Breast Cancer Oncology

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

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Submitted: 25 December 2022
Accepted: 31 December 2022
Published: 30 January 2023

HUMAN JOURNALS
www.ijppr.humanjournals.com

Keywords: Breast Cancer; Nano-formulation; Hormone; Tumour; Targets; Drugs.

ABSTRACT

Among cancers, the incidence of breast cancer in women is high. Breast cancer can occur due to various reasons like hormonal imbalances, dietary causes and family history, etc. Several therapies such as radiation therapy, hormone therapy, and chemotherapy are used to treat breast cancer. Paclitaxel, doxorubicin, tamoxifen, exemestane, bevacizumab, and 5- fluorouracil are a few drugs currently used to treat breast cancer. One of the reasons for toxicity associated with chemotherapeutics is the lack of tumour tissue targeting. To overcome the drawbacks of chemotherapy, researchers are investigating the science of nanotechnology to create formulations that lower drug toxicity, improve systemic circulation, reduced drug resistance, and increased uptake and drug accumulation at the site of action when compared to traditional breast cancer treatments. Cancer nanomedicine, an interdisciplinary discipline concentrating on the creation and medical uses of nanoscale materials and technology, has made significant contributions to the progress of cancer treatment in recent decades (typically up to 100 nm) and this Nano formulation can be used to increase the pharmacological activity of conventional cytotoxic drugs in use, reduce dose, increase bioavailability, reduce multiple drug resistance and many more. . Nano size of formulation allows passage or permeation of drugs through vasculature resulting in the release of encapsulated drugs at tumor tissue This review focuses on various Nano formulations such as liposomes, polymeric nanoparticles, dendrimers, quantum dots, carbon nanotubes, etc. used for treating breast cancer till date along with certain examples which are in clinical trials and marketed formulations.

INTRODUCTION:

Cancer is second only to cardiovascular illnesses in terms of prevalence worldwide, and the likelihood of contracting the disease is rising. One of the most prevalent cancers is breast cancer[1] Women have a 30% chance of acquiring breast condition and the mortality rate is 14%. Mainly due to metastasis. Metastatic breast cancer claims the lives of almost 40,000 women each year [1,2] Breast cancer is a diverse illness with several subtypes depending on progesterone receptor, estrogenic receptor, and HER-2/neu receptor expression levels (human epidermal growth factor receptor 2) [3] The lymph nodes, brain, lung, and liver are the most common sites where breast cancer has spread. Several different types of breast cancer have had their biological and clinical behaviour elucidated in great depth. Symptoms such as breast heaviness or soreness, ulceration, erythema, thickness, and edema may indicate breast cancer [4] Most common causes of breast cancer are Genetic predisposition (abnormal inherited genes BRCA1 and BRCA2), previous history, Significant family history, Hormonal causes, Lifestyle and dietary causes (alcohol consumption), Anthropometry (higher weight, weight gain during adulthood, and body fat distribution) Environmental factors etc.[4]

Receptors of breast cancer cells are important in the prognosis and treatment of the disease. It will serve as the foundation for the treatment's focused approach. Surgery, radiation, chemotherapy and cell therapy are the foundations of breast cancer treatment, however no fully effective therapeutic technique has been established yet to address this issue[1] . Chemotherapy is one of the most prevalent treatments for treating cancer which includes Hormonal treatment. Women with ER-positive breast cancer are treated with chemotherapeutics to inhibit particular hormones that drive cancer development. The medicine tamoxifen is an example of hormonal treatment. This medicine inhibits the effects of estrogen, which aids in the survival and growth of breast cancer cells [5] This medicine is used to treat the majority of women with estrogen-sensitive breast cancer. Aromatase inhibitors, such exemestane (Aromasin), have been found to work as well as or better than tamoxifen in postmenopausal women with breast cancer. Aromatase inhibitors prevent the production of estrogen.

