NANOCARRIER-BASED DELIVERY OF 5-FLUOROURACIL IN BREAST CANCER: TARGETING TUMOR MICROENVIRONMENT AND OVERCOMING CHEMORESISTANCE

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Abstract

Despite improvements in screening and treatment, breast cancer is still one of the most common cancers diagnosed in women globally and a major cause of cancer-related death. Although 5-fluorouracil (5-FU), a pyrimidine derivative, has long been used in systemic treatments for breast cancer, its low oral bioavailability, dose-limiting toxicities, and acquired resistance restrict its clinical efficacy. By enhancing drug stability, permitting controlled and stimuli-responsive release, and facilitating both passive and active tumor targeting, nanocarrier-based delivery platforms such as lipid-based systems, polymeric nanoparticles, dendrimers, nanogels, inorganic nanostructures, and hybrid nanoplatforms offer promising ways to get around these restrictions. This review synthesizes recent high-impact literature on nanocarrier-mediated delivery of 5-FU for breast cancer, covering pharmacological considerations, nanocarrier classes, targeted and co-delivery approaches, stimuli-responsive designs, challenges to clinical translation, and emerging trends such as personalized nanomedicine and AI-guided carrier optimization.

Keywords: *5-Fluorouracil; Nanocarrier; Targeted drug delivery; Breast cancer*

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1. INTRODUCTION

1.1 Global Burden of Breast Cancer

With an increasing frequency in many low- and middle-income countries, breast cancer is the most prevalent cancer diagnosed in women worldwide and contributes significantly to cancer-related fatalities (Sha et al., 2024). Recent epidemiological evaluations indicate that lifestyle risk factors and demographic changes contribute to the approximately 2 million new instances of breast cancer that occur globally each year (Zhang et al., 2025). Despite improvements in systemic therapy and early identification, metastatic breast cancer is still largely incurable, underscoring the need for more effective and safer treatment methods (Agostinetto et al., 2022).

1.2 Current Therapeutic Strategies and Limitations

Surgery, radiation, endocrine therapy, HER2-targeted drugs, and cytotoxic chemotherapy are all part of standard management for breast cancer; regimens are chosen based on molecular subtype and stage (Debbi et al., 2023). Triple-negative breast cancer (TNBC) still primarily depends on traditional chemotherapy and has a high recurrence rate, despite the fact that targeted and endocrine therapies have improved results in hormone receptor-positive and HER2-positive illness. Systemic toxicities, emergent resistance, and non-specific biodistribution limit the effectiveness of conventional chemotherapy, resulting in unsatisfactory therapeutic indices and restricting dosage intensification (Tripathi et al., 2024).

1.3 Role of Chemotherapy and Significance of 5-Fluorouracil (5-FU)

5-FU is a fluorinated uracil analog that is frequently used in combination treatments for head and neck, colorectal, breast, and other malignancies (Mahoney et al., 2013). In the past, 5-FU has been added to multi-drug regimens for breast cancer, such as FEC (5-FU, epirubicin, cyclophosphamide) and CMF (cyclophosphamide, methotrexate, 5-FU), improving disease-free survival in certain situations. It is a desirable option for optimization through cutting-edge delivery systems rather than replacement due to its extensive anticancer activity and extensive clinical experience (Larsson et al., 2024).

1.4 Challenges Associated with Conventional 5-FU Therapy

A narrow therapeutic index and serious dose-limiting toxicities, such as myelosuppression, gastrointestinal damage, and cardiotoxicity, are linked to systemic administration of 5-FU. These side effects are made worse by interpatient variation in dihydropyrimidine dehydrogenase (DPD) activity. The medication exhibits quick catabolism and a brief plasma half-life, requiring high bolus doses or extended infusions to sustain cytotoxic concentrations, which raises the risk of poisoning even more. Long-term efficacy is further diminished by

innate and acquired resistance mechanisms, such as increased thymidylate synthase, changes in drug transporters, and improved DNA repair (Valencia-Lazcano et al., 2023).

1.5 Rationale for Nanocarrier-Based Drug Delivery

By preventing quick degradation, allowing for extended release, and enhancing tumor accumulation through the increased permeability and retention (EPR) effect, nanocarrier systems can modify the pharmacokinetics of 5-FU (Ejigah et al., 2022). By enabling active targeting and immune evasion, surface engineering with ligands, polymers, or biomimetic coatings improves selectivity towards breast tumor cells and metastatic niches while lowering exposure to healthy tissues. Additionally, 5-FU can be combined with other treatments or imaging agents using nanocarriers, which supports combination therapy and theranostic applications specific to the heterogeneity of breast cancer (Ruman et al., 2020).

2 Pharmacological Profile of 5-Fluorouracil

2.1 Chemical Structure and Physicochemical Properties

A fluorine atom replaces the hydrogen atom at the C-5 position of uracil in 5-FU, a tiny, hydrophilic pyrimidine analog that has unique biological reactivity and structural resemblance to natural nucleobases (Katritzky et al., 2010). In addition to facilitating systemic delivery, its high-water solubility and low molecular weight also contribute to limited passive diffusion across biological barriers and quick renal elimination. Encapsulation in hydrophobic nanocarrier cores is difficult when intrinsic lipophilicity is lacking, frequently requiring prodrug tactics or particular formulation processes (Gmeiner, 2020).

