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Chapter 6: Nanocarriers-based Nanomedicine: Polymer Loaded Nanocarriers in Breast Cancer

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Abstract

Breast cancer continues to be one of the most widespread cancers globally, and the effectiveness of treatment is frequently constrained by systemic toxicity, multidrug resistance, and low bioavailability of standard chemotherapeutic agents. As a means of addressing these challenges, polymeric nanocarriers have emerged as a promising option, allowing for site-specific delivery, controlled release, and enhanced pharmacokinetics of anticancer agents. This chapter offers a detailed examination of polymer-based nanocarriers and their contribution to the development of breast cancer treatment. An exploration of the essentials of nanocarrier design is provided, highlighting their categorization into nanospheres, nanocapsules, micelles, and dendrimers. It also addresses key design factors like particle size, zeta potential, drug loading capacity, and the choice of polymer. Both natural and synthetic polymers are investigated, focusing on their biocompatibility, biodegradability, and potential for engineering into smart stimuli-responsive systems for tumor-selective delivery. Mechanisms that underpin targeted delivery—such as passive targeting through the enhanced permeability and retention (EPR) effect, active targeting via receptor–ligand interactions, and triggered release within the tumor microenvironment—are examined. Special emphasis is placed on drug-specific polymeric formulations like carriers loaded with doxorubicin, paclitaxel, and tamoxifen. This includes co-delivery strategies that combine chemotherapy with gene or phototherapy to achieve synergistic effects. To illustrate translational potential, case studies and in vivo evaluations are underscored, especially with regard to tackling therapeutic resistance in triple-negative breast cancer (TNBC). Overall, polymeric nanocarriers offer versatile and adaptable platforms for next-generation breast cancer therapeutics, bridging the gap between laboratory research and clinical application.

Keywords: *Breast cancer, Polymeric nanocarriers, Stimuli-responsive polymers, Targeted drug delivery, Triple-negative breast cancer (TNBC).*

1. Introduction

Breast cancer is the most common cause of mortality, and the most common cancer diagnosed in women. In the treatment of breast cancer, metastasis and tumor recurrence are creating new issues. Nanotherapeutics for breast cancer are advancing steadily and are being employed to overcome the various limitations of traditional methods used for diagnosing and treating breast cancer. Nanoparticles offer an interdisciplinary research domain in the fields of imaging, diagnosis, and targeting breast cancer. Nanomedicine is the use of nanotechnology for treating and detecting diseases. There has been extensive research into nanoscale particles created from organic molecules that can be used for drug and gene delivery. For example, liposomes, polymersomes, polymer constructs for controlled release of proteins and macromolecules, polymeric micelles, and long-circulating polymeric nanoparticles are in various stages of preclinical and clinical development. (Sharma *et al*., 2013; Guan *et al*., 2024,)

One of the main difficulties in treating breast cancer is drug resistance. Multiple nanomaterials have been found and created in recent years that can selectively aim at tumor cells and are vital to the progress of breast cancer treatments. Nanomaterials can be classified based on various criteria. Common classifications include zero-dimensional, one-dimensional nanomaterials, and polymers, as determined by their dimensions. (Huang *et al*., 2011) Nanomaterials used in breast cancer treatment are often categorized according to their chemical composition, as shown in Table 6.1.

Table 6.1 Advantages and disadvantages of several nanomaterials

Sr. No.	Nanomaterials	Advantages	Disadvantages
1	Solid lipid nanoparticles	Enhanced biopharmaceutical performance	Low encapsulation efficiency
2	Liposomes	Good biocompatibility	
3	Polymeric nanoparticles	Multifunctional delivery	Prone to easy aggregation and toxicity
4	Magnetic nanomaterials	Controllable sustained release	Toxicity and solubility limitations
5	Magnetic nanomaterials	Stability and very high encapsulation efficiency	
6	Quantum dots	Tunable optical properties, a large surface-to-volume ratio, high brightness, and resistance to photobleaching	

Nanotechnology is the manipulation of matter's molecular and cellular constituents. Nanoparticles hold promises for substantially enhancing the therapeutic efficacy of pharmaceuticals because of their superior protective capabilities and their ability to aid in drug distribution at targeted sites of action (Bobo *et al*., 2016). With special focus on polymeric nanoparticles, which consist of polymer building blocks. These nanoparticles differ from earlier drug-delivery devices due to their polymeric nature, which allows for a wide range of highly intricate designs. Polymeric nanoparticles offer significant advantages for drug delivery due to their size, shape, and surface charge. Due to these advantages, polymeric nanoparticles are garnering significant interest in innovative drug-delivery designs. With the development of more advanced therapeutic cargo and treatments, their significance will increase (Sartaj *et al*., 2021).