Radiation therapy serves as an adjuvant treatment for women who have had a lumpectomy and mastectomy surgery. The goal of radiation in these circumstances is to lower the chances of cancer recurrence. Radiation is particularly successful in destroying cancer cells that may persist after surgery or regrow in the area where the tumour was removed. External beam

radiotherapy or brachytherapy can be used to give radiation therapy (internal radiotherapy) [6]

Apart from all these therapies used in management of breast cancer, our main focus of this review is on the use of chemotherapeutic anti-cancer agents in Nano-formulations.

2. Chemotherapeutic drugs used in breast cancer:

Table No. 1: List of chemotherapeutic drugs with their molecular targets [7]

Drugs	Molecular Targets
Tamoxifen	Er (Estrogen Receptor)
Raloxifene	(Estrogen Receptor)
Exemstane (Steroidal)	Aromatase /Estrogen
Anastrazole And Letrozole	Aromatase / Estrogen
Herceptin	Her-2 Receptor
Pertuzumab	Her-2 Receptor
Gefitinib	Egfr (Epidermal Growth Factor Receptor)
Zactima	Vegfr (Vascular Endothelial Growth Factor Receptor)
Taxane	(Paclitaxel, Docetaxel) B-Subunit Of Tubulin, Bcl-2
Bevacizumab	Vegfr (Vascular Endothelial Growth Factor Receptor)
5-Fluorouracil	Thymidylate Synthase
Doxorubicin	Topoisomerase-2 Complex

The lack of specificity and unwanted toxicity associated with this therapy is a serious issue. As a result, Cancer nanomedicine, an interdisciplinary discipline concentrating on the creation and medical uses of nanoscale materials and technology, has made significant contributions to the progress of cancer treatment in recent decades (typically up to 100 nm) and this Nano formulations can be used to increase the pharmacological activity of conventional cytotoxic drugs in use [8] Pharmacological side effects, non-Specific cell

targeting, off-target effects and drug instability are just a few of the most serious faults in conventional medicine. Nanoparticles (NPs) deliver drugs to the site of action and may be able to overcome resistance by focusing on tumour cells specifically and to eliminate the above-mentioned shortcomings due to use of conventional medications [9]

3. NANO FORMULATIONS IN BREAST CANCER:

Due to limitations of chemotherapeutic drug regimens used in treatment of breast cancer, growing interest is seen for Nano formulations as effective treatment strategies for breast cancer. Enhanced properties of conventional drugs and specificity to targeted sites of delivery are some of the reasons for increased development of Nano formulations. In this review, various Nano formulations were discussed briefly which have been approved or in clinical trials and have excellent documented anti-cancer properties when administered in a Nano-formulated manner. Nano formulations are the formulations which consist of drugs that are dissolved, entrapped, encapsulated or attached to a nanoparticle of nano sizes. In nanoparticle systems, size, shape, and charge are key factors that determine nanoparticle distribution, targeting ability, and biological destination in vivo[10] Examples of such nanoformulations are liposomes, nano emulsions, polymeric nanoparticles, dendrimers, gold nanoparticles, magnetic nanoparticles, carbon nanotubes, quantum dots and nanogels have been developed by researchers to treat breast cancer efficiently. [11] Nanoparticles with hydrodynamic size diameters below 10 nm are rapidly cleared by the kidney. The liver and spleen absorb the bulk of nanoparticles that are injected into the body. In the cellular environment, macrophages with the help of phagocytes will destroy nanoparticles, digest a tiny fraction of them, and then eliminate both the intact and digested nanoparticles. Hence, Particles must be less than 200 nm to avoid mechanical filtration by the liver and spleen [12] Surface charge (zeta potential) plays an important role in enhancing direction of nanoparticles. Positively charged nanoparticles have been shown to increase binding and cell uptake due to interaction with negatively charged cell components. However, neutral particles showed lower interaction and lower electrostatic interactions with cell components [10,13] Surface modification of nanoparticles proved to be useful as it offers bio compatibilities, modulation of interaction between nanoparticle and cells, tissues, and biomolecules, and increased biodistribution [10,14] Some critical criteria must be addressed while building an acceptable nanocarrier for speedy and successful cancer treatment. The nanocarriers must be made of an easily functionalized material and biocompatible that is clearly defined, soluble, has long

circulation, does not aggregate, and target cells must uptake high concentrations of drug incorporated [10].