2.2 Mechanism of Action

Thymidylate synthase (TS) inhibition and misincorporation into RNA and DNA following metabolic activation to fluoronucleotides are the main ways that 5-FU produces its anticancer effects (Garg et al., 2010). The metabolite 5-fluoro-2′-deoxyuridine monophosphate (FdUMP) depletes deoxythymidine monophosphate pools and hinders DNA synthesis in proliferating cells by forming a stable ternary complex with TS and decreased folate. Other metabolites that are incorporated into RNA and DNA, like 5-fluorouridine triphosphate (FUTP) and 5-fluoro-2′-deoxyuridine triphosphate (FdUTP), interfere with RNA processing and cause DNA damage reactions that lead to apoptosis (Chen et al., 2024).

2.3 Pharmacokinetics and Metabolism

5-FU exhibits quick distribution and clearance after intravenous injection, with DPD usually catabolizing over 80% of the dosage into inactive metabolites like dihydrofluorouracil in the liver. The elimination half-life is frequently less than 30 minutes, which complicates outpatient management but encourages continuous infusion procedures to maintain effective

plasma levels. The argument for controlled delivery systems that separate exposure from enzymatic variability is supported by the fact that genetic polymorphisms and deficiencies in DPD dramatically modify systemic exposure, resulting in severe toxicity in poor metabolizers and under-treatment in ultra-rapid metabolizers (Diasio & Offer, 2022).

2.4 Dose-Limiting Toxicities and Resistance Mechanisms

Neutropenia, mucositis, diarrhoea, hand-foot syndrome, and cardiotoxicity are common side effects of 5-FU therapy. The severity of these side effects is significantly determined by the dosage schedule, route, and pharmacogenetic background. Resistance mechanisms encompass upregulation of TS, alterations in nucleoside transporters, enhanced DNA damage repair, and activation of pro-survival pathways, often resulting in cross-resistance to related fluoropyrimidines. By delivering higher localized concentrations to tumor regions, modifying release kinetics, and permitting logical combinations that co-target resistance pathways, nanocarrier-based techniques seek to get around some of these restrictions (Manavi et al., 2024).

3. Breast Cancer Pathophysiology and Therapeutic Targets

3.1 Molecular Subtypes

Clinically and biologically diverse, breast cancer is frequently divided into molecular subtypes as shown in figure 1, such as luminal A, luminal B, HER2-enriched, and triple-negative/basal-like disease, according to gene expression profiles and hormone receptor and HER2 status. The design of nanomedicines and the choice of targeting ligands are influenced by the differences between these subtypes in terms of prognosis, metastatic patterns, and susceptibility to endocrine, HER2-targeted, and chemotherapeutic treatments. For example, TNBC lacks ER, PR, and HER2 expression, making it a prime candidate for chemotherapy-enhancing nanocarriers, whereas HER2-positive tumors may benefit from nanoplatforms incorporating anti-HER2 antibodies (Nagini, 2017).

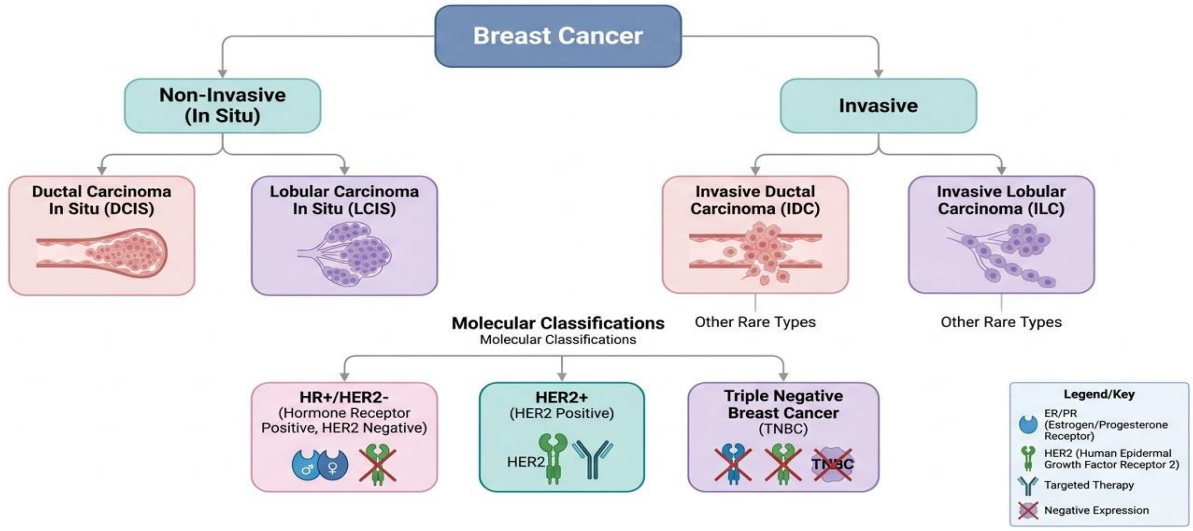

Figure 1. Classification of Breast Cancer Based on Molecular and Histopathological Subtypes

3.2 Tumor Microenvironment and Drug Resistance

Cancer cells, stromal fibroblasts, immune cells, extracellular matrix, and aberrant vasculature make up the breast tumor microenvironment (TME), which affects treatment response and nanoparticle delivery (Ni et al., 2021). Dense stromal components, hypoxia, and high interstitial fluid pressure all hinder medication penetration and encourage the selection of resistant cell populations. While TME-responsive devices seek to take advantage of acidic pH, enzymatic activity, or redox gradients for site-specific 5-FU release, nanocarriers can be adjusted in size, surface charge, and stiffness to enhance extravasation and interstitial transport.