The delivery of multiple drugs using polymeric nanoparticles results in a down-regulation of the absorption process. This can help to overcome drug resistance seen with single agents (such as in chemotherapy) and lead to synergistic or additive therapeutic effects. These systems of polymeric nanoparticles provide an alternative method for improving the targeting of medication (Chan *et al*., 2010).

2. Polymer-based nanocarriers: fundamentals

The targeted delivery of therapeutic moieties in cancer has been investigated using a variety of polymeric nanocarriers. Both natural and synthetic polymers can be used to create these nanocarriers. These polymeric nanoparticles can carry a range of medications to their target sites in a controlled way over a prolonged duration, thereby achieving enhanced antitumor efficacy while minimizing systemic side effects. The stability and target specificity of the medicine are further enhanced by these nano systems, which shield it from the liver, kidney, and reticuloendothelial system's quick metabolism during systemic circulation (Nicolas *et al*., 2013).

2.1 Classification of Polymeric Nanocarriers

Attempting to classify the nanocarriers precisely is a challenging undertaking. Since there are no clear borders in the field of pharmaceutical and biomedical nanotechnology, various viewpoints may be pertinent. They can also be classified as natural or synthetic polymeric nanoparticles based on where they come from. Often referred to as polymeric (biodegradable and biocompatible) nanoparticles, dendrimers, nanoemulsions, polymersomes, polymeric micelles, biopolymer complexes, or cubosomes, these are characterized by their simultaneous polymeric design and colloidal (1–1000 nm) measurements (De Jong *et al*., 2008). The classification of polymeric nanocarriers is shown in figure 6.1.

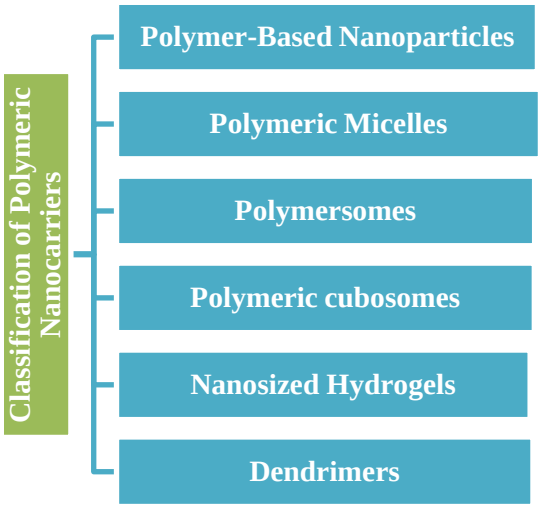

Figure 6.1 Classification of polymeric nanocarrier

2.1.1 Polymer-Based Nanoparticles

Nanocarriers based on polymers are generated from either natural or synthetic polymers that undergo modification to create submicroscopic particles. The polymer matrix can be tailored to offer particular characteristics, including surface chemistry and flexibility. Polymeric nanoparticles, for instance, have been utilized for targeted drug or gene delivery and are also employed in tissue engineering. The typical polymers utilized in the synthesis of polymeric nanocarriers are poly (lactic acid) (PLA), chitosan, and poly (ethylene glycol) (PEG), which are low-toxic and biodegradable.

It is possible to create a hybrid polymer using both natural and synthetic polymers, which possess the beneficial characteristics of each. For example, the combination of chitosan and PLGA can enhance the biocompatibility and drug release kinetics of the nanocarrier. Drugs are protected from chemical degradation and have improved pharmacokinetic features when entrapped in NPs, which results in a long-term regulated release. With the help of targeting ligands, NPs can easily functionalize their surfaces to deliver drugs to specific sites, increasing the effectiveness of treatment (Roy *et al*., 2023).

2.1.2 Polymeric Micelles

Under the right temperature or concentration, amphiphilic block copolymers may self-assemble into nanoscale core-shell micelles in aqueous settings. Drugs that are poorly soluble in water can be encapsulated thanks to their hydrophobic cores. They provide better stability and less toxicity than conventional solubilizers like Cremophor EL. For instance, paclitaxel is used to treat breast cancer using Genexol-PM, a polymeric micelle

formulation that makes parenteral administration safer and more efficient. (Popovici *et al*., 2022).

2.1.3 Polymersomes

Compared to liposomes, polymersomes have better mechanical and colloidal stability since they are made of amphiphilic block copolymers with one or more bilayers around an aqueous core. They are perfect for targeted medication administration and diagnostics because of their tuneable structure. The size and structure of the vesicle affect the cellular absorption and therapeutic response of the active medication, which can be encapsulated, dissolved, or bonded to it. For instance, because of its improved intracellular delivery and less systemic toxicity, doxorubicin delivered via polymersomes has demonstrated promise in the treatment of breast cancer. (Leong *et al*., 2018).