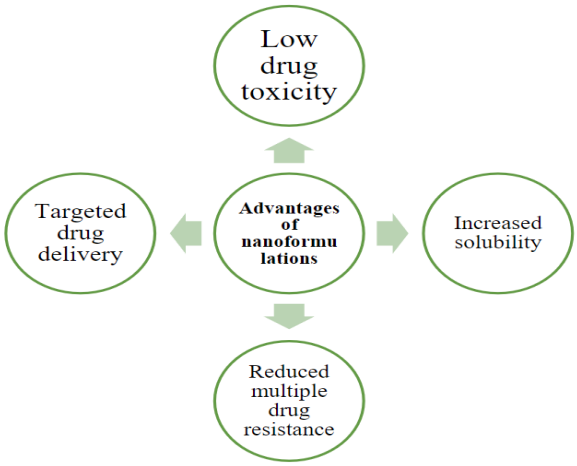

Figure No. 1: Advantages of Nano formulations

All the above-mentioned advantages have helped in overcoming the challenges faced by the conventional drugs used in treatment of breast cancer.

Table No. 2: List of approved Nano formulations for metastatic breast cancer [9]

PRODUCT	DRUG	FORMULATION	COMPANY
Myocet	Doxorubicin	Liposome	Teva
Genexol	Paclitaxel	Polymer-based	Samyang
Abraxane	Albumin and paclitaxel	Protein-drug conjugate	Celgene
Kadcyla	Trastuzumab emtansine	Protein-drug conjugate	Genentech

3.1 Different types of Nano formulations in breast cancer:

Various approved Nano formulations for breast cancer treatment are available in market for breast cancer treatment. They are classified into three classes:[9,10]

A. Lipid based Nano formulations: Liposomes, solid lipid, phospholipid, nano emulsions.

B. Polymeric Nano formulations: Micelles, Dendrimers, polymer-drug conjugate.

C. Inorganic Nano formulations: gold nanoparticles, quantum dots, silica nanoparticles, magnetic nanoparticles, carbon nanotubes.

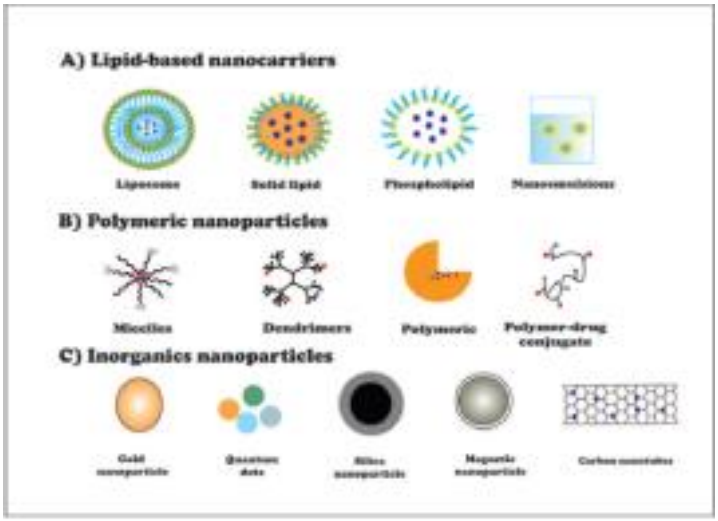

Figure No. 2: Different types of Nano formulations [10]

Table No. 3: Types of Nano formulations for drug delivery [9,14]