3.3 Cancer Stem Cells and Signalling Pathways

Tumour initiating, metastasis, and therapy resistance are all influenced by breast cancer stem cells (CSCs), which are identified by markers including CD44+CD24−/low and ALDH1. Important signaling pathways that control CSC maintenance, such as PI3K/AKT, Wnt/β-catenin, Notch, and Hedgehog, are frequently dysregulated in aggressive subtypes (Palomeras et al., 2018). To obtain long-lasting responses and avoid relapse, nanocarrier devices that co-deliver 5-FU with medicines targeting these pathways or siRNA against CSC-related genes are being investigated (Wang et al., 2026).

3.4 Barriers to Drug Delivery in Breast Tumors

The EPR effect is supported by the aberrant vasculature found in breast cancers, which is characterized by heterogeneous perfusion, fenestrated endothelium, and high vascular permeability. However, this also creates areas of poor drug availability. Conventional chemotherapeutics have limited penetration into tumor cores due to elevated interstitial

pressure and dense extracellular matrix, which restrict convective transport, as illustrated in figure 2. Therefore, in order to maximize EPR while guaranteeing sufficient intratumoral distribution and reducing sequestration by the reticuloendothelial system, nanocarrier design must strike a compromise between size and surface characteristics (Chen et al., 2026).

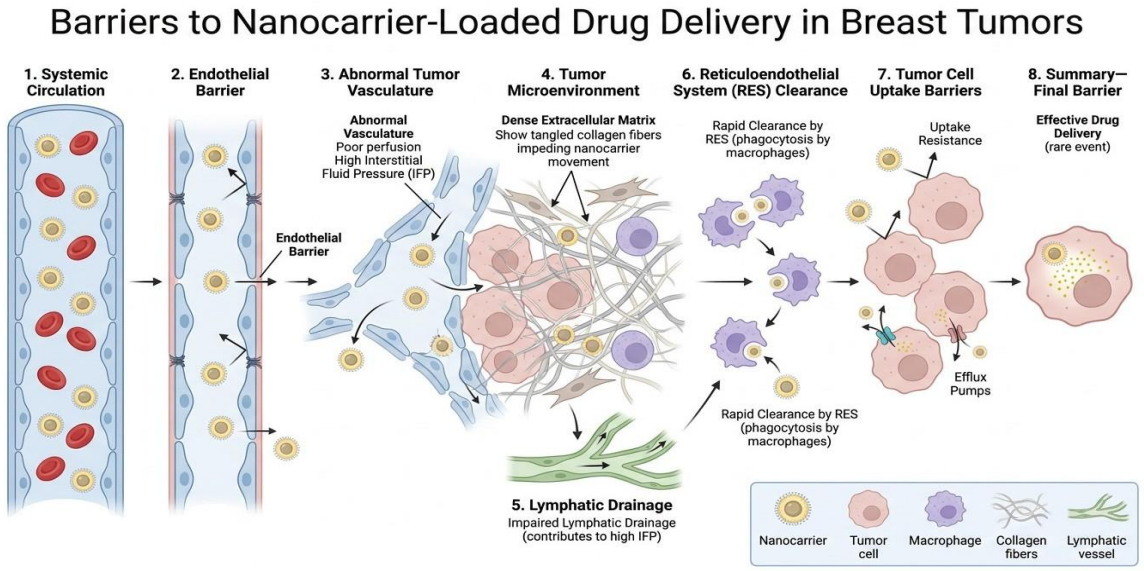

Figure 2 Schematic Diagram Showing the Different Barriers For Nanocarrier-Loaded Drug Delivery In Breast Cancer

3.5 Nanocarrier Systems for 5-FU Delivery: An Overview

3.5.1 Classification of Nanocarriers

Lipid-based systems (liposomes, solid lipid nanoparticles, nanostructured lipid carriers, lipid-polymer hybrids), polymeric nanoparticles (micelles, nanogels, and dendrimers), inorganic nanoparticles (gold, silica, magnetic), and carbon-based nanostructures (graphene, carbon nanotubes) are the general categories of nanocarriers for 5-FU delivery (Silva et al., 2019). A toolkit for customizing formulations to particular breast cancer indications is provided by each class's unique tunability in terms of size, surface chemistry, mechanical characteristics, and release mechanisms. In order to combine high loading capacity, structural resilience, and multifunctionality like imaging capabilities, hybrid platforms that blend organic and inorganic components have arisen (Zhao et al., 2018).

3.5.2 Advantages over Conventional Delivery Systems

Nanocarrier formulations frequently achieve better plasma stability, longer circulation times, and increased tumor accumulation as compared to free 5-FU. This leads to higher antitumor activity at lower systemic dosages in preclinical animals. While controlled-release profiles sustain therapeutic levels over time, encapsulation can reduce peak plasma concentrations and off-target dispersion linked to acute toxicity. Additionally, co-encapsulation of several

medicines with different physicochemical characteristics is made easier by nanoformulations, allowing for synchronized delivery in the ideal ratio (Bhattacharjee, 2022).