2.1.4 Nanosized Hydrogels

Hydrogel-based local drug delivery systems (DDS) minimize systemic adverse effects by delivering medications directly to the tumor site, providing targeted treatment for solid tumors. These hydrogels are helpful in sophisticated cell culture systems such as cell microarrays because they promote cell adhesion and biocompatibility. Both passive and active targeting are improved by their nanomaterial composition. To treat localized cancer, for instance, injectable, visible light-cured glycol chitosan hydrogels have been created, allowing for precise distribution close to tumor areas. (Chabria *et al*., 2021).

2.1.5 Polymeric cubosomes

Block copolymers self-assemble to generate nanoscale particles known as polymeric cubosomes, which have a distinctive inverse continuous cubic shape. Their linked nanoscopic channels make them perfect for regulated medication delivery. Usually, hydrophilic PEG and hydrophobic polyisoprene blocks are used to make them. Through their structure, drugs that are hydrophilic or hydrophobic can be efficiently encapsulated. The administration of anticancer medications, for example, has been studied using PEG-polyisoprene-based cubosomes due to its excellent stability and long-term release properties. (Kim *et al*., 2019).

2.1.6 Dendrimers

Because they have a central core and are extremely branching, tree-like synthetic polymeric macromolecules, dendrimers are perfect drug delivery vehicles. Anticancer medications can be conjugated or encapsulated thanks to their tuneable surface and well-defined structure. This improves controlled release, targeting, and solubility. For instance, methotrexate has been administered using polyamidoamine (PAMAM) dendrimers in breast cancer treatment, increasing medication absorption and lowering toxicity (Mital *et al*., 2021, Bober *et al*., 2022).

2.2 Critical Parameters of Polymeric Nanocarriers in Breast Cancer

The use of polymeric nanoparticles to carry genes, small-interfering RNAs, and chemotherapy drugs is growing in popularity. They are excellent nanocarriers for increasing the efficacy and bioavailability of therapeutic agents while reducing toxicity because of their special qualities, which include high stability, ease of surface modification, responsiveness to stimuli, controlled drug release, the ability to encapsulate multiple therapeutic agents simultaneously, the ability to target tumors for payload delivery, and improved permeation and retention effects. (Powers *et al*., 2007)

2.2.1 Stimuli-Responsive Polymeric Nanoparticles:

The chemistry of polymers and co-polymers can be modified, enabling post-polymerization modifications through chemical processes. One such process is covalent coupling, which provides numerous opportunities for refining the polymers at both sub-molecular and molecular levels. Functional groups such as alcohols, carboxylic acids, and amines are found in polymers and copolymers, and they are typically utilized for the chemical modification of these polymers. Such stimuli-responsive NPs have garnered significant interest in delivering payloads to targeted tumor locations under specified conditions. A variety of stimuli, including both extrinsic (light, ultrasound, temperature, and magnetic) and intrinsic (pH, hypoxia, ROS, enzyme, and redox) factors related to the biological structure, have been utilized to regulate payload release from NPs. Stimuli-responsive blocks with polymeric NPs experience desired changes in their properties, including pH-Responsive Polymeric Nanoparticles, Temperature-Responsive Polymeric Nanoparticles, Redox-Responsive Polymeric Nanoparticles, and Light-Responsive Polymeric Nanoparticles (Chithrani *et al*., 2006, Mozar *et al*., 2017, Fatima *et al*., 2022).

2.2.2 Size and Surface Area

Surface area and nanocarrier size have a significant impact on how the nanocarriers are dispersed and absorbed by cells, how they build up at the tumor site, and how much of the medicine they contain is released. The vast surface area and compact size of nanocarriers dictate their pharmacological characteristics. Numerous research studies have indicated that the toxicity increases with increasing size due to their capacity to access different biological systems. Nanocarriers between 100 and 200 nm in size have a shorter half-life and limited capacity to target different tissues when they enter the reticuloendothelial system. Nanocarriers' size has an impact on their cytotoxicity, intracellular localization, and cellular absorption; this is particularly true when it comes to their interactions with living cells. For nanocarriers to be absorbed by cells, their particles must be at least 30 to 50 nm in size, regardless of their substance. The size of nanocarriers also had a major impact on their dispersion. The likelihood of small

nanocarriers being absorbed by cells is higher than that of larger ones. It is therefore concluded that the stability of the nanocarriers to cellular absorption, cytotoxicity, cellular uptake, and toxicity was significantly influenced by their size and surface area (Hosino *et al*., 2004, Slowing *et al*., 2006).

2.2.3 Shape

Finding the nanocarriers is one of the key components of focused treatment. It's been demonstrated that spherical nanoparticles are easier for cells to absorb than rod-shaped ones. The nonspherical nanoparticles, which have a higher propensity to enter capillaries than spheres, have also been shown to exhibit toxicity. In terms of blood circulation and tumor absorption, nanospheres outperform nanorods, nanocages, and nano discs. Most of the studies also show shape-dependent toxicity. More research suggests that nanospheres are absorbed more quickly than Au nanorods (Alexis *et al*., 2010).