Nano Carrier System	Size (Nm)	Characteristics
Liposomes	5-100	Biodegradability, Enhanced circulation time of drugs in blood.
Dendrimers	1-10	High drug loading capacity, surface functionalization
Polymer Based Nanoparticles	10-100	Prolong drug release, cheaply fabricated, biocompatible
Quantum Dots Iron Oxide Nanoparticles	Less than 10 1-100	Surface modification, Magnetic response, small particle size, targeted delivery
Gold Nanoparticles	1-150	Unique size and shape,diagnosis and therapeutic in tumor ablation
Carbon Nanotubes	0-3 by 20-1000	Controlled release delivery of drugs, unique geometry
Nanogels	10-200	Protection of molecules from the immune system, high drug loading. biodegradable

3.1.1 Liposomes:

Liposomes are tiny vesicles with an aqueous interior compartment surrounded by a bilayer lipid membrane. The membranes are made up of biodegradable amphiphilic substances like phospholipids and glycolipids. Bangham described liposomes as the first nanocarriers in 1965 [10,15]. The biodistribution and pharmacokinetics of a medicine are improved by liposomal drug preparation. This means that higher medication concentrations in tumors can be produced while drug concentrations in normal tissue are reduced [16] Drug loading occurs in either the hydrophobic core or the lipid membrane, which depends on the active pharmaceutical ingredient's solubility. Liposomes based preparation such as Doxil has achieved success in breast cancer treatment in which doxorubicin is entrapped in the phospholipid bilayer. Due to these properties, drugs can be released slowly at the tumour site and reduces the toxicity of chemotherapeutic drugs by changing the biodistribution pattern of drugs [1,17]. In the treatment of triple-negative breast cancer, thermosensitive liposomes containing indocyanine green which are activated by near infrared photodynamic therapy revealed significant reductions in cell survival, tumor development, and accumulation as reported by Shemesh and colleagues[4,18] .Apart from these advantages of liposome, use of this drug delivery system has been found to have several drawbacks. According to several reporting's, 15–30 minutes after intravenous delivery, the reticuloendothelial system (RES) absorbs 50–80 percent of liposomes, largely via liver cells (Kupffer cells). Other issues include their stability, batch-to-batch repeatability, and sterilizing difficulties[10,19,20]

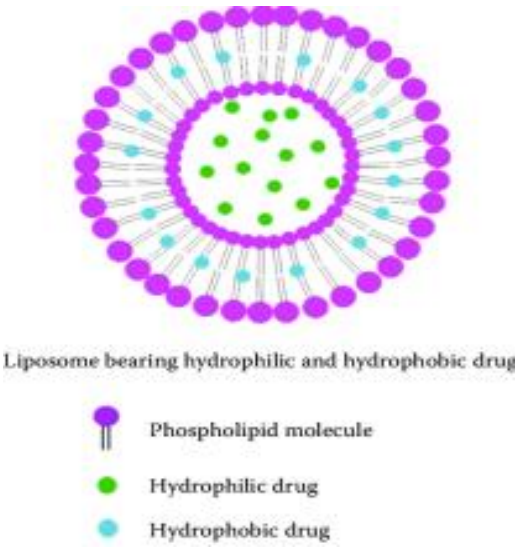

Figure No. 3: liposome NPs carrying drug either inside bilayer of lipid or inside core [21]

3.1.2 Nano emulsions:

Nano emulsions are nanoscale emulsions that were created to increase drug delivery. The Nano emulsion has a droplet size range of 10-1000 nm and is thermodynamically stabilized by a combination of surfactant and co-surfactant [22] This dosage form is made up of a heterogeneous dispersion of nanoscale droplets in another liquid, resulting in a high level of stability and solubility [23] Nano emulsions based on natural substances, such as the one created by Periasamy and colleagues with Nigella sativa L essential oil, could be a good therapy for breast cancer. This nano emulsion induces apoptosis in in-vitro breast cancer cell lines like MCF-7, demonstrating anti-cancer capabilities. This nano emulsion could be used to entrap active medicines for breast cancer treatment. [24,25]