3.5.3 Passive Targeting via EPR Effect

By taking advantage of the EPR effect caused by leaky tumor vasculature and poor lymphatic drainage, passive targeting enables nanoscale carriers to preferentially aggregate in tumor tissues. In order to optimize EPR-mediated deposition while limiting renal clearance and arterial blockage, many 5-FU nanocarrier systems are designed with diameters between roughly 50 and 200 nm. However, the EPR effect's strength and consistency differ significantly between tumor kinds and patients, underscoring the necessity of combining passive and active or stimuli-responsive tactics for effective targeting (Deng et al., 2025).

3.5.4 Active Targeting Strategies

Using ligands that identify overexpressed receptors on breast cancer cells or endothelium, such as the folate receptor, transferrin receptor, HER2, integrins, and other peptide-recognized patterns, on nanocarrier surfaces is known as active targeting. In vitro and in vivo, ligand-mediated binding and receptor-mediated endocytosis can increase the cellular absorption of 5-FU-loaded nanoparticles and boost their effectiveness in comparison to their non-targeted counterparts. To avoid opsonization and off-target interactions, however, ligand density, orientation, and possible immunogenicity must be carefully controlled (Harris and Cohen, 2024).

3.5.5 Stimuli-Responsive Nanocarriers

In response to particular internal (pH, redox state, enzymes) or external (temperature, light) signals linked to tumor tissues or used in therapeutic settings, stimuli-responsive nanocarriers are made to release drugs (Zhao et al., 2021). While staying largely stable at physiological pH, pH-responsive polymeric and lipidic carriers for 5-FU take advantage of the slightly acidic TME or endosomal compartments to speed release following tumor buildup. By combining pH, redox, and enzymatic response, multi-stimuli platforms seek to improve the temporal and geographical regulation of 5-FU exposure, potentially lowering systemic toxicity and overcoming microenvironmental variability (Solanki and Bhatia, 2024).

3.6 Lipid-Based Nanocarriers

3.6.1 Liposomes

Liposomes, which are spherical vesicles with an aqueous core encircled by one or more phospholipid bilayers, are very useful for encasing hydrophilic medications like 5-FU. For a number of chemotherapeutics, conventional and PEGylated liposomal formulations have shown improved pharmacokinetics, decreased cardiotoxicity, and increased anticancer

efficacy; comparable advantages have been documented for 5-FU in preclinical breast cancer models. In comparison to non-targeted variations, targeted liposomes decorated with ligands such RGD peptides, antibodies, or folate have demonstrated greater absorption in breast cancer cell lines and xenografts, indicating their potential clinical value (Vishvakrama and Sharma, 2014).

3.6.2 Solid Lipid Nanoparticles (SLNs)

Biocompatible solid lipids stabilized by surfactants make up SLNs, which are nanoscale particles that stay solid at body temperature. Although drug loading may be restricted for highly hydrophilic molecules, they can integrate 5-FU into the lipid matrix or at the lipid-water interface, providing protection from degradation and sustained release. 5-FU-loaded SLNs have demonstrated increased cytotoxicity and decreased systemic toxicity in comparison to free drug in breast cancer models, indicating improved therapeutic indices (Mehnert and Mäder, 2012).

3.6.3 Nanostructured Lipid Carriers (NLCs)

NLCs are second-generation lipid nanocarriers made of solid and liquid lipid mixes that produce a less ordered matrix with a greater capacity for drug loading and a lower chance of expulsion during storage. In order to provide localized or sustained distribution, NLC-based formulations for breast cancer have been studied for co-loading 5-FU with other medicines and for integration into in situ gels or other depot systems. According to recent research, 5-FU-loaded NLCs embedded in thermosensitive gels can reduce systemic exposure while increasing cytotoxicity in breast cancer spheroid models (Elmowafy and Al-Sanea, 2021).

3.6.4 Lipid-Polymer Hybrid Nanoparticles

The goal of lipid-polymer hybrid nanoparticles is to combine the biocompatibility and stealth qualities of lipids with the controlled release and structural stability of polymers. In order to improve encapsulation efficiency and enable complex surface functionalization for targeting, these systems have been used to deliver 5-FU in conjunction with other chemotherapeutics or molecular medicines. When creating multifunctional platforms that include targeting, imaging, and responsive release modalities for breast cancer treatment, their modular architecture is very appealing (Carini et al., 2025).

3.6.5 Advantages, Limitations, and Clinical Status

As demonstrated by a number of approved liposomal cancer medications, lipid-based nanocarriers typically have positive biocompatibility, scalable manufacturing, and proven regulatory precedents. But issues including batch-to-batch variability, drug loss during storage, and physical instability still exist, particularly for labile drugs like 5-FU. There is

still a gap between laboratory development and clinical application, despite the fact that many 5-FU lipid nanoformulations have demonstrated promise preclinically and have not yet been translated into clinical studies specifically for breast cancer.

