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Chapter 2: Smart Nanocarriers for Targeted Breast Cancer Therapy: Liposomes, Dendrimers, and Beyond

Vasanth S[1], Mythili S R[1], Akilan A[1], Priyadharshini N[2], Deepa V C[2], Habibur Rahman S M[1]*, Susovan Borat[3]

[1] *Department of Pharmaceutics, PSG College of Pharmacy, Coimbatore, Tamil Nadu, India*
[2] *Department of Pharmaceutical analysis, PSG College of Pharmacy, Coimbatore, Tamil Nadu, India*
[3]*Department of Pharmacy, Jagannath University, Jaipur, Rajasthan, India.*
Corresponding Author
S. M. Habibur Rahman
Email: **vasanthnkl500@gmail.com**

Abstract

The possibility of smart nanocarriers for targeted drug delivery in breast cancer therapy, providing solutions for some major challenges in treating breast cancer, such as unselective drug delivery, drugs induced systemic toxicity, and multi-drug resistance. Using receptor-mediated targeting combined with the by Enhanced Permeability and Retention effect, it show here that the use of nanoparticle delivery systems allows for increased drug delivery to tumors, while sparing normal organs. The presence of biodegradable and biocompatible nanocarriers such as liposomes, dendrimers and polymeric Nanoparticles further improves the therapeutic effect by defeating the chemotherapeutic resistance. Both in vitro and in vivo studies demonstrate marked tumor shrinking and metastases decreasing, as well as prolonged overall survival. Although scalability, product-to-product synchrony, and chronic toxicity represent considerable bottlenecks in the development of these therapeutics, lessons learned from these studies could guide future development, especially with enhanced, smart nanocarriers that supports in situ sensing, on-demand drug release and combinations with precision medicine or immunotherapy. This study offers a roadmap to better, tailored breast cancer treatments that could make a huge difference to outcomes for patients and reduce the cost of treatment.

Keywords: *Smart nanocarriers, biocompatibility, EPR effect, PEGylation, receptor-mediated targeting, and clinical translation.*

1. Introduction to Smart Nanocarriers in Breast Cancer Therapy

1.1 Smart nanocarriers

Chemotherapy for breast cancer traditionally consists of cytotoxic drugs that kill both cancerous and healthy cells and cause severe side effects, such as immune suppression, hair loss and nausea. This non-targeted strategy has generally been associated with low efficacy and poor quality of life for the patients (Gupta *et al*., 2021). These challenges are resolved by the targeted delivering of drugs to tumors sites via nanocarriers that include liposomes, dendrimers, polymeric-nanoparticles. This treatment specificity of nanocarriers is increased by factors such as passive targeting (EPR effect) and active targeting (receptor binding such as HER2), which can eventually allow treatment with less side effects in healthy tissue (Edis *et al*., 2021). They also enhance drug stability, circulation, tumor uptake, and overcome drug resistance by escaping efflux pumps. These innovations place nanocarriers in the exciting position of potentially enabling more efficient, safer, and individualized breast cancer therapies (Nayak *et al*., 2025).
Important nanocarrier milestones in the field of oncology include: 1950s-1960s, early roots of nanomedicine, including the introduction of the first polymer-drug conjugate and identification of liposomes; 1995, Food and Drug Administration approval of Doxil (liposomal doxorubicin) the first nanocarrier drug approved by the F.D.A., enhancing safety and minimizing cardiotoxicity; 2004, Abraxane (albumin-bound paclitaxel) is approved, increasing drug solubility and efficacy in the treatment of breast cancer; 2011, approval is granted to Marqibo (liposomal vincristine), another advance in liposomal chemotherapy; 2013, Onivyde (liposomal irinotecan) is approved for mPC patients and had a better PK profile, leading to less toxicity; and 2017, Braftovi and Mektovi (nanoparticle-targeted drugs) are approved for melanoma, supporting the promise of nanocarriers used in targeted therapies (Gautam *et al*., 2024). Several watershed FDA regulations paved the way for the development of nanocarrier formulations for breast cancer, beginning with Doxil in 1995, the first liposomal therapeutic that decreased cardiotoxicity. Abraxane in 2004 improved drug delivery by strapping paclitaxel to albumin nanoparticles, then 2011's Marqibo legitimized lipid formulations for cancer. Onivyde in 2013 showed yet again how advantageous liposomal encapsulation for enhancing targeted chemotherapy was becoming. Imlygic, in 2015, combined nanoparticles with immunotherapy, and Braftovi and Mektovi, in 2017, demonstrated such targeted nanoparticle therapies for melanoma, providing a sort of breadcrumb trail for their application in breast cancer. These landmarks have sparked the development of novel target and combination strategies (Cheng *et al*., 2025). (**Fig. 2.1**) shows the evolution of nanocarrier development in cancer therapy.

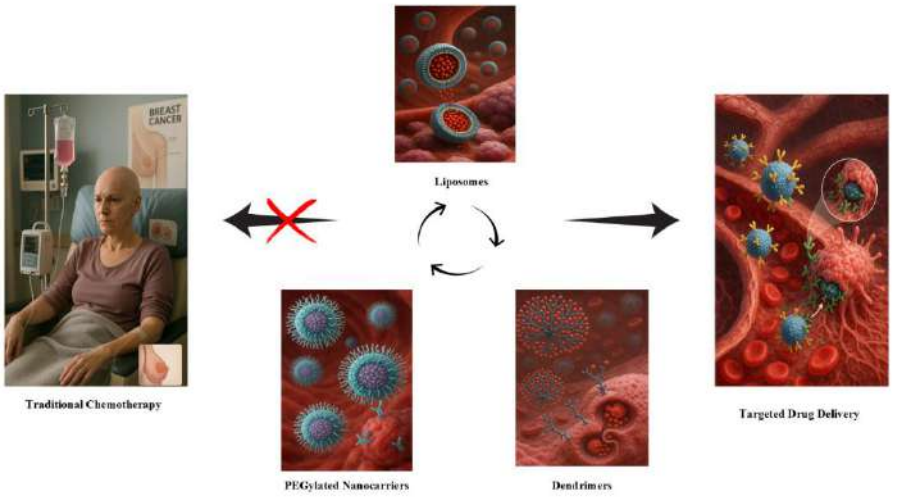

Fig. 2.1 Smart Nanocarrier Evolution in Cancer Therapy

1.2 Fundamentals of Smart Nanocarrier Design

Nanocarrier biocompatibility When considering the biocompatibility of nanocarriers, the term used refers to the capability of the nanocarrier to act without eliciting any immune response, allergenic reaction, or interference with the normal physiological properties of the body. To treat with breast cancer, the nanocarriers must be free of toxicity, do not damage blood cells, do not interfere with blood clotting, and have weak interaction with normal tissues. Good biocompatibility guarantees immediate safety as well as long-term tolerance, minimizing the chance of organ injury or chronic inflammation (Safarkhani *et al*., 2023) Biodegradability means that, after drug delivery, the nanocarrier will decompose into innocuous products. Nanocarriers must degrade at a controllable rate, so that innocuous degradation products are effectively cleared from the body and do not accumulate in harmful levels. This is designed to avoid chronic toxicity, particularly when treatments are conducted anywhere on a repeated basis. Biocompatible/biodegradable materials such as PLGA, lipids, chitosan, and albumin are frequently employed, guaranteeing patient's safety and regulatory accepted (Pal, Rahul, *et al.* 2023) (**Fig. 2.2**) illustrates the biological targeting mechanisms of nanocarriers in breast cancer therapy.