3.1.3 Polymeric Micelles:

Polymeric micelles (PMs) are nanoscale core-shell structures formed by self-aggregating copolymers with an average diameter of 10–100nm having an amphiphilic nature.[26] A dense hydrophobic region makes up the core, whereas hydrophilic co-polymers make up the shell. PMs differ in medication release rate and blood stability and they can be modified by surface alterations with chemical linkage such as esters[27] Since they have a hydrophilic surface, they are protected against non-specific absorption, allowing them for the administration of hydrophobic chemotherapy agents throughout the body [28]The disintegration of the polymeric membrane triggers the release of chemotherapeutic agents. Albumin, polylactic-glycolic acid, polylactic acid, poly-alkyl cyanoacrylates polycaprolactone, chitosan, and gelatin are all often utilized polymers in the manufacture of polymeric nanoparticles[4,29] Advantage of polymeric micelles involves clearance of the micelles by renal filtration, reticulo endothelial system (RES) absorption or by spleen is hindered by PMs' hydrophilic shell and nanoscopic size, allowing for prolonged blood circulation [9]

Example of successful polymeric formulation is Abraxane which has been approved by FDA in 2005. Abraxane is albumin bound paclitaxel suspension injection used in the treatment of breast cancer. When compared to an equal dose of conventional paclitaxel, preclinical tests in athymic mice with human breast cancer showed that ABI-007 has a greater penetration into Tumor cells and greater anticancer efficacy [30]Paclitaxel is a poorly soluble drug, which is frequently mixed with Cremophor EL (polyoxyethylated castor oil) for

solubilization of paclitaxel, which causes hypersensitivity reactions. Genexol-PM (polymeric micelle) has been approved in Korea for metastatic breast cancer treatment and to address the solubility issue. Hence, eliminating the hypersensitivity reaction [9,31]

3.1.4 Polymeric Nanoparticles: Manaspon and colleague [32] reported, folate-conjugated pluronic F127/chitosan nanoparticles loaded with doxorubicin to target cancer cells are taken by cells via endocytosis and then released intracellularly. Folate conjugated nanoparticles had a higher rate of absorption than chitosan nanoparticles and also showed greater cytotoxicity towards breast cancer cells like MCF-7 [32] Despite their benefits, polymeric nanoparticles have disadvantages such as scaling difficulties, polymer cytotoxicity, and residual solvent in the formulation [4]

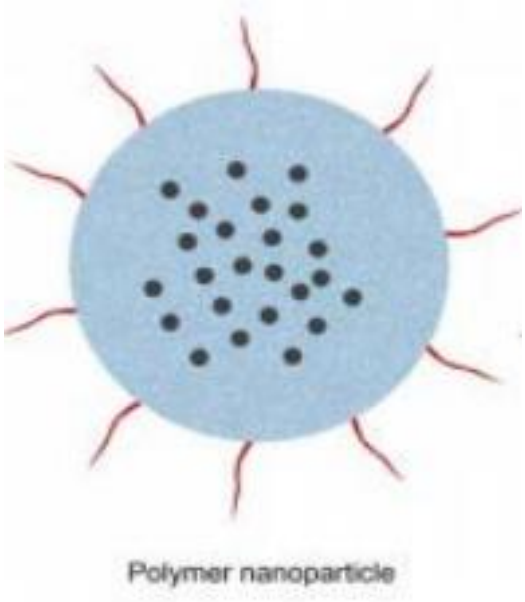

Figure No. 4: polymeric nanoparticle with polyvinyl alcohol coating [33]