3.7 Polymeric Nanocarriers

3.7.1 Polymeric Nanoparticles

PLGA, polycaprolactone (PCL), and chitosan are examples of biodegradable polymers that are frequently utilized to create nanoparticles that offer regulated and prolonged release of encapsulated medications. In comparison to free drug, nanoencapsulation of 5-FU in PEGylated PLGA or comparable polymers has been demonstrated to increase encapsulation efficiency, generate sustained in vitro release profiles, and improve antitumor effectiveness in breast cancer models. To balance release kinetics, stability, and biocompatibility, polymer composition, molecular weight, and surface modification must be optimized (Rahman et al., 2023).

3.7.2 Polymeric Micelles

Amphiphilic block copolymers self-assemble to form polymeric micelles with a hydrophobic core and hydrophilic shell that can solubilize and protect poorly water-soluble substances throughout circulation. Despite the hydrophilic nature of 5-FU, combination therapy can be achieved using micellar systems through prodrug methods and co-loading with hydrophobic partners. Additionally, the corona can be functionalized with targeted ligands for breast cancer. Additionally, micelles have options for stimuli-responsive design, such as breakdown in tumor microenvironments induced by redox or pH (Perumal et al., 2022).

3.7.3 Dendrimers

Dendrimers are monodisperse, highly branched macromolecules with several surface functional groups and clearly defined generations that are ideal for encapsulating or conjugating drugs. 5-FU can be chemically bound by cleavable bonds or physically trapped within the interiors of dendrimers; in breast cancer models, studies have shown improved cellular absorption and anticancer effects when compared to free drug. However, their translational development has been slowed by worries about complicated production and dendrimer-associated toxicity (Wilbers, 2019).

3.7.4 Nanogels

High water content and drug loading are possible with nanogels, which are crosslinked polymeric networks at the nanoscale that are often made to react to pH, temperature, or redox conditions. For the administration of 5-FU, ionic and covalently crosslinked nanogels have shown enhanced penetration, controlled release, and synergistic efficacy when paired with

other treatments in breast cancer cell lines. Although mechanical stability and repeatable synthesis are still difficulties, their soft, pliable character may promote penetration into tumor tissues (Campea et al., 2021).

3.7.5 Smart and Stimuli-Responsive Polymeric Systems

In order to enable on-demand 5-FU release at the disease site while protecting healthy tissues, smart polymeric systems include labile links or structural motifs that react to tumor-associated stimuli. Examples include disulfide connections reducible in the glutathione-rich intracellular milieu and hydrazone or imine bonds cleavable in acidic environments, which can be incorporated into drug-polymer conjugates or polymer backbones. These designs can be further integrated with imaging moieties and targeted ligands to produce multifunctional theranostic platforms for individualized treatment of breast cancer (Bedoya et al., 2020).

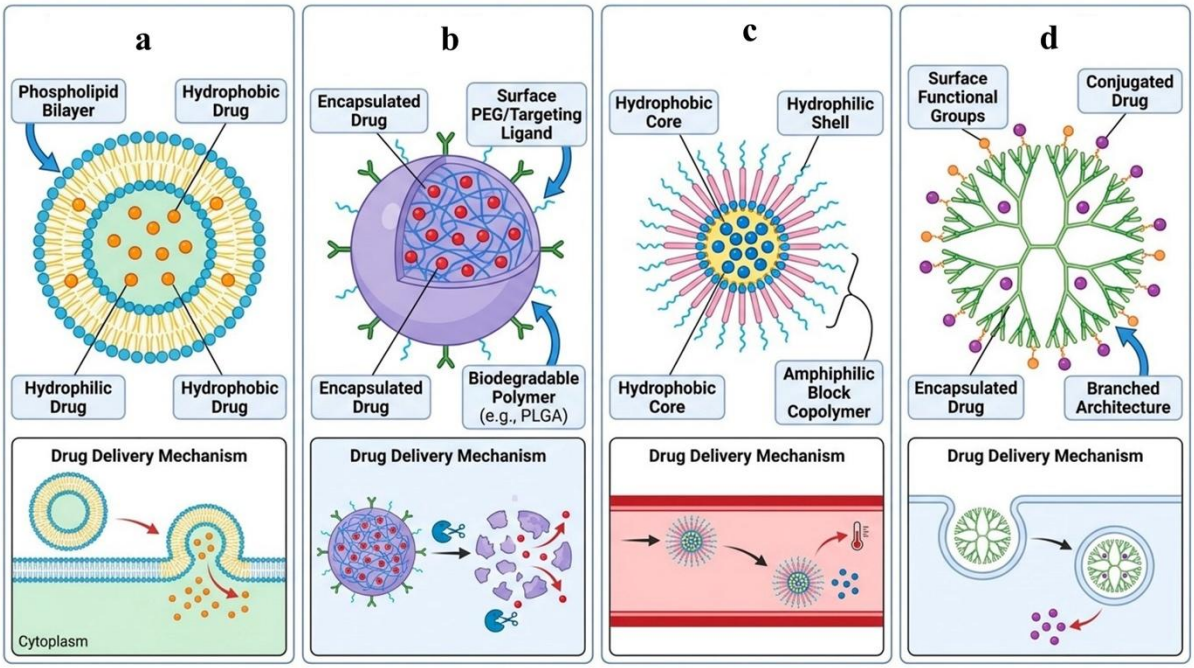

Figure 3. Mechanisms of action of nanocarrier-based drug delivery systems. **(a)** Phospholipid bilayer vesicles capable of encapsulating both hydrophilic (aqueous core) and hydrophobic (lipid bilayer) drugs. They accumulate in tumor tissue primarily via the enhanced permeability and retention (EPR) effect and can be further modified with targeting ligands for active targeting. **(b)** Polymeric nanoparticles: Solid colloidal carriers composed of biodegradable polymers that encapsulate or adsorb therapeutic agents. These nanoparticles enhance drug stability, prolong circulation time, and facilitate tumor accumulation via passive (EPR) and active targeting mechanisms. Cellular uptake typically occurs through endocytosis, followed by controlled or stimuli-responsive drug release within the intracellular environment.