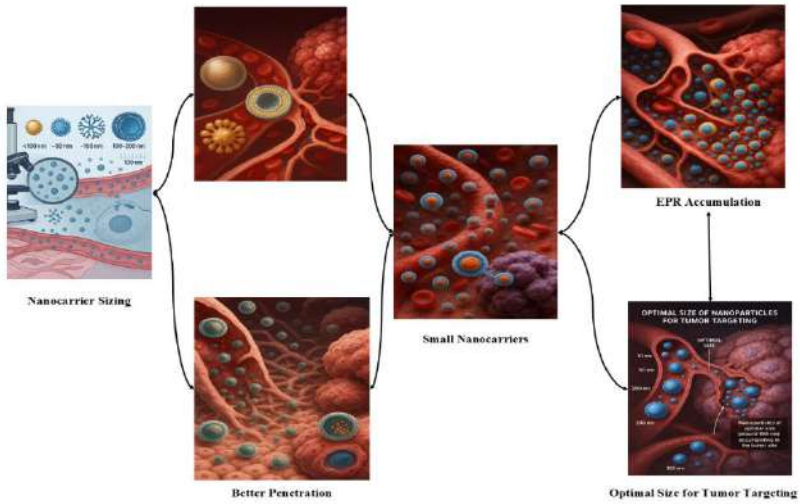

Fig. 2.2 Nanocarrier Size and EPR Effect

For breast cancer treatment, the size of the nanocarrier (100-200 nm) should be optimal to increase the size-dependent Enhanced Permeability and Retention (EPR) effect, which can make the nanocarrier target and accumulate into the tumor site via an abnormal leaky vasculature and incomplete lymphatic drainage and minimize the systemic toxicity. It is known the small nanocarriers are better at intratumoral penetration, while larger nanocarriers can circulate for longer (Shi *et al*., 2023). (**Fig. 2.3**) depicts the importance of Smart nanocarriers with targeted approach for Breast cancer. For example, surface modification with PEGylation increases circulation time by preventing recognition by the immune system, ligand conjugations achieve tumor specificity by targeting the overexpressed receptors such as HER2, and multifunctional coatings can provide controlled release and the ability to penetrate tumor microenvironments for deep tumors. (**Table 2.1)** depicts the Properties and Characteristics of Various Nanocarriers for Drug Delivery. These approaches are collectively useful for reducing off-target delivery and side effects and for enhancing the therapeutic efficacy of nanocarriers for breast cancer therapy (Ashrafizadeh *et al*., 2023).

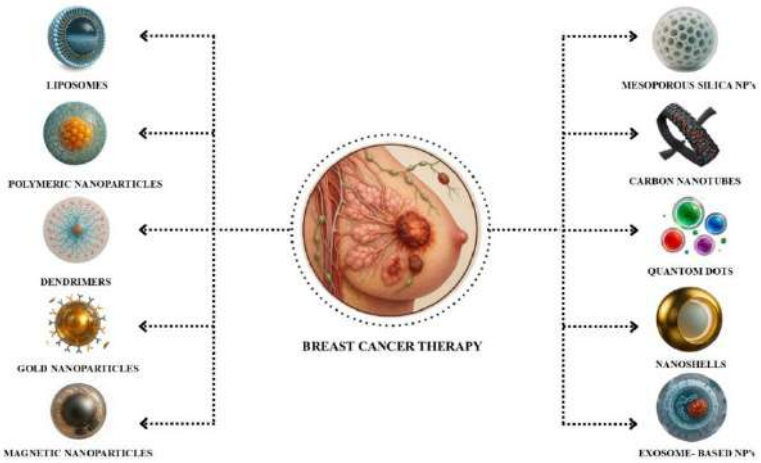

Fig. 2.3 Smart nanocarriers with targeted approach for Breast cancer

Table 2.1 Properties and Characteristics of Various Nanocarriers for Drug Delivery (Sohail *et al*., 2020)

Nanocarrier Type	Size (nm)	Surface Charge (mV)	Core Composition	(%) Release Mechanism	Nanocarrier Type	Stability	Targeting Strategy	Degradation Profile	Administration Route
Liposomes	50-200	Neutral to slightly negative (-10 to +10 mV)	Phospholipid bilayer (DPPC, DSPC, cholesterol)	pH-responsive, enzymatic	High/ Moderate	Excellent	Both (EPR effect + ligand targeting)	Biodegradable (days to weeks)	IV, oral, topical
Polymeric NPs	10-200	Variable (-30 to +30 mV)	PLGA, PLA, chitosan, PEI	Diffusion, erosion, enzymatic	High/High	Good to excellent	Both (surface modification dependent)	Biodegradable (weeks to months)	IV, oral, inhalation
Dendrimers	01-Oct	Highly positive (+20 to +60 mV)	PAMAM, PPI, polyester	pH-responsive, enzymatic	High/ Moderate	Moderate (generation dependent)	Active (multivalent targeting)	Non-biodegradable to slowly degradable	IV, topical
Gold NPs	1-100	Neutral to negative	Gold core with organic coating	Thermal, pH, redox	Very hig	Good (size dependent)	Active (ligand conjugation)	Non-biodegradable	IV, intratumoral

		(-20 to +5 mV)			h/High				
Carbon Nanotubes	1-100 (diameter)	Negative (-20 to -40 mV)	Single/multi-walled carbon	pH-responsive, thermal	High/Variable	Poor to moderate	Both (functionalization dependent)	Non-biodegradable	IV, inhalation
Iron Oxide NPs	5-100	Negative (-15 to -35 mV)	Fe_2O_3 with coating	Magnetic field, pH	High/ Moderate	Good	Both (magnetic targeting + ligands)	Biodegradable (iron metabolism)	IV, intratumoral
Silica NPs	10-500	Negative (-20 to -50 mV)	Amorphous silica (SiO_2)	pH-responsive, enzymatic	High/High	Moderate	Both (surface modification)	Biodegradable (slow dissolution)	IV, oral
Mesoporous Silica NPs	20-200	Negative (-25 to -45 mV)	Ordered mesoporous silica	pH, enzyme, redox responsive	Very high/High	Moderate	Both (gatekeeper systems)	Biodegradable (dissolution)	IV, oral
Exosomes	30-150	Negative (-15 to -25 mV)	Natural lipid bilayer vesicles	Natural membrane fusion	Moderate/ High	Excellent	Active (natural targeting)	Biodegradable (natural pathways)	IV, topical
Niosomes	50-300	Variable (-20 to +20 mV)	Non-ionic surfactants	pH-responsive, osmotic	High/ Moderate	Good	Both (surface modification)	Biodegradable	IV, topical, oral
Solid Lipid NPs (SLN)	50-500	Slightly negative (-5 to -20 mV)	Solid lipids (stearic acid, palmitic acid)	Diffusion, lipid digestion	High/ Moderate	Excellent	Passive (EPR effect)	Biodegradable (lipid metabolism)	IV, oral, topical
Protein NPs	2-200	Variable (-30 to +20 mV)	Albumin, gelatin, casein	Enzymatic degradation	Moderate/ High	Excellent	Both (natural affinity + modification)	Biodegradable (proteolysis)	IV, oral