3.1.5 Dendrimers:

Dendrimers are nanoscale branched structures. They are made up of synthetic polymer with repeated units and a regular pattern that forms a nanosized branching structure[2] Dendrimers are made up of three basic components: a central core with two or more than two groups attached, surface having peripheral functional group which determines physicochemical properties of dendrimers and last, the peripheral groups which can be altered to obtain both charged lipophilic and hydrophilic properties[10] Dendrimer features can be adjusted by modifying surface groups, interiors, and cores to provide advantages like

biodistribution, physical features and receptor-mediated targeting. They have shown potential in bio medical applications due to their ease of conjugation with targeted molecules, biodegradability, biocompatibility, and high-water solubility [34,35] G4 polyamidoamine dendrimer (G4 PAMAM-D) conjugate containing antisense oligodeoxynucleotides (ASODN) was produced by Wang and colleagues [36]. The conjugation was more stable, had lower toxicity, and had higher bioavailability. In vivo investigations on xenograft mice models revealed that the compound had a higher accumulating efficacy than naked ASODN in inhibiting tumour vascularization in breast tumors [2,36]. Another study in 2005 by Jiang and colleague showed a successful formulation of dendrimers with methotrexate coupled to Polyamidoamine (PAMAM) dendrimers resulting in a reduction of around 10 folds in tumor size when compared to free systemic methotrexate [10,37]. Despite their promising outcomes, dendrimers are bit expensive compared to other nanoformulations and their manufacturing requires numerous repeating stages, making large-scale manufacture difficult [38]

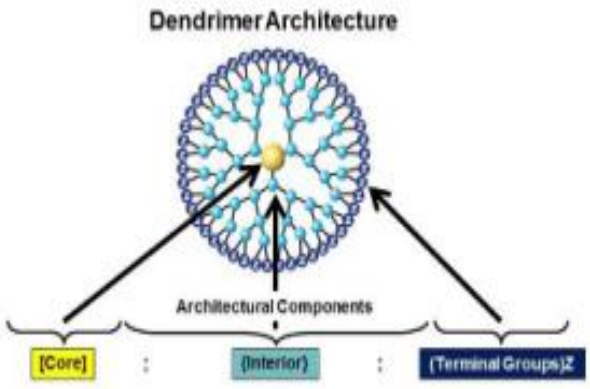

Figure No. 5: Components of Dendrimer [39]

3.1.6 Inorganic nanoparticles:

The majority of NPs fall into one of two categories: organic nanoformulation which are made up of organic materials and inorganic nanoformulations made up of inorganic elements present physical and chemical qualities that can be traced to their inorganic constituents, such as metals. The inorganic nanoparticles are made up of two parts: a core which contains metals such as iron oxide, gold, and quantum dots and a shell which contains no metals (metals or organic polymers which shield the core from chemical reactions and act as a substrate for biomolecule conjugation) [40,41]

3.1.6.1 Gold nanoparticles:

Gold nanoparticles are biocompatible, inert and non-toxic nanoparticles have a diameter of 130 nm [42]Coatings of nanoparticles containing gold are used as a biomarker in cancer diagnosis. However, gold nanoparticles, such as magnetic nanoparticles, are used as nanocarriers in the therapy of cancer[1,43] Targeting, transport dynamics, circulatory half-life, size-enhanced tumor uptake, and biocompatibility are all advantages of these nanoparticle conjugates. These nanoparticles are among the most stable and simple to functionalize surfaces for molecular conjugation [44]It was reported that Surface modification of Paclitaxel-bound gold nanoparticles by functionalized groups such as PEG and biotin could help with breast cancer diagnosis and treatment [9]

Gold nanoparticles conjugated with quercetin (AuNPs-Qu-5) were used to explore the EGFR (Epidermal Growth Factor Receptor) /VEGFR-2 (Vascular Endothelial Growth Factor Receptor-2) signaling pathway in breast cancer to evaluate its involvement in the prevention of migration, metastasis and angiogenesis of cancerous cells. As a result, AuNPs-Qu-5 nanoparticles decrease many proteins in these cells, including PI3K (phosphatidylinositol 3-kinase), slug, N-cadherin ,vimentin, Akt (protein kinase-B), and p-GSK3b reported by Balakrishnan and colleague [1,45] Many studies showed that gold nanoparticles could be of great potential in treatment and diagnosis of breast cancer.