(c) Self-assembled amphiphilic structures with a hydrophobic core and hydrophilic shell, suitable for solubilizing poorly water-soluble drugs. Micelles preferentially accumulate in tumor tissues via the EPR effect and release their payload through core destabilization or environmental triggers such as pH or enzymatic activity.

(d) Highly branched, monodisperse macromolecules with well-defined architecture and multiple surface functional groups. Drugs can be encapsulated within their internal cavities or conjugated to surface groups. Dendrimers enable precise control over drug loading, targeting ligand attachment, and release kinetics, facilitating efficient cellular uptake and targeted intracellular drug delivery.

3.8 Inorganic and Hybrid Nanocarriers

3.8.1 Gold Nanoparticles

Gold nanoparticles (AuNPs) are appealing pharmacological and imaging agent carriers due to their distinct optical characteristics, easy surface chemistry, and relative biocompatibility. Studies showing increased cytotoxicity against breast cancer cells and the possibility of photothermal synergy under near-infrared irradiation suggest that 5-FU can be conjugated or adsorbed onto AuNP surfaces. To prevent accumulation in the reticuloendothelial system, long-term biodistribution and clearance of inorganic cores must be carefully assessed (Sardar et al., 2009).

3.8.2 Mesoporous Silica Nanoparticles

With their large surface area, adjustable pore diameters, and adaptable surface functionalization, mesoporous silica nanoparticles (MSNs) enable high drug loading and regulated release. To stop premature leakage and initiate release in acidic or enzyme-rich tumor microenvironments, MSNs have been functionalized with gatekeepers for 5-FU, such as pH- or enzyme-cleavable caps. To improve absorption by breast cancer cells, targeting ligands can be co-grafted onto the MSN surface (Wu et al., 2013).

3.8.3 Magnetic Nanoparticles

External magnetic field-guided accumulation and theranostic imaging using magnetic resonance techniques are made possible by magnetic nanoparticles, which are usually based on iron oxide. For magnetofection and localized hyperthermia-enhanced chemotherapy in breast cancer models, encapsulation or surface loading of 5-FU onto magnetic nanocarriers has been investigated. Although encouraging, problems with stability, aggregation, and possible iron overload need to be resolved for clinical application (Colombo et al., 2012).

3.8.4 Carbon-Based Nanocarriers

Drug loading and sensing can benefit from the high surface area and special mechanical and electrical characteristics of carbon-based nanomaterials like carbon nanotubes (CNTs) and graphene derivatives. 5-FU and similar fluoropyrimidines have been delivered via PEGylated or functionalized CNTs and graphene oxide, showing improved antitumor activity in vitro at lower dosages. However, worries regarding immunogenicity, biodegradability, and long-term toxicity continue to be major obstacles to their widespread use (Debnath and Srivastava, 2021).

3.8.5 Hybrid Nanoplatforms

To combine high loading capacity, structural resilience, and multimodal functioning, hybrid nanoplatforms combine organic (lipid/polymer) and inorganic (carbon) components. Examples include PEG/rosin ester nanocarriers co-loaded with carmofur and 5-FU, which show strong cytotoxicity against breast cancer cells without harming healthy endothelium cells. In order to treat primary and metastatic breast tumors in a synergistic manner, these platforms are also being designed to integrate chemotherapy with photothermal, photodynamic, or imaging capabilities (Chauhan et al., 2026).

3.9 Targeted Delivery Approaches

3.9.1 Ligand-Based Targeting

Ligand-based targeting directs nanocarriers to overexpressed receptors on breast cancer cells using small molecules (like folate), peptides (like RGD, bombesin), antibodies (like anti-HER2), or nucleic acid aptamers. For example, when compared to non-targeted formulations, RGD-decorated liposomes co-delivering 5-FU and curcumin showed improved absorption in MCF-7 cells and synergistic cytotoxicity. The target breast cancer's molecular subtype and receptor expression profile usually influence the ligand selection (Yang et al., 2021).

3.9.2 Receptor-Mediated Endocytosis

Receptor-mediated endocytosis internalizes nanocarriers after ligand-receptor attachment, directing the payload into endosomal and lysosomal compartments where 5-FU must be released in order to reach its intracellular destinations. Endosomal escape and improved cytosolic distribution of 5-FU and co-loaded medicines can be achieved by including pH-sensitive or membrane-disruptive components into the carrier. Optimizing therapeutic benefit while preventing excessive off-target membrane disruption requires fine-tuning these processes (Schwartz, 1995; Azarifar et al., 2023).