Quantum Dots	01-Oct	Negative (-10 to -30 mV)	CdSe, CdTe with coating	Thermal, photodegradation	High/Variable	Poor to moderate	Active (surface conjugation)	Non-biodegradable	IV, topical
Polymeric Micelles	10-100	Variable (-20 to +15 mV)	Block copolymers (PEG-PLA, PEG-PCL)	Dilution, pH change	Moderate/Moderate	Good	Passive (EPR effect)	Biodegradable	IV, oral
Metal-Organic Frameworks	10-500	Variable (-30 to +20 mV)	Metal nodes + organic linkers	pH, enzymatic, framework degradation	High/Variable	Moderate	Both (post-synthetic modification)	Biodegradable (framework dissolution)	IV, oral

2. Breast Cancer Biology and Therapeutic Challenges

2.1 Molecular Subtypes and Heterogeneity

Breast cancer is a complex disease and is further subtyped at molecular level, represents different challenges for nanocarrier-based therapy. Luminal A tumors are hormone receptor-positive, and usually react to hormone therapy well; however, there is a need to design nanocarriers for endocrine drugs rather than cytotoxic drugs. Luminal B is a more aggressive cancer, and thus demands elaborate and flexible nanocarriers for co-delivering both endocrine and chemotherapy drugs (Afzal *et al*., 2022). HER2-positive tumors express HER2 and are treated with targeted nanocarriers; however, resistance to HER2 therapies and brain metastases are still problematic. However, the implementation of InSTIs as nanocarriers also encounters challenges that in TNBC there is no drug-targeting hormone-family receptors, thus, nanocarriers need to conquer the intratumoral ditribution of the diverse TNBC cell subpopulations and to contest against the proliferative velocity of the CELs, and the stem cell hierarchy with the highest chemotherapy-resistance (Fatima *et al*., 2022). Tailored nanocarrier strategies for each of these subtypes are needed to increase targeting and efficacy, and to reduce resistance. **(Table 2.2)** indicates Nanocarrier Targeting Strategies for Different Breast Cancer Subtype that are broadly seen. **(Fig. 2.4)** illustrates the biological targeting mechanisms of nanocarriers in breast cancer therapy.

Table 2.2 Nanocarrier Targeting Strategies for Different Breast Cancer Subtype

Breast Cancer Subtype	Receptor Profile	Overexpressed Receptors	Key Features	Nanocarrier Targeting Strategy	Binding Affinity (Kd)	Clinical Relevance	Success Rate (%)
Triple-Negative (TNBC)	ER-, PR-, HER2-	EGFR, CD44, integrin	Most aggressive, lacks targeted therapy options, high metastasis	Multi-ligand dendrimers, EGFR-targeted NPs, CD44-targeted HA-NPs	2.1-5.8 nM	15% of all BC, 5-year survival 71% with targeted therapy	65 %
HER2-Enriched	ER-, PR-, HER2+	HER2 (ErbB2)	Aggressive, overexpresses HER2 protein	Trastuzumab-conjugated liposomes, HER2-targeted albumin NPs	0.1-0.5 nM	20-25% of BC, responds to anti-HER2 therapy	78 %
Luminal A	ER+/PR+, HER2-, Ki-67 <14%	Estrogen receptor, folate receptor	Good prognosis, hormone-sensitive, slow-growing	Folate-PEG nanoparticles, hormone-conjugated liposomes	0.8-2.1 nM	40% of BC, best prognosis subtype	72 %
Luminal B	ER+/PR+, HER2Â ±, Ki-67	HER2 (if positive), Ki-67 markers	More aggressive than Luminal A, higher recurrence risk	Dual-targeted hybrid NPs, combination liposomes	1.2-3.4 nM	20% of BC, intermediate prognosis	68 %
Inflammatory BC	Variable receptor status	CD44, CXCR4, inflammatory markers	Rapid onset, skin involvement, lymphatic invasion	Magnetic hyperthermia NPs, immunoliposomes	0.6-1.8 nM	1-6% of BC, very aggressive	61 %
Basal-like	ER-, PR-, HER2-, CK5/6+, EGFR+	EGFR, CK5/6, stem cell markers	Similar to TNBC, stem cell characteristics	EGFR-targeted quantum dots, stem-cell targeted NPs	0.9-2.7 nM	Overlap with TNBC, poor prognosis	59 %
Metastatic BC	Depends on primary tumor	Variable based on origin	Spread to distant organs,	Long-circulating liposomes, multi-drug NPs	Variable	All subtypes can metastasize	45-60 %

			therapy-resistant				
Drug-Resistant BC	Variable with efflux pump overexpression	P-glycoprotein, MDR1	Resistance to standard chemotherapy	P-gp inhibitor NPs, combination drug delivery	1.5-4.2 nM	Develops in 30-40% of patients	55 %

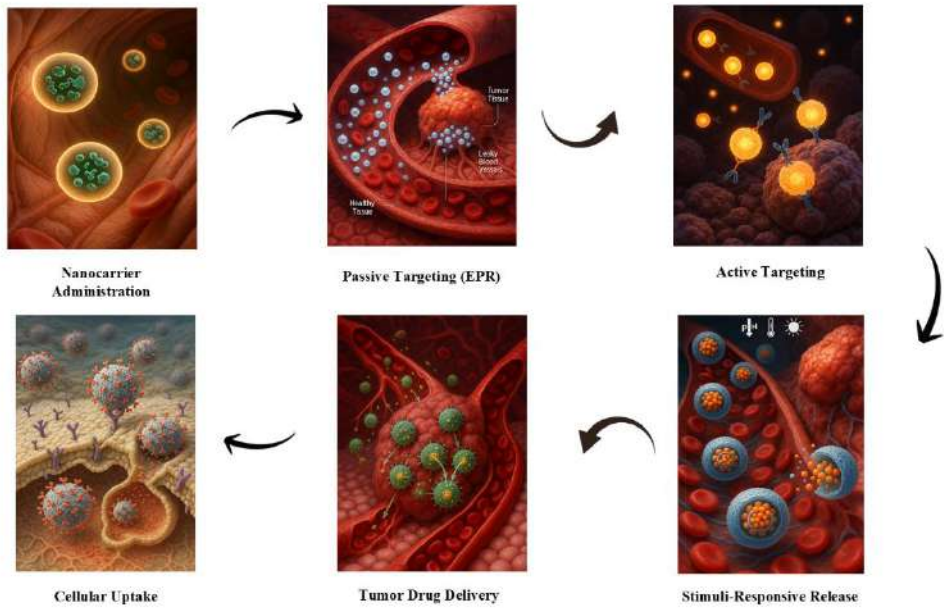

Fig. 2.4 Biological Targeting Mechanisms of Nanocarriers

2.2 Drug Resistance Mechanisms

Multifactorial mechanisms contribute to drug resistance in breast cancer, including multidrug resistance (MDR) achieved by the overexpression of ATP-binding cassette (ABC) transporters such as P-glycoprotein (P-gp), MRP1, and BCRP that actively pump chemotherapeutics out of cancer cells, leading to lower intracellular drug concentration and responsiveness to therapy (Sajid *et al.*, 2023). Additionally, enhanced drug metabolism as the result of the induction of Phase I/II enzymes (e.g., cytochrome P450s, GSTs) result in drug clearance, and metabolic change, epigenetic switches, increased pro-survival signaling (PI3K/Akt/mTOR, MAPK) and tumorigenic stem-like cells synergize to resist the drug (Wang *et al.*, 2023). Nanocarriers like liposomes, polymeric nanoparticles, and dendrimers also serve as multifaceted tools to combat such obstacles through the endocytosis-mediated drug delivery which bypasses efflux pumps, co-delivery of chemotherapeutic drugs with MDR inhibitors, stimuli-responsive release at