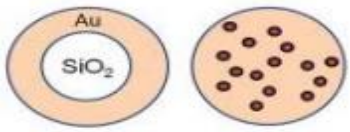

Figure No. 6: gold nanoparticle with silica loaded core [46]

3.1.6.2 Magnetic nanoparticles:

A magnetic nano system's ability to become oriented after being exposed to a magnetic field is intriguing, however, once the field is turned off, it does not retain permanent magnetism. These nanoparticles must be minuscule in order to be superparamagnetic and remain in circulation when the magnetic field is turned off, avoiding agglomeration and immune system removal [47] Magnetic materials, such as iron, are used to produce them. Nanoparticles are

triggered in the presence of an external magnetic field and have a cytotoxic impact [9]In this type of nanoparticles, Iron oxide magnetic nanoparticles are shown to be more effective.

There are the three types of iron oxide nanoparticles (IO) [10]

Standard superparamagnetic iron oxides (SSPIOs) with a diameter of 60 to150 nm

Ultra-small superparamagnetic iron oxide (USPIO) with a diameter of 5 to 40 nm

Monocrystalline iron oxides (MION) with a diameter of 10 to 30 nm

The use of antibody-conjugated magnetic nanoparticles in the treatment of HER2 breast cancer was studied by Hathaway and colleagues. The carbodiimide approach was used to create a conjugated anti-HER2 antibody and superparamagnetic iron oxide nanoparticle. These were discovered to have higher specificity and sensitivity for detecting breast cancer [9,48]. Shaik et al. [49] in their study on super paramagnetic iron oxide (SPIOs) nanoparticles attached with antibodies reported inhibition by polyethylene glycol (PEG) polymer in a 4T1 cells of breast cancer in one investigation (SPION IL4R α). In 4T1 cells, blocking IL4Rα receptors caused apoptosis and severely reduced cell viability. The findings show that combining SPIONIL4Rα with doxorubicin increases oxidative stress and cell death as compared to SPION-IL4Rα or doxorubicin alone [1,49]

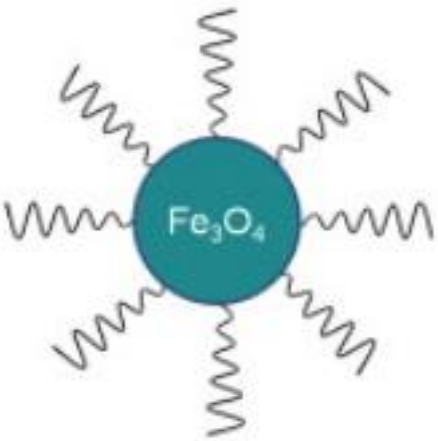

Figure No. 7: Iron oxide nanoparticle conjugated with PEG[50]

3.1.6.3 Carbon nanotubes:

Carbon nanotubes have a cylindrical nanostructure and are carbon allotropes. These nanostructures have mechanical and electrical properties that are unmatched. Carbon nanotubes resemble the layers of graphene rings in appearance. Carbon nanotubes, a more dynamic substance, are used in tumour visualization and drug delivery systems[1] An advantage of carbon nanotubes is they provide thermally and electrically stable as well as large surface area. Due to this, they adhere to many materials such as DNA, cytotoxic agents and fluorescence agents, therefore they could be used in treatment of cancer and diagnosis of the same. Owing to their high surface area, several anticancer medicines can become entrapped in the interior cavity or on their surface. Carbon nanotubes with surface modifications are less harmful and non-immunogenic [51]

Artemisinin reacts with iron to create radicals, which kill cancer cells, however simultaneous delivery of hydrophobic artemisinin and iron is a serious issue. Zhang and colleagues conducted a study on hyaluronic acid-derivatized multi walled carbon nanotubes containing the targeting ligand transferrin and the medication artemisinin. Artemisinin cytotoxicity was observed due to intracellular build-up. According to studies, artemisinin and transferrin have a synergistic antitumor action in vitro and in vivo [4,52] More research is needed to determine the therapeutic applications of nanotube drug delivery systems in the treatment of breast cancer.