2.2.4 Surface Charge

The interaction between nanocarriers and biological components is determined by their surface charge. Absorption, plasma protein binding, colloidal nature, membrane permeability, and toxicity are all impacted by the surface charge of nanocarriers. It was demonstrated that both positively and negatively charged nanocarriers were absorbed by cells far more quickly. The targeted delivery and aggregation of nanocarriers are controlled by the surface charge. The surface coating has the potential to change the surface charge of the nanocarriers and shield them from endosomal trapping. The study showed that surface-modified silica nanoparticles with different charged functional groups might be internally trapped. The findings suggested that the negatively charged nanocarriers would have an easier time avoiding endosomal entrapment. Scientists found that altering the surface charge might impact the way medications are administered to a specific tissue, which is believed to be brought on by the alteration. Thus, the surface charge of the nanocarriers has a major impact on permeability, targeted drug delivery, escape from endosomal entrapment, toxicity, plasma protein binding, and absorption. (Maji *et al*., 2014).

2.3 Nanocarrier Polymer employed in breast cancer

The several nano formulations designed to enhance the distribution of natural and synthetic cancer fighting agents, either individually or in combination, exhibit superior pharmacokinetics and effectiveness.

2.3.1 Natural Polymers

Animals, plants, bacteria, and fungi are all sources of natural polymers. Protein-based polymers and polysaccharides are the two primary categories. For the delivery of drugs, both have been thoroughly studied. As a viable extracellular matrix (ECM), both can create scaffolds. In this manner, less invasive behaviour and greater loading efficiency can be obtained for targeted medication delivery. Natural polymers and their

combinations delivered using nanotechnology for the treatment of breast cancer are shown in table 6.2.

Table 6.2 Natural polymers and their combinations delivered using nanotechnology for the treatment of breast cancer

Material	References	Composition of nanoparticle	Significance
Chitosan	(Santos *et al*., 2015, Nascimento *et al*., 2014, Esfandiarpour *et al*., 2017)	Ascorbic acid, Penta sodium tripolyphosphate	Antioxidative; reduced viability of cervical cancer cells; nontoxic to human normal cells
		EGFR binding peptide, PEG2000, Mad2 siRNA	Selective uptake by NSCLC cells; stronger tumor inhibition in a drug-resistant model
		Folate, curcumin	Targeted folate receptors; enhanced toxicity to breast cancer cells; controlled release in acidic environments
		Glycyrrhizin acid, doxorubicin	Enhanced cellular uptake and cytotoxicity of doxorubicin
		PNVCL, cell-penetrating peptide, doxorubicin	Controlled in acidic and hyperpyrexia conditions; selective cellular uptake; stronger tumor inhibition and lower systemic toxicity
Hyaluronic acid	(Ganesh *et al*., 2013, Yan *et al*., 2019, Han *et al*., 2015, Zhnag *et al*., 2019)	Cisplatin, siRNA, near IR dye indocyanine green (ICG), various fatty amines or cationic polyamines	Targeted CD44 receptors; effective in combination treatments against resistant cancers
		L-lysine methyl ester, lipoic acid, doxorubicin	Controlled release of doxorubicin triggered by GSH;

			targeted CD44 receptors
		PEGylated cationic quaternary amine, *n*-octyl acrylate segments, doxorubicin	Controlled release in acidic environments; antibacterial; overcame bacteria-induced tumor resistance
		Glycyrrhizin acid, L-histidine, doxorubicin	Controlled release in acidic environments; improved antitumor efficacy of doxorubicin
		Polycaprolactone, 2-(Pyridyldithio)-ethylamine, doxorubicin	Improved performance of doxorubicin; targeted delivery; controlled release in acidic environments
		Dodecylamide, docetaxel	Inhibited the growth of A549 cells; stable in human plasma
		PLGA, PEI, docetaxel, α-naphthoflavone	Overcame the multidrug resistance; improved bioavailability of docetaxel
Alginate	(Chiu *et al*., 2020, Bhattachryya *et al*., 2016, Gao *et al*., 2017)	Thiolated sodium alginate, fluorescein-labeled wheat germ agglutinin (fWGA), docetaxel	Selective uptake by cancer cells; stronger cytotoxicity toward HT-29 cells; degraded by GSH
		Disulfide crosslinked alginate, doxorubicin	Improved safety profile of doxorubicin; selective uptake by cancer cells;
		Poly(allylamine hydrochloride), poly(4-styrenesulfonic acid-co-	Selective uptake by HT-29 cells;

		maleic acid) sodium salt, paclitaxel	induced cell death to the cancer cells
		pheophorbide A, doxorubicin	GSH dose-dependent release manner of payloads; accumulated in the tumor site; combination of chemotherapy and photodynamic therapy
Dextran	(Curcio *et al*., 2019, Lee *et al*., 2017, Forester *et al*., 2016)	Carboxymethyl dextran, lithocholic acid, doxorubicin	Release triggered by GSH; improved therapeutic efficacy and biodistribution profile of doxorubicin
		Curcumin, methotrexate	Sustained release; synergistic effect in treating MCF-7 cells.
		Chlorin e6, gold nanoparticles	Efficient cellular uptake; no leakage; accumulation of chlorin e6 at tumor site
		Dextran acrylate, stearyl amine microRNAs	Stabilized and delivered microRNAs into the carcinoma cells; suppressed osteosarcoma cell proliferation
		PEGylated dextran, siRNA	Changed biodistribution and cellular uptake without affecting cytotoxicity
		Folic acid, doxorubicin	Enhanced tumor inhibition; targeting folate receptors