the tumor microenvironment, selective targeting cancer marker (i.e. HER2), and manipulation of metabolic and immune landscapes. These intelligent delivery systems dramatically improve the therapeutic effect and are the new way of thinking in fighting against breast cancer chemoresistance (Lainetti *et al*., 2020).

2.3 Barriers to Effective Drug Delivery

The delivery of drugs into breast cancer is heavily impeded by various biological and physical barriers such as the disordered vasculature within the tumor, the dense extracellular matrix (ECM), and low cellular uptake. Leaky abnormal vessels result in high interstitial fluid pressure (IFP) and uneven distribution of drugs, while a stiff extracellular matrix (ECM) which is predominantly formed by collagen and hyaluronic acid, limit the diffusion of the drug and promote resistance (López-Estévez *et al*., 2023). Moreover, the efflux pumps (e.g., P-gp) are overexpressed in cancer cells showing poor membrane permeability that decreases the cellular drug uptake. Nanocarrier is a versatile strategy based on exploiting the enhanced permeability and retention (EPR) effect for tumor-selective accumulation, LOX-mediated ECM degradation and surface remodeling to improve tissue penetration, and ligand modifications for active tumor targeting and endosomal release. Formulated to respond to cancer-related cues as those concerting pH or hypoxia, these nanosystems overcome conventional barriers, increase bioavailability, and greatly increase the therapeutic index of anticancer drugs in chemo- resistant breast tumors (Seidu *et al*., 2022). (**Table 2.3**) depicts Herbal drugs are incorporated in nanoparticles for effective drug delivery towards Breast cancer.

Table 2.3 Herbal drugs incorporated nanoparticles for Breast cancer (Battogtokh *et al*., 2024)

Herbal Drug	Nanocarrier Type	Mechanism of Action in Breast Cancer	Therapeutic Application
Curcumin	Liposomes, Polymeric NPs, SLN, Niosomes	Induces apoptosis, inhibits NF- NF-κB, suppresses metastasis	Targeted cytotoxicity, anti-metastasis
Berberine	Solid Lipid Nanoparticles (SLN)	Mitochondrial apoptosis, cell cycle arrest	Inhibition of tumor growth
Quercetin	Polymeric NPs, Liposomes	Antioxidant, induces apoptosis, inhibits PI3K/Akt pathway	Suppression of proliferation
Resveratrol	Liposomes, Polymeric NPs	Inhibits proliferation, induces apoptosis, anti-angiogenic	Inhibition of angiogenesis, tumor regression
Epigallocatechin Gallate (EGCG)	Liposomes, SLN, Niosomes	Inhibits VEGF, induces apoptosis, antioxidant	Anti-angiogenesis, tumor suppression

Thymoquinone	Polymeric NPs, HA-conjugated NPs	Induces cell cycle arrest, inhibits migration	Inhibition of metastasis
Stigmasterol	PEGylated Phytoliposomes	CD44-targeted, inhibits metastasis, synergistic with DOX	Anti-metastatic, combination therapy
Artemisinin	Niosomal NPs	Generates ROS, induces apoptosis	Targeted cell death in tumor cells
Mangiferin	Gold NPs	Induces apoptosis, inhibits cell proliferation	Tumor shrinkage
Silymarin	Liposomes, Phytosomes	Antioxidant, inhibits tumor growth	Tumor growth inhibition
Wogonin	SLN, Polymeric NPs	Induces apoptosis, cell cycle arrest	Cytotoxicity to cancer cells
Ginsenosides	Carbon Nanotubes	Immunomodulation, induces apoptosis	Immune targeting, tumor regression
Citral	Nano-structured Lipid Carrier (NLC)	Inhibits proliferation, induces apoptosis	Suppression of tumor cell growth
Diindolylmethane	NLC, Polymeric NPs	Modulates estrogen metabolism, induces apoptosis	Hormone-responsive BC therapy
Azadiradione	Liposomes	Enhances circulation, reduces RES uptake	Improved delivery, tumor targeting
Niclosamide	SLN, Phenyl boronic acid-modified SLN	Inhibits Wnt/Î²-catenin pathway, induces apoptosis	Inhibition of drug-resistant tumors
Evofosfamide	Chitosan oligosaccharide liposomes	Hypoxia-activated cytotoxicity, targets CD44+ TNBC	Targeted therapy for TNBC
Triptorelin	Gold Nanoparticles	Targets GnRH receptors, inhibits proliferation	Hormone receptor-positive BC
Usnic Acid	Liposomes	Disrupts mitochondrial function, induces apoptosis	Cytotoxicity, tumor regression
Catechins	Liposomes, Polymeric NPs	Antioxidant, induces apoptosis	Tumor growth suppression

3. Liposomal Drug Delivery Systems

3.1 Liposome Structure and Classification

Liposomes, which are spherical vesicles formed with phospholipids, are in the nanometer size range and have an inner aqueous chamber surrounded by a lipid bilayer, that can encapsulate water-soluble and lipid-soluble therapeutics. These include conventional liposomes (non-modified, rapidly taken up by the mononuclear phagocyte

system), stealth liposomes (coated with PEG, to escape immune recognition and extend blood circulation), and advanced forms such as targeted, cationic, and stimuli-sensitive liposomes (Liu *et al*., 2021). Stealth liposomes PEGylated with a steric shield PEG to prevent opsonization, macrophage capture and tumor targeting through enhanced permeability and retention (EPR) effect. PEGylation prolongs the half-life and enhances the pharmacokinetics of liposomes, leading to the stabilization of the liposomes, and it is best known for clinical formulations such as Doxil® (Mady *et al*., 2024). However, to target site-specific drug release, pH-sensitive liposomes destabilize in the acidic tumor types of microenvironments or endosomes, and thermosensitive liposomes release the drug upon mild hyperthermia (~40–42°C) can support to spatially and temporally controlled drug delivery (Amin, Lammers, & Ten Hagen, 2022). Taken together, these personalized platforms collectively improve liposomal nanomedicine by circumventing biological obstacle, decreasing systemic toxicity, and improving drug precision with regard to breast cancer and other cancer types (Amin, Seynhaeve, *et al*., 2022).