3.9.3 Dual-Targeting Strategies

To improve specificity and get around intratumoral heterogeneity, dual-targeted designs integrate two or more targeting modalities, such as receptor ligands with TME-responsive

elements or dual ligands addressing distinct receptors. Dual-targeted 5-FU nanoformulations have been suggested for breast cancer in order to combine cell-targeting ligands with organelle-targeting patterns or to concurrently engage integrins and growth factor receptors. Improved accumulation in tumors and within particular cell types, like CSCs, is the goal of these structures (Agiba et al., 2024).

3.9.4 Organelle-Specific Targeting

By directing 5-FU to subcellular locations like the nucleus or mitochondria, organelle-specific targeting may increase effectiveness and alter particular cell death pathways. While ligands that target mitochondria may work in concert with substances that cause intrinsic apoptosis, nuclear localization sequences or DNA-binding moieties can help concentrate 5-FU close to its main site of action in DNA synthesis. These designs show the promise of precise nanomedicine, but they are still mostly at the preclinical stage (Soukar et al., 2025).

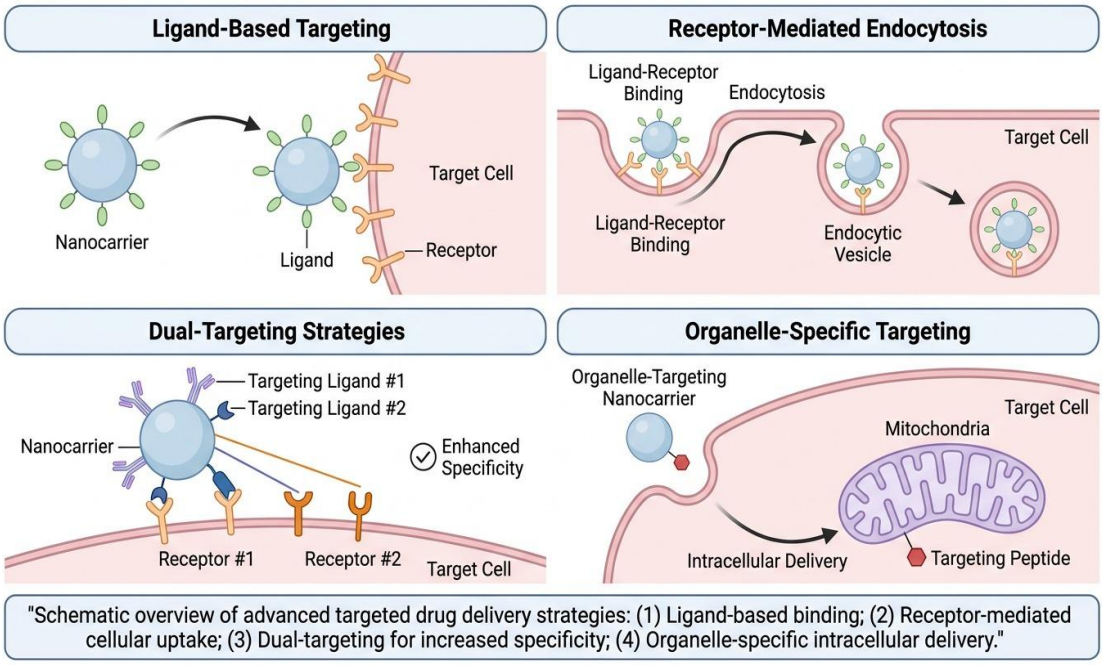

Figure 4 Schematic illustration of major targeted drug delivery strategies. The diagram depicts four key approaches employed to enhance the specificity and efficacy of nanocarrier-mediated drug delivery. **(a)** Nanocarriers functionalized with specific ligands selectively bind to overexpressed receptors on the surface of target cells, enabling site-specific drug delivery. **(b)** Following ligand-receptor interaction, the nanocarrier is internalized into the cell via endocytic pathways, facilitating intracellular delivery of the therapeutic payload. **(c)** Nanocarriers conjugated with two distinct ligands simultaneously interact with multiple receptors on the target cell surface, enhancing binding affinity, selectivity, and cellular uptake. **(d)** After cellular internalization, nanocarriers are directed

toward specific intracellular organelles (e.g., mitochondria) using targeting moieties such as peptides, enabling precise subcellular drug localization and improved therapeutic outcomes. All relevant components, including nanocarriers, ligands, receptors, cellular membranes, and intracellular organelles, are clearly labelled to illustrate the underlying mechanisms of targeted drug delivery.

3.10 Co-Delivery and Combination Therapy

3.10.1 5-FU with Phytochemicals

The goal of co-delivering 5-FU with phytochemicals like resveratrol or curcumin is to take advantage of their complementing processes, which include anti-inflammatory, antioxidant, and signaling-modulatory properties. In MCF-7 breast cancer cells, RGD-decorated nanoliposomes co-loaded with 5-FU and curcumin have demonstrated synergistic cytotoxicity, with increased apoptosis and lower dosages needed for each drug. Through dose-sparing effects, these combinations may also aid in reducing off-target toxicity and combating chemoresistance (Karthika et al., 2022).

3.10.2 5-FU with Other Chemotherapeutics

By allowing 5-FU to be co-encapsulated with other chemotherapeutics such as doxorubicin, paclitaxel, or platinum agents, nanocarriers can preserve predetermined synergistic ratios at the tumor site and enhance the medications' pharmacokinetic alignment. Combining 5-FU with complimentary medicines that target other cell cycle phases or DNA damage pathways has been shown to improve tumor suppression and survival in animal models. Optimizing loading efficiency, release kinetics, and toxicity profiles is still a significant formulation problem, though (Ciaffaglione et al., 2021).

3.10.3 Gene and siRNA Co-Delivery Systems

Co-delivery of 5-FU with siRNA or gene treatments in a single nanocarrier enables cytotoxic chemotherapy and gene expression modification to occur simultaneously. For instance, siRNA that targets anti-apoptotic proteins or TS can make breast cancer cells more susceptible to 5-FU, thereby circumventing resistance mechanisms. Chemotherapeutic payload requirements must be weighed against additional carrier design constraints imposed by nucleic acid payloads, such as nuclease protection and effective endosomal escape (Carvalho et al., 2021).

3.10.4 Synergistic Mechanisms and Therapeutic Outcomes

Convergent effects on DNA synthesis, repair pathways, apoptosis, and the TME create synergy in 5-FU-based combination nanoformulations, allowing for increased tumor cell death at lower dosages. In breast cancer models, quantitative assessments like combination

index and isobologram studies have shown supra-additive effects for a number of 5-FU-containing nanocombinations, which are correlated with better tumor regression and survival. To prevent antagonism or excessive toxicity, rational design of such systems necessitates a thorough understanding of pharmacodynamics and resistance biology (Jha et al., 2026).

3.11 Stimuli-Responsive and Smart Nanocarriers

3.11.1 pH-Sensitive Systems

pH-sensitive carriers expedite the release of 5-FU by taking advantage of the more acidic endosomal-lysosomal compartments and the somewhat acidic extracellular pH of tumors. Polymeric or lipidic systems with ionizable groups or pH-labile bonds have shown little leakage at physiological pH and quick release in acidic environments, boosting medication exposure to breast cancer cells while protecting healthy tissues. After EPR-mediated accumulation, several formulations have added pH-sensitive charge reversal to improve tumor cell uptake (Al-Zuhairy et al., 2025).

3.11.2 Redox-Responsive Nanocarriers

Redox-responsive designs use disulfide-containing linkers or crosslinks that cleave in the reductive intracellular milieu to exploit the higher intracellular glutathione levels in tumor cells compared to the circulation. 5-FU can be contained in disulfide-crosslinked nanogels or covalently bonded to polymers; it remains stable in circulation but releases quickly when internalized by cells. These approaches aim to increase intracellular delivery in breast cancer cells while minimizing premature leakage (Yang and Sun, 2022).

3.11.3 Enzyme-Responsive Systems

Enzyme-responsive carriers are designed to react to matrix metalloproteinases, lipases, or proteases that are overexpressed in the breast TME. For example, MMP-cleavable peptide crosslinkers might destabilize liposomes or nanogels in tumor sites, releasing co-therapeutics and 5-FU precisely where these enzymes are active. Enzyme expression heterogeneity among patients and tumor sites must be carefully validated before translating enzyme-responsive systems, notwithstanding their conceptual appeal (Hu et al., 2014).

3.11.4 Thermo- and Photo-Responsive Systems

In reaction to hyperthermia, which can be locally produced by magnetic nanoparticles or external energy sources, thermoresponsive nanocarriers release 5-FU. Chromophores that undergo structural alterations or heat production in response to light irradiation are incorporated into photo-responsive systems, allowing for spatiotemporally precise release and possible integration with photodynamic or photothermal therapy. Although light penetration

and off-target heating issues need to be addressed, these methods are especially useful for accessible breast lesions (Wang et al., 2019).

3.11.5 Multi-Stimuli Responsive Platforms

To improve release control and handle the complicated, heterogeneous TME, multi-stimuli responsive carriers combine two or more triggers, such as pH and redox or enzyme and temperature. Sequential response designs, such as pH-triggered deshielding and redox-triggered release, can optimize intracellular payload delivery and improve circulation stability. Despite their advanced technology, these platforms create new manufacturing and regulatory challenges that need to be properly handled for clinical translation (Dai et al., 2022).

3.12 Challenges and Limitations

3.12.1 Biological Barriers and Heterogeneity

Nanocarrier distribution in humans is limited by biological constraints such as opsonization, uptake by the mononuclear phagocyte system, and interpatient heterogeneity in EPR magnitude, despite encouraging preclinical results. Consistent targeting of 5-FU nanoformulations across breast cancer patients is further complicated by tumor heterogeneity in vascularization, receptor expression, and TME composition. Real-time imaging of nanoparticle biodistribution and biomarker-guided patient selection may be necessary to overcome these obstacles (El-Sayes et al., 2021).

3.12.2 Stability and Drug Leakage

The performance of 5-FU nanocarriers during storage and circulation may be hampered by physical and chemical instability, such as aggregation, lipid oxidation, and hydrolysis of labile connections. The significance of thorough formulation optimization and stability testing is highlighted by premature drug leakage, which lowers effective tumor dosage and reintroduces systemic toxicity concerns. Manufacturability and reconstitution requirements must be weighed against techniques like lyophilization, cryoprotectants, and strong