Comparing natural material-based Drug Delivery Systems to traditional therapies, positive outcomes have been seen. Biocompatible, biodegradable, nontoxic, nonimmunogenic, and easily functionalized through structural change are just a few of their many advantages. Different approaches can be taken into consideration when creating a Drug Delivery Systems formulation for cancer treatment using natural ingredients.

2.3.2 Synthetic Polymer

Nanomaterials used as carriers for the anticancer drugs utilized in the breast cancer treatment are broadly classified into two categories: organic and inorganic. Liposomes, micelles, dendrimers, and cyclodextrin are examples of organic materials, whereas inorganic materials include iron oxide, gold nanoparticles, and mesoporous silica nanoparticles. Furthermore, depending on the intended biological uses, synthetic polymers can be easily functionalized and changed. The Synthetic polymers are shown in table 6.3. These synthetic polymers or their derivatives can break down into non-toxic oligomers or monomers, which the body can subsequently get rid of through regular metabolic processes. Nanotechnology can help achieve improved treatment in many ways including cancer targeting, increased endocytosis and extended circulation time which improves the access of anticancer drugs to the tumor sites (Kumar *et al*., 2023, Aljibali *et al.*, 2020). Table 6.4 lists the characteristics of the synthetic and natural polymers utilized in breast cancer.

Table 6.3 Synthetic polymers and their combinations delivered using nanotechnology for the treatment of breast cancer

Materials	Drugs
Liposomes	Exemestene
Phospholipid Complex	Docetaxel
β-Cyclodextrinsinclusion complex	Genistein
PEGylated liposomes	Doxorubicin + Umbelliprenin

Table 6.4 Features of Natural and synthetic polymer used in breast cancer

Features	Natural Polymers	Synthetic Polymers
Biocompatibility	High	Variable
Biodegradability	Natural enzymatic pathway	controlled via design
Reproducibility	Low	High
Targeting ability	Natural Ligand affinity	Engineered targeting ligand
Toxicity	Low	Possible
Drug Loading	Lower	Higher

2.4 Biodegradability and Biocompatibility Considerations

Biodegradable polymer nanoparticles can be used to construct a variety of formulations, such as solid nanoparticles, core-shell structures, polymeric micelles, and polyplexes. Although polymeric nanoparticles are often generated by either self-assembly or emulsion, the ideal nanoparticle formulation and synthesis process depends on the characteristics of the selected polymer and payload. To put it briefly, self-assembly techniques consist of A range of formulations, including solid nanoparticles, core-shell structures, polymeric micelles, and polyplexes, can be created using biodegradable polymer nanoparticles. Although polymeric nanoparticles are often generated by either self-assembly or emulsion, the ideal nanoparticle formulation and synthesis process depends on the characteristics of the selected polymer and payload.

Several methods can be used by biodegradable polymeric nanocarriers to achieve anti-cancer targeting. The capacity to enable transport across the endothelium to the tumor, ligand-mediated targeting, and prolonged circulation in the bloodstream all contribute to delivery straight to the tumor cells. Polymeric nanocarriers can also target other cells that are part of the tumor microenvironment. The tumor-associated neo vasculature is essential for enabling a tumor to receive enough oxygen and nutrients to support growth, making the tumor vasculature a prime target. The equilibrium between an anti-cancer immune response and a tumor's immunosuppressive microenvironment can influence whether a tumor goes into remission or spreads, making immune cells another crucial target. (Darge *et al*., 2019; Jiang *et al*., 2017; Waks *et al*., 2019)

3. Mechanisms of targeted drug delivery in breast cancer

Polymeric nanoparticles are favoured in targeted drug delivery due to their numerous advantages. They offer controlled drug release, minimising dosing frequency and allowing sustained release profiles. The different mechanism of drug delivery in breast cancer are shown in figure 6.2.

Figure 6.2 Mechanisms of Targeted Drug Delivery in Breast Cancer

3.1 Enhanced Permeability and Retention (EPR) Effect

The Enhanced Permeability and Retention (EPR) effect is a cornerstone of passive drug targeting in solid tumor, including breast cancer. This phenomenon arises due to the unique anatomical and pathophysiological characteristics of tumor vasculature.