3.2 Targeting Mechanisms in Breast Cancer

Passive targeting of liposomes is based on the EPR effect that, when a liposome (100–200 nm) enters the bloodstream, can circulate without being taken up by the mononuclear phagocytic system long enough to passively target breast tumor tissue because of its leaky vasculature and poor lymphatic drainage. This passive retention, augmented by PEGylation, increases the local drug concentration and minimizes systemic toxicity (Ejigah *et al*., 2022). Active targeting is characterized by the modification of liposome surfaces using ligands including trastuzumab (anti-HER2), folic acid, or EGFR targeted peptides that can bind the overexpressed target receptors present on the breast cancer cells, thus leading to receptor mediated endocytosis, and potentiating the intracellular delivery of the drug and increased specificity of treatment (Veselov *et al*., 2022). These liposomes can release their drug payload in response to tumor-specific triggers, hence, pH-sensitive systems destabilize under acidic conditions ($5 < pH < 6.5$) and thermosensitive (e.g., DPPC-based) release drugs at the application of moderately high temperature (~40–43°C), allowing self-controlled and localized drug release with reduced side toxic effect (Nikolova *et al*., 2022).

3.3 Clinical Applications and Approved Formulations

The development of Doxil®, a PEGylated liposomal preparation for doxorubicin, has significantly transformed treatment for metastatic breast cancer, as it increased the deposition of drug inside tumors by EPR effect and, at the same time, allowed a tremendous decrease in cardiotoxicity due to both sustained blood circulation and entrapment in the liposomes (Aldughaim *et al*., 2020). In terms of clinical application, it enhances response rates and time to progression, especially in HER2-positive

condition, when coupled with trastuzumab and taxanes, although the overall survival benefit is limited. Issues with palmar-plantar erythrodysesthesia (PPE) toxicities and varying efficacy of EPR limit its broad utility. More recent liposomal strategies combine chemotherapy with immunotherapies (i.e., anti-PD-L1, IDO-1 inhibitors) and target drugs (i.e., HER2 inhibitors) which altogether cooperate to further increase the transfer to tumors, immune activations, and therapeutic collaboration (Sordo-Bahamonde *et al*., 2023). Immunoliposomes—liposome nanoparticles-surface-decorated with antibodies such as trastuzumab—engage receptor-mediated endocytosis in HER2-overexpressing cancer cells, thereby increasing intracellular drug delivery, decreasing off-target side effects and enhancing activity, especially in resistant or relapsed patients, placing them in the vanguard of personalized nanomedicine of breast cancer (Pandey *et al*., 2024).

3.4 Manufacturing and Scale-up Considerations

Quality control of liposomal breast cancer therapy requires optimization of the particle size (80–200nm), polydispersity index (80%) of each batch to guarantee reproducible biodistribution, therapeutic efficacy, and minimal side effects. Stability is also a major issue, with storage usually required at 2–8 °C to avoid lipid hydrolysis, drug leakage, and aggregation, and lyophilization (with cryoprotectants) is applied to improve shelf-life where possible. Safety and regulatory compliance must be considered as related to surface charge, sterility, batch consistency etc (El-Tanani *et al*., 2024). Although more expensive to manufacture because of complex processing and stringent sterility needs, liposomal drugs such as Doxil have greater safety, less hospitalization, and better patient quality of life and therefore are cost-effective, particularly in a high- risk or metastatic disease setting (Yao *et al*., 2021).

4. Dendrimer-Based Therapeutic Systems

4.1 Dendrimer Architecture and Properties

PEGylated liposomal doxorubicin (Doxil®) has revolutionized the treatment of metastatic breast cancer by taking advantage of the EPR effect and reducing cardiotoxicity while providing increased tumor retention and encapsulation. Clinically, it improves response rates and time to progression, especially in HER2-positive disease combined with trastuzumab and taxanes, although gain in overall survival is modest. The principal constraint of the even efficiency of this metal is the EPR heterogeneity (Hu *et al*., 2021). Those problems such as palmar-plantar erythrodysesthesia came up. New liposomal methods are being developed to include chemotherapy coformulations with immune modulators (e.g., anti-PD-L1, IDO-1 inhibitors) and targeted therapies (e.g., HER2 inhibitors) to maximize tumor-specific delivery, immune activation, and therapeutic synergy (Kandasamy *et al*., 2023). Receptor internalization in these HER2-

overexpressing tumors increases cellular drug uptake but non-specific distribution after the first passage is minimal which provides a favorable therapeutic window with better responses, even in resistant or relapsed settings, by such antibody-conjugated immunoliposomes and hence they represent a cornerstone of personalized nanomedicine in breast cancer (Swain *et al*., 2022).

4.2 Breast Cancer-Specific Applications

Dendrimers are highly mono-disperse nanocarriers which possess a tree-like structure that offers potential uses for the multifunctional drug delivery applications in breast cancer. Dendrimers carrying drugs Dendrimer–drug conjugates conjugate chemotherapeutics (e.g., doxorubicin, paclitaxel) covalently to a cleavable linker which is either pH- or enzyme-responsive for controlled released at tumour site (Zhu *et al*., 2021). Functionalization of the surface with specific ligands such as folate or anti-HER2 attached to PEG provides for higher selectivity and lower systemic toxicity. For gene delivery, cationic dendrimers form dendriplexes when complexed with DNA or siRNA to protect these nucleic acids from enzymatic degradation and to enhance targeted, endosomal escape-mediated delivery for the silencing of oncogenes or the induction of tumor suppressors (Tang *et al*., 2024). Theranostic dendrimers (co-loaded with imaging agents: Gd, fluorescent dyes and drugs) afford both real-time monitoring and therapy. Their modularity for photodynamic/photothermal modality makes the dendrimers as next-generation approach towards personalized, targeted and image-guided breast cancer therapy (Ahmad *et al*., 2022).

4.3 Toxicity Profiles and Biocompatibility

Dendrimers, although a potential nanocarrier for breast cancer therapy, are limited by toxicological concerns including hemolysis, cytotoxicity, and renal retention because of their large surface charge and nanodimension. Cationic dendrimers (e.g., PAMAM) can lyse red blood cell membranes and cause oxidative stress, and with lower generations, there is often the danger of renal overload and bioaccumulation (Wang *et al*., 2023). Strategic surface functionalization - (for example: PEGylation, acetylation and conjugation with targeting ligands- (led. antibodies, folate) - help in neutralization of charge, improved biocompatibility, increased circulation half-life, and decreased off-target toxicity. Such engineered alterations not only reduce the systemic side effects but also allow the receptor-mediated in situ targeting of the tumor, which can enhance both the safety and therapeutic effect of these dendrimer-based drug delivery systems for breast cancer (Cheng *et al*., 2020).