Figure No. 8: carbon nanotube loaded drugs [46]

3.1.6.4 Quantum dots:

Quantum dots (QDs) are semiconducting nanocrystals having a core made of inorganic materials with a shell made of organic materials, ranging in size from 2 to 10 nm [9,53] QDs

have a unique property that makes them a helpful tool for imaging and tracking intracellular processes. When tested in vitro for immediate localization of HER-2 receptors, targeted chemotherapy, and imaging-guided therapy, QDs showed encouraging results [9,54] To depict quantum dots, inorganic binary compounds such as Cadmium selenide (CdSe), Cadmium Telluride (CdTe), Zinc sulfide (ZnS), and Lead sulfide (PbS) are used, although the most common quantum dot system is a CdSe inner semiconductor core coated with a ZnS outer shell. [55] Wu and colleague[56,57] labeled the breast cancer marker Her2 on the surface of fixed and live cancer cells,to stain actin and microtubule fibers in the cytoplasm, and detect nuclear antigens inside the nucleus, QDs were coupled to immunoglobulin G (IgG) and streptavidin. It was discovered that a single QD coupled to streptavidin and IgG may detect two biological targets with different emission spectra. Hence, QDs can be used for diagnostic purposes and could be of great potential in future breast cancer treatment.

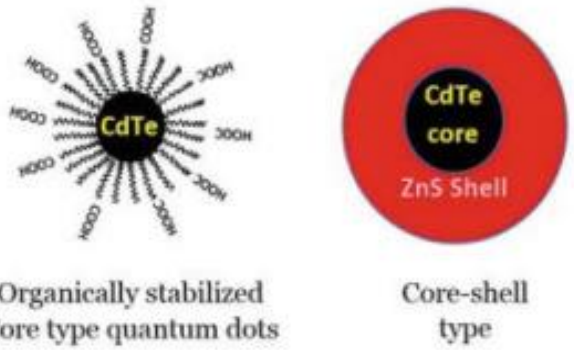

Figure No. 9: Different types of quantum dots [58]

3.1.6 Polymeric nano gels:

Nano gels are formed by connecting polymer chains to create an inner porous part that can retain a large amount of medicament [59] Properties of an ideal nanogel include biocompatibility, biodegradability, particle size between 10 and 200 nm, higher volume of drug loading, enhanced blood circulation time and molecules are protected from the body's defense system[56] Natural materials are appropriate for nanogel formulation, but the significant positive charge on the surface of particles causes inflammatory reactions., whereas synthetic materials have well defined morphologies which can be altered to produce biocompatible and degradable gel networks. Chemical functional entities, cross-linking density modifications, and stimuli responsive constituents could be used to achieve properties of nanogels [60] For example, for targeted therapy of ovarian cancer, Nukolova and

colleagues created nanogels attached to folic acid and preloaded various drugs such as cisplatin or DOX using the di block copolymer poly (ethylene oxide)-b-poly (methacrylic acid) (PEO-b-PMA) [61].

CONCLUSION:

As breast cancer is the leading cause of death due to cancer in women, it is necessary to look out for viable alternatives. One of the alternatives is the use of Nano formulations which paved the way forward for the treatment and diagnosis of breast cancer. Advances in Nano formulations such as liposomes, polymeric nanoparticles, quantum dots, dendrimers, Nanoemulsions, carbon nanotubes, nanogels, etc. have been studied and concluded that this treatment strategy can deliver drugs with low side effects as compared to conventional drugs. Despite that, many Nano formulations are in clinical practice and efforts are being made to produce Nano formulations onto new platforms and to be considered as a new field of drug therapy. A detailed overview of the mechanism of action of Nano formulation will be required in order to produce many effective Nano formulations. However, the field of breast cancer oncology has numerous concerns to cope with because of the present chemotherapeutic regime resulting in it being less than optimal and this therapy must be shifted onto Nano formulations as the treatment option.

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