Tumor require a constant supply of nutrients and oxygen to sustain their rapid growth. As a result, they stimulate the formation of new blood vessels through a process known as angiogenesis. However, these neo vessels are often abnormal—poorly aligned, leaky, and lacking the tight junctions found in normal vasculature. This leakiness allows macromolecules and nanoparticles (typically 10–200 nm in size) to extravasate more readily into tumor tissues than into normal tissues.

Moreover, tumor generally have deficient lymphatic drainage, which limits the clearance of these macromolecules from the interstitial space. The combination of increased vascular permeability and reduced lymphatic drainage leads to the preferential accumulation of nanocarriers in tumor tissues.

In breast cancer, the EPR effect can be leveraged using nanocarrier systems such as liposomes, polymeric nanoparticles, dendrimers, and micelles, which encapsulate chemotherapeutic agents and preferentially accumulate in tumor tissues. Doxil®, a PEGylated liposomal formulation of doxorubicin, is a prime example of an EPR-based drug delivery system approved for clinical use.

Despite its advantages, the EPR effect is not uniform across all tumor types or even within different regions of the same tumor. Variability in vascular density, interstitial fluid pressure, and perfusion can influence drug delivery efficiency. Consequently, while the EPR effect provides a foundation for passive targeting, it is often complemented by active targeting strategies. (Yara *et al*., 2025; Wen *et al*., 2024)

3.2 Active Targeting: Receptor-Ligand Interactions

Active targeting involves the use of ligands that specifically recognize and bind to receptors overexpressed on the surface of cancer cells, facilitating the selective delivery of therapeutic agents. In breast cancer, several surface biomarkers have been identified and exploited for active targeting:

3.2.1 HER2 Receptors

Approximately 20–30% of breast cancers overexpress the human epidermal growth factor receptor 2 (HER2), a tyrosine kinase receptor associated with aggressive disease and poor prognosis. Monoclonal antibodies like trastuzumab specifically bind to HER2, inhibiting its signalling and inducing immune-mediated cytotoxicity. Conjugating chemotherapeutic drugs or nanoparticles to trastuzumab allows for receptor-mediated endocytosis, enhancing cellular uptake and specificity.

3.2.2 Estrogen and Progesterone Receptors

Hormone receptor-positive breast cancers, which express estrogen receptors (ER) or progesterone receptors (PR), represent another subtype amenable to active targeting. While direct targeting of these nuclear receptors with ligands is more challenging due to

intracellular localization, hormone-responsive gene expression can be manipulated to enhance the selectivity of delivery systems. (Hong *et al*., 2022; Smolarz *et al*., 2022)

3.2.3 Folate Receptors

Folate receptors are overexpressed in many epithelial cancers, including subsets of breast cancers. Folate, a small molecule vitamin, can be conjugated to nanoparticles, facilitating receptor-mediated uptake into cancer cells. This approach benefits from folate's high binding affinity and the minimal expression of its receptor in normal tissues.

3.3 Integrins and Other Surface Proteins

Other surface proteins such as integrins (e.g., αvβ3), transferrin receptors, and epidermal growth factor receptors (EGFR) have also been targeted using corresponding ligands, peptides (like RGD), or antibodies to promote selective drug delivery. By incorporating these ligands onto the surface of nanocarriers, active targeting enhances cellular internalization, reduces off-target effects, and improves the therapeutic index of anticancer agents. Importantly, the combination of active and passive targeting strategies often yields synergistic effects in drug delivery. (Obeagu *et al*., 2022; Xiong *et al*., 2025)

3.4 Endosomal Escape and Intracellular Trafficking

After successful internalization of drug-loaded nanoparticles via receptor-mediated endocytosis, the next critical challenge is endosomal escape. Without efficient escape, the payload risks degradation within lysosomes, where acidic pH and hydrolytic enzymes can inactivate therapeutic agents—particularly proteins, nucleic acids, and some small molecules.

3.4.1 Proton Sponge Effect

One widely explored mechanism for endosomal escape is the proton sponge effect, typically employed by cationic polymers such as polyethyleneimine (PEI). These polymers buffer the acidic endosomal environment, leading to an influx of protons, chloride ions, and water. The resulting osmotic swelling causes the endosome to rupture, releasing its contents into the cytosol.

3.4.2 pH-sensitive Carriers

Nanocarriers can also be engineered with pH-sensitive components that destabilize under acidic conditions (pH ~5.5), typical of endosomes. Liposomes containing pH-sensitive lipids or polymers undergo structural changes that promote membrane fusion or pore formation, facilitating cargo release.

3.4.3 Fusogenic Peptides

Another strategy involves the use of Fusogenic peptides, derived from viral proteins (e.g., influenza hemagglutinin), that mimic the natural mechanisms viruses use to escape endosomes. These peptides undergo conformational changes in acidic environments, disrupting the endosomal membrane.

3.4.4 Intracellular Trafficking

Once in the cytosol, drug molecules may need to reach specific subcellular compartments, such as the nucleus (for DNA-targeting drugs) or mitochondria (for apoptosis-inducing agents). This necessitates the incorporation of nuclear localization signals (NLS) or organelle-targeting ligands to direct intracellular trafficking. Enhancing endosomal escape and intracellular delivery is crucial for maximizing therapeutic efficacy, especially for nucleic acid-based therapies like siRNA, mRNA, and CRISPR-Cas systems. (Smolarx *et al*., 2022; Lukasiewicz *et al*., 2021; Xiong *et al*., 2025)

3.5 Triggered Drug Release in Tumor Microenvironment

The tumor microenvironment (TME) of breast cancer is characterized by unique physicochemical features, including acidic pH, hypoxia, elevated levels of glutathione (GSH), overexpression of matrix metalloproteinases (MMPs), and reactive oxygen species (ROS). These hallmarks can be exploited to design drug delivery systems that release their cargo specifically in response to these stimuli.

3.5.1 pH-sensitive Systems

Most solid tumor, including breast cancer, have a slightly acidic extracellular pH (~6.5–6.8), compared to normal tissues (~7.4). Nanocarriers can be designed to disassemble or undergo conformational changes at acidic pH, releasing their payload selectively in the tumor milieu. Examples include acid-labile linkers (such as hydrazone bonds) or pH-sensitive polymers like poly(histidine).

3.5.2 Redox-responsive Systems

The intracellular concentration of glutathione in cancer cells is up to 1000 times higher than in extracellular fluids. Drug carriers incorporating disulfide linkages or redox-sensitive moieties can remain stable in circulation but rapidly degrade in the reductive intracellular environment, releasing the drug.

3.5.3 Enzyme-responsive Systems

Matrix metalloproteinases (particularly MMP-2 and MMP-9) are overexpressed in breast tumor and play a role in tissue remodelling and metastasis. Nanocarriers designed with MMP-cleavable peptides can undergo structural changes or drug release upon enzymatic cleavage, enhancing site-specificity.

3.5.4 ROS-sensitive Systems

Reactive oxygen species (ROS) levels are elevated in many tumor. Drug carriers incorporating ROS-cleavable bonds (e.g., thioketals) can respond to oxidative stress, releasing their cargo preferentially in tumor cells. (Yara *et al*., 2025; White *et al*., 2020)

4. Therapeutic applications and formulations of nanocarriers

One of the hallmarks of effective cancer therapy is the use of combination regimens that target multiple pathways simultaneously. Co-delivery of two or more therapeutic agents in a single nanocarrier ensures synchronized pharmacokinetics and overcomes multi-drug resistance (MDR) mechanisms often seen in breast cancer.

4.1 Chemotherapy–Chemotherapy Combinations

Formulations combining two chemotherapeutic agents like doxorubicin and paclitaxel, or cisplatin and gemcitabine, have been designed to exploit synergistic effects. Dual drug loaded liposomes or polymeric nanoparticles maintain the optimal drug ratio at the tumor site, improving efficacy and reducing toxicity. For example, PLGA nanoparticles co-loaded with doxorubicin and curcumin (a chemosensitizer and antioxidant) have demonstrated improved cytotoxicity and reduced MDR in breast cancer cell lines.

4.2 Chemo–Gene Therapy Combinations

Combining chemotherapy with gene therapy enhances therapeutic outcomes by sensitizing cancer cells to drugs or by silencing resistance genes. Nanocarriers have been developed to co-deliver drugs like paclitaxel and siRNA targeting P-glycoprotein, a key efflux pump responsible for MDR.
Cationic liposomes and dendrimers are commonly used for such strategies, as they can encapsulate nucleic acids and provide intracellular delivery via endosomal escape mechanisms.

4.3 Chemo–Immunotherapy

Integrating immunomodulatory agents with chemotherapy enhances anti-tumor immune responses. Nanoparticles co-encapsulating doxorubicin and immune checkpoint inhibitors (such as anti-PD-L1 antibodies) are under investigation. These platforms not only induce immunogenic cell death (ICD) but also help reverse the immunosuppressive tumor microenvironment.

4.4 Phototherapy and Chemotherapy

Photodynamic therapy (PDT) and photothermal therapy (PTT) have been used alongside chemotherapy for synergistic effects. Nanoparticles containing a photosensitizer (e.g., indocyanine green) and a chemotherapeutic drug (e.g., doxorubicin) allow spatial and temporal control over drug release upon light activation. This approach is particularly valuable for localized tumor like certain breast cancers, where external light can be precisely delivered. (Tran *et al*., 2020; Oehler *et al*., 2024)

4.5 Case Studies and in-vivo Evaluations

To validate the therapeutic potential of these advanced formulations, preclinical and clinical evaluations are essential. In vivo models provide critical insights into biodistribution, tumor uptake, efficacy, and toxicity profiles.

4.5.1 Doxil in Breast Cancer

As one of the earliest nanomedicines, Doxil has shown improved safety and prolonged survival in metastatic breast cancer patients. In vivo studies confirmed its preferential accumulation in tumor via the EPR effect and a marked reduction in cardiotoxicity compared to free doxorubicin.

4.5.2 Trastuzumab–Emtansine (T-DM1)

T-DM1 (Kadcyla) is an antibody-drug conjugate (ADC) combining trastuzumab with the cytotoxic agent DM1. Clinical trials in HER2+ breast cancer patients demonstrated superior progression-free survival and reduced systemic toxicity. The targeted mechanism ensures selective internalization and intracellular drug release.

4.5.3 Nanoparticle Albumin-Bound Paclitaxel (Abraxane)

Abraxane, a solvent-free formulation of paclitaxel bound to albumin nanoparticles, overcomes solubility issues and enhances delivery to tumor. Clinical data show improved response rates and fewer hypersensitivity reactions compared to conventional paclitaxel formulations.

4.5.4 Experimental Co-Delivery Systems

A 2021 animal study demonstrated that lipid–polymer hybrid nanoparticles co-delivering doxorubicin and siRNA against Bcl-2 reduced tumor volume in orthotopic breast cancer models by over 70% compared to free drug treatment. The study highlighted enhanced cellular uptake, sustained drug release, and gene silencing effects.

4.5.5 Immunoliposomes in HER2+ Models

Liposomes surface-modified with anti-HER2 antibodies and loaded with docetaxel have been shown to significantly reduce tumor growth in HER2+ xenograft mouse models. These formulations exhibited enhanced binding, uptake, and cytotoxicity compared to non-targeted liposomes. (Alshareeda *et al*., 2024; Mugundhan *et al*., 2024; Yang *et al*., 2023)

4.5.6 Special Focus: Polymeric Strategies in Triple-Negative Breast Cancer (TNBC)

Triple-negative breast cancer (TNBC) is an aggressive subtype characterized by the absence of Estrogen receptors (ER), progesterone receptors (PR), and HER2 expression. It accounts for approximately 15–20% of breast cancer cases and is associated with poor prognosis, early metastasis, and limited treatment options. Due to the lack of molecular targets, systemic chemotherapy remains the standard treatment. However, novel

polymeric drug delivery systems are showing promise in addressing the challenges of TNBC therapy.

PLGA Nanoparticles

PLGA-based nanoparticles offer controlled release, biocompatibility, and tumor-specific accumulation. Docetaxel-loaded PLGA nanoparticles, modified with surface ligands like folic acid or EGFR-targeting peptides, have demonstrated enhanced cytotoxicity in TNBC cell lines (e.g., MDA-MB-231).

Stimuli-Responsive Polymers

Smart polymeric systems responsive to pH, redox potential, and enzymes are being designed for TNBC. pH-sensitive micelles that release drugs in the acidic tumor microenvironment show greater efficacy and reduced side effects. For example, poly (β-amino ester)-based carriers rapidly release doxorubicin under acidic conditions, promoting selective toxicity.

Polymeric Micelles for siRNA Delivery

Gene silencing offers a powerful approach to overcome TNBC resistance. PEG-b-poly (lactic acid) micelles co-delivering siRNA against STAT3 and doxorubicin suppressed tumor growth significantly in orthotopic TNBC mouse models. These systems enable co-localization of gene and drug therapy in the same cancer cell.

Immunomodulatory Polymers

Polymeric nanoparticles can be used to deliver toll-like receptor (TLR) agonists or cytokines to reprogram the immune microenvironment of TNBC tumor. For example, PLGA nanoparticles loaded with TLR7 agonists stimulate dendritic cells and promote anti-tumor immunity in murine models.

Combination Strategies

Several polymeric systems are being designed for co-delivery of multiple drugs such as PARP inhibitors with chemotherapeutics to exploit synthetic lethality in BRCA-mutated TNBC. Such formulations provide enhanced tumor targeting, improved pharmacokinetics, and reduced systemic toxicity. (Tang *et al*., 2017; Sharam *et al*., 2010)

Conclusion

Polymeric nanocarriers have revolutionized the field of drug delivery by offering solutions to longstanding therapeutic challenges, especially in the treatment of complex diseases like breast cancer. When paired with certain design criteria, their many structural forms including dendrimers, micelles, and nanospheres allow for accurate and effective drug delivery. The choice between natural and synthetic polymers allows for customization based on biocompatibility, degradation rate, and functionality, while stimuli-responsive systems add another layer of control. These carriers effectively exploit mechanisms like the EPR effect and active targeting to enhance drug accumulation in tumor tissues. Emerging therapeutic strategies, including co-delivery and polymer-based approaches for triple-negative breast cancer, highlight their clinical potential.

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Conflicts of Interest

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