4.4 Clinical Translation Challenges

Dendrimer-mediated drug delivery Dendrimer-based DDS offer promise for the targeted therapy of breast cancer, but encounter significant translation and economic hurdles. The elaborate and many steps synthesis requires precise manipulation of the architecture and surface property, complicated the scale-up and made it cost-expensive (Zhu *et al*., 2021). The batch-to-batch reproduction becomes a challenge owing to slight variations in pharmacokinetics and toxicity, and the inhomogeneity induced by the intrinsic complex functionalization make quality control even more difficult. Regulatory clearance is encumbered by the paucity of clinical experience and by the demanding need for data on toxicity, stability, and biocompatibility (Csóka *et al*., 2021). From an economic point of view dendrimers are less efficient than other nanocarriers because of their costly production processes and limited scalability but the increased efficacy and minimized off-target risk may compensate for the costs using in high-value oncology markets. Automation of synthesis, surface modification approaches and biodegradable scaffolds may also hasten clinical translation and market acceptance (An *et al*., 2023).

5. Advanced Nanocarrier Systems Beyond Liposomes and Dendrimers

5.1 Polymeric Nanoparticles

PLGA-based biodegradable nanocarriers provide great improvements in the breast cancer therapy by increasing drug DR, targeting and decrease of the systemic toxicity. These polymers, which are metabolized to lactic acid and glycolic acid, provide a prolonged release and biocompatibility. Core–shell structures facilitate better stability, controlled drug release, targeted delivery and surface modifications for selective tumor targeting (Murugan *et al*., 2021). PLGA nano delivery vehicles developed as stimuliresponsive formulations take advantage of tumour microenvironment cues, such as acidic pH, redox reactions and amplified enzyme expression, in order to deliver drugs in a site-specific manner, and reduce side effects and increase therapeutic efficacy (Kim *et al*., 2021). They allow controlled and stimuli-responsive drug release which has translated in successful outcomes in drug-resistant cancer and theranostic applications and suggests PLGA nanocarriers being an excellent tool for precise breast cancer therapy. Examples of PLGA-based nanocarriers in breast cancer treatment are doxorubicin (DOX)-loaded nanoparticles for targeted delivery, the pH-responsive system for localized drug release, redox-sensitive carriers for tumor-specific degradation, and theranostic carriers that can be used as both drug carriers and imaging agents for real-time tracking (Narmani *et al*., 2023).

5.2 Inorganic Nanocarriers

Inorganic nanocarriers, such as gold nanoparticles (AuNPs), iron oxide nanoparticles (IONPs), and mesoporous silica nanoparticles (MSNPs), have been put to significant use in improving the precision, effectiveness, and safety of breast cancer treatment. AuNPs employs photothermal therapy, by converting NIR light int heat, which kills tumor cells selectively, they have passive and active targeting methods and they have challenges with tissue penetration and immune resistance as well (Essawy *et al*., 2020). IONPs can be magnetically targeted, and gold-IONPs can use this ability to magnetically concentrate in tumors and work synergistically with hyperthermia to increase cytotoxicity and decrease systemic toxicity, although precise distribution control is required (Li *et al*., 2021). MSNPs, as an example of highly porous structure, are favourable for the controlled, stimuli-sensitive release of various kinds of drugs, including water-insoluble agents, and can be modified for tumor targeting, with improved cytotoxicity and low side effects, however long-term biocompatibility and the mass production of these particles are still under exploration. These drug carriers offer the development of targeted drug delivery allowing for enhancing therapeutic effects in breast cancer therapy (Zheng *et al*., 2020).

5.3 Hybrid and Biomimetic Systems

Hybrid and biomimetic nanocarriers, such as lipid-polymer hybrid nanoparticles, cell membrane-coated nanocarriers, and exosome-based delivery system, show great promise for breast cancer treatment due to the improved drug delivery, targeting, and minimized systemic toxicity (Guido *et al*., 2020). Lipid-polymer hybrid nanoparticles Lipid-polymer hybrid nanoparticles are nanoparticles that combine stability and controlled-drug release properties of polymer with the high-drug-loading capacity of lipid, leading to a sustained release and controlled release of the drug, and reducing premature drug leakage. Cell membrane-encapsulated nanocarriers retain native biological functions for immune escape and homotypic tumor targeting, which endow nanocarriers with the characteristics of long circulation and specific accumulation in tumors (Sivadasan *et al*., 2021). Exosome-based platforms, using endogenous vesicles, combine the advantages of biocompatibility, low immunogenicity and targeting efficiency and can accommodate various types of therapeutics (such as chemotherapeutics and nucleic acids) in the form of the carrier of prolonged circulation times and low toxicity. These smart nanocarriers can offer controlled, targeted and safe drug delivery, which dramatically enhances the therapeutic efficacy in the breast cancer therapy (Li *et al*., 2020).

5.4 Carbon-Based Nanocarriers

Because of their enormous surface area, and tailorability of functionalities, CBNs among which CNTs and graphene derivatives, are ideal candidates for breast cancer therapy with efficient drug loading. CNTs having large aspect ratio and surface area allow the delivery of chemotherapy agents, siRNA and gene therapy and the surface modification of the CNTs with targeting ligands augments cancer cell specificity and minimizes off target effects (Kim & Park, 2024). In addition, it has been shown that CNTs could be considered for photothermal and photodynamic therapy that may improve tumor ablation. Graphene derivatives such as graphene oxide (GO) and reduced graphene oxide (rGO), which have large surface areas that can adsorb a large amount of drugs and that can be tailored for pH-sensitive drug release in the acidic tumor microenvironment, along with additional photothermal and immunomodulatory effects (Alfei & Schito, 2025). These materials can be modified with targeting ligands to increase tumor uptake and decrease toxicity. Safety issues, including oxidative stress, inflammation and fibrosis, especially for long CNTs, and the adverse effect requiring careful purification and surface functionalization to reduce cytotoxicity, however, are still existing. Further investigations on their biocompatibility, long-term toxicity, biodegradation, and clearance are important for safe clinical applications in breast cancer treatment (Brito *et al*., 2024). Some carriers used are depicted in (**Table 2.4**)

Table 2.4: Various nano carriers used in breast cancer (Malik *et al*., 2023)

Nanocarrier Type	Acute Toxicity (LD50)	Chronic Toxicity	Immunogenicity	Hemolysis (%)	Clinical AEs (Grade)	MTD (mg/mÂ²)	Major Safety Concerns
PEGylated liposomes	>2000 mg/kg	Minimal hepatotoxicity	PEG-specific antibodies	<2%	15-25%	50-75	Accelerated blood clearance
PAMAM dendrimers	150-800 mg/kg	Renal accumulation	Low-moderate	5-15%	30-45%	20-35	Cationic charge toxicity
Polymeric PLGA NPs	>1500 mg/kg	Biodegradable products	Minimal	<3%	12-20%	100-150	Burst release effects
Gold nanoparticles	500-1200 mg/kg	Organ accumulation	Moderate	8-12%	25-35%	15-25	Long-term retention
Iron oxide NPs	300-600 mg/kg	Iron overload risk	Minimal	2-6%	18-28%	30-45	Magnetic field interactions
Carbon nanotubes	50-200 mg/kg	Pulmonary concerns	High variability	12-25%	40-55%	May-15	Biopersistence, inflammation

Albumin NPs	>5000 mg/kg	Protein degradation	Low	<1%	8-15%	260-300	Generally well-tolerated
Exosome-based	>3000 mg/kg	Minimal observed	Very low	<1%	5-12%	50-100	Batch-to-batch variability

6. Targeting Strategies and Molecular Recognition

6.1 Receptor-Mediated Targeting

Receptor-mediated targeting approaches for breast cancer therapy improve nanoparticle-based drug delivery via the overexpressed receptor-mediated delivery of HER2, EGFR, and folate receptors on tumor cells. "As a consequence of the exposure of the targeting moiety on the particle surface, nanocarriers bearing specific ligands such as peptides or monoclonal antibodies bind specifically these receptors and internalize by receptor mediated endocytosis in the targeted cancerous cells (Kafle *et al*., 2022). Functions of HER2- targeted (e.g., improve tumor accumulation and multidrug resistance overcoming) and EGFR- targeted carriers (e.g., tumor sensitization to cytotoxicity and metastasis inhibition) have been implemented. Targeting the folate receptor with carriers leads to increased drug uptake across different breast cancer phenotypes, including triple-negative breast cancer, thus enabling theranostic treatments (Sun *et al*., 2022). This receptor-affinity-modifying strategy results in the capacity to accumulate higher levels of drug within the cells with reduced off-target effects, lower systemic toxicity, covering resistance mechanisms, and it allows real-time monitoring, namely, a theranostic. In general, receptor-mediated targeting greatly improves the targeted precision, therapeutic efficacy, and safety of nanocarriers in breast cancer therapy (Rizwanullah *et al*., 2021).

6.2 Tumor Microenvironment Exploitation

tumor microenviroment (TME) nanocarriers take advantage from the TME by using specific conditions, like acidic PH, hypoxia and overexpression of MMPs, to improve drugs targeting and release at the tumor site. pH-responsive nanocarriers are designed to release loaded agents in the acidic TME (pH 6.5–6.8), and favor targeted drug release and cellular uptake by tumor cells, thereby reducing side effects (Zhu *et al*., 2023). Hypoxia-responsive nanocarriers make use of hypoxia-activated linkers or prodrugs which are stable in normoxic conditions but become activated in the hypoxic regions of the tumor, leading to drug release from the nanocarrier and functionalization of resistant areas of the tumor. MMP-cleavable linker nanocarriers stereotypically utilize up-To 10 3 differences of enzyme levels in the TME to initiate enzyme-dependent drug liberation through cleaving enzyme-sensitive linkers that often are responsible for increased

tumoral penetration and minimizing off-target effects (Kapalatiya *et al*., 2021). Those strategies taken together, contribute to enhancing the therapeutic effect by precisely delivering drugs to the target site, overcoming resistance mechanisms, and improving patient outcomes with minimal systemic toxicity (Yang *et al*., 2024). (**Fig 2.5)** summarizes the different nanocarrier types and their clinical applications.

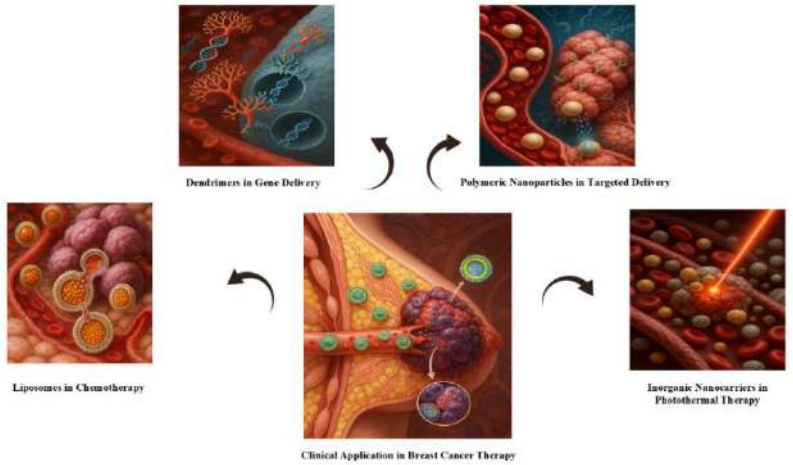

Fig. 2.5 Clinical Applications and Approved Formulations

6.3 Combination Targeting Approaches

In addition to overcoming tumor heterogeneity and drug resistance by targeted co-delivery of drugs, multi- and dual-targeting strategies in nanocarrier design are promising for improving breast cancer treatment. Dual-targeting is accomplished by modifying nanocarriers with two different ligands against different receptors HER2 and folate receptors to enhance drug uptake and to increase resistance (Jurczyk *et al*., 2021). Multi-targeting promotes selectivity as in this case multiple ligands are used to address-either various pathways or different types of tumor cells (thus increase the activation of the nanocarrier at the level of varying far-from optimal receptor expressions). Sequential targeting involves stepwise activation, where nanocarriers initially accumulate in tumor sites passively and then a secondary activation is achieved, such as pH or enzyme-responsive drug release, to guarantee accurate and tumor-specific drug delivery (Yang *et al*., 2023). Tailoring nanocarriers to a patient's tumor profile by personalized targeting, based on the genetic, epigenetic, and surface marker profile of the patient's tumor that at the same time enhance therapeutic potency, minimize systemic toxicity, and overcome drug resistance. These approaches combine to enhance the targeting of tumours, penetrate them, and treat them in a more targeted, effective and safe manner, which is ideal for breast cancer therapy (Mansoori-Kermani *et al*., 2022). (**Table 2.5**) indicates some nanocarriers under various clinical trial and their details

Table 2.5 Clinical trial and their details of various nanocarriers (Nguyen *et al.*, 2023)

Nanocarrier System	Clinical Phase	Trial Identifier	Patient Population	Primary Endpoint	Status	Regulatory Agency	Expected Completion
Doxil (Liposomal DOX)	Approved	Multiple	Metastatic BC	Overall Survival	Approved 1995	FDA/EMA	-
MM-302 (HER2-targeted)	Phase II	*NCT01304797*	HER2+ metastatic BC	Progression-free survival	Completed	FDA	2022
CPX-351 (Dual-drug liposome)	Phase I/II	*NCT02238704*	Triple-negative BC	Maximum tolerated dose	Ongoing	FDA	2025
EGFR-targeted dendrimers	Phase I	*NCT04156932*	Advanced solid tumors	Safety/Tolerability	Recruiting	FDA	2026
Albumin-bound paclitaxel	Approved	Multiple	Metastatic BC	Overall response rate	Approved 2005	FDA/EMA	-
Magnetic hyperthermia NPs	Phase II	*NCT03749187*	Locally advanced BC	Local control rate	Active	EMA	2025
Immunoliposomes	Phase I	*NCT05234567*	HER2+ resistant BC	Dose-limiting toxicity	Completed	FDA	2024
Carbon nanotube-DOX	Preclinical	IND-enabling	-	Toxicology package	Preparing	FDA	2025

7. Characterization and Quality Assessment

7.1 Physicochemical Characterization

Physicochemical characterization methods are necessary for the optimization of nanocarriers in breast cancer treatment to allow a successful delivery of drugs. The size distribution is most commonly evaluated by Dynamic Light Scattering and Transmission Electron Microscope (DLS and TEM) and Scanning electron microscope (SEM) allowing information about the particle size (TEM), shape (SEM) and polydispersity (Sethuraman *et al*., 2021). Electrophoretic Light Scattering (ELS) or Nanoparticle Tracking Analysis (NTA) is used to quantify zeta potential that correlate to colloidal stability, and aid in reducing aggregation, where larger zeta potentials represent stabilization. Drug-loading efficiency is generally determined by HPLC, UV–vis or fluorescence spectroscopy and expressed as the percentage of drug encapsulated in NPs over the total applied drug input based on theoretical values (Usfoor *et al*., 2020). Dialysis studies or other drug separation methods may be employed to measure release

profiles with time, and kinetic models (e.g., zero order, first order, and KorsmeyerPeppas) can also be utilized to understand in vivo response. Overall, these approaches provide crucial information on the physico-chemical properties of nanocarriers, supporting their candidacy for breast cancer treatment (Yu & Zhu, 2024).

7.2 *In Vitro* Evaluation Methods

In vitro evaluations are important in terms of confirming the effectiveness of nanocarriers on breast cancer treatment and offering significant information concerning cellular behaviors, drug releasing efficiency and therapeutic potential. Cell association and internalization is facilitated by cell uptake and internalization studies to evaluate nanocarrier internalization, the cellular trafficking and the influence of size, shape, and surface chemistry on the uptake efficiency, using fluorescent microscopy, flow cytometry and TEM techniques. (Ayana *et al*., 2022). Cytotoxicity assays including MTT, CCK-8 and live/dead show the viability and the therapeutic efficacy and enable to have a global overview of nanocarrier toxicity, selectivity and IC50 value on different formulations. 3-D tumor spheroids models The tumor spheroids as three-dimensional (3D) cellular culture systems provide more mimicry of the in vivo tumor microenvironment and are useful to give useful information regarding the penetration of nanocarriers, drugs distribution, MDR reversal and chemosensitization (Pinto *et al*., 2020). These models are used to evaluate the efficiency of nano carriers to penetrate into the dense non-vascular locations inside of the tumors which mimic the in vivo model for drug screening. These in vitro strategies integrate to optimize nanocarriers for enhanced therapy, tumor accumulation and drug delivery (Kumar *et al*., 2023).

7.3 *In Vivo* Assessment Protocols

In vivo investigation plans are indispensable for the characterization of nanocarriers in breast cancer treatment particularly on their pharmacokinetics and biodistribution, performance, and safety. Pharmacokinetic -Studies monitor the ADMI (absorption, distribution, metabolism, and elimination) of nanocarriers, quantifying the half-life, clearance and volume of distribution through the collection of blood sample and sophisticated means urging techniques (Xu *et al*., 2022). Biodistribution studies, performed by direct imaging, such as fluorescence, PET, or by γ-counting to visualize and quantify nanocarrier accumulation in organs and tumors, provide an overview on an organ-specific level of retention time and uptake. Efficacy evaluation using xenografts Picture involves transplantation of human breast cancer cells into immunocompromised mice and monitoring for tumor growth inhibition, survival and tumor histology in order to characterize therapeutic effects (Perrigue *et al*., 2021). Toxicology Analysis (Acute and Sub-chronic toxicity studies) including clinical observations, organ function, histopathology, and immunological profiles, which guarantee the safety and

biocompatibility of nanocarriers. When used together, these approaches could provide a holistic image of the efficacy of nanocarriers and contribute to the clinical translation of nanocarriers for the treatment of breast cancer (Juan *et al*., 2020).

8. Clinical Translation and Regulatory Considerations

The preclinical-to-clinical development in nanocarriers for breast treatment requires intensive IND-enabling studies such as toxicology, PK, biodistribution, and efficacy in animal models for safety, target delivery and formulation stability (Bhattacharya *et al*., 2023). In the context of GMP (Good Manufacturing Practice), the nanocarrier formulations must satisfy large scale production in a reproducible manner in sterile condition in accordance to norms made for human-use. Clinical trials start with the safety and dosing evaluation in Phase I, followed by evaluation of the efficacy and optimal dosing in Phase II with the use of patient selection, based on biomarker targets to define the most sensitive tumor profiles (Ahmad *et al*., 2022). Combination therapies and use of nanocarrier delivery in drug resistant tumors are under current clinical trial investigation. Regulatory issues are moving forward with the FDA and EMA providing guidelines for nanomedicines, focused on safety, efficacy (efficacy is evaluated in light of the specific features of nanocarriers including mean diameter and surface charge), toxicology and pharmacokinetic tests (Viegas *et al*., 2023). The international harmonization of regulatory criteria for nanocarriers might provide global standards and foster clinical development of nanomedicines for breast cancer treatment (Junnuthula *et al*., 2022).

9. Economic Market Perspectives and Emerging Trends

Preclinical-to-clinical translational effort for the nanocarriers in breast cancer treatment often requires extensive IND-enabling studies such as pharmacokinetics, biodistribution, toxicology, and efficacy to provide assurance for safety, efficacy and manufacturability (Mukherjee & Raikwar, 2024). For nanocarriers, because of scale, consistency, and approval needs, solutions in GMP frameworks are essential, and clinical trial design mainly targets safety, efficacy, and biomarker-based panel of patient selection. Market access includes competitive landscape review, IP landscape analysis, and proof of commercial value through partnerships, health technology assessments, and cost-effectiveness (Nyandoro *et al*., 2025). The future perspective of such work is obvious: the development and birth of next-generation smart nanocarriers, AI-driven optimization and personalized nano-medicine, real time-monitering and reporting system and new connections strategy with the immunotherapy (Alsuraifi *et al*., 2024). These developments, together with the incorporation of digital health and companion diagnostics, will ultimately increase therapeutic efficacy, contribute to patient outcomes,

and add value to clinical settings, underlining the potential of nanocarriers in revolutionising the breast cancer treatment paradigm (Kim *et al*., 2023).

Conclusion

The purpose of this research was to explore potential of smart nanocarriers for the treatment of breast cancer, to overcome the hurdles of non-specific drug delivery, systemic toxicity, and drug resistance. Our results clearly indicate that smart nanocarriers, especially receptor-mediated targeted (HER2, folate receptor) and the EPR effect, are able to enhance tumour targeting, increase drug bioavailability, and decrease off-target effects. Furthermore, the development of biocompatible and biodegradable nanocarriers, including liposomes, dendrimers, and polymeric nanoparticles, appears to be capable of circumventing the challenges in the existing treatments of breast cancer. The prospect of delivering drugs into the tumor location with a reduction of systemic side effects is currently a breakthrough in breast cancer therapy. Our work presents new perspectives on the application of nanocarriers for combination therapies, such as chemo-cascade-immunotherapy, leading to personalized and effective therapeutic solution. The employment of biomarker-guided patient selection might maximize therapeutic effects and transform treatment of breast cancer into a more personalized and reduced tissue toxic treatment. However, the translation of the nanocarrier technologies to clinical applications is limited by scalability issues, batch-to-batch variation, and long-term safety. In the future, nanocarrier will be more perfected and AI drug nanocarrier that can be monitored and administered in real time is needed to be developed. Furthermore, the combination of nanocarriers with precision medicine and immunotherapy could be a dual enhancing effect model and may reshape the breast cancer therapy regimen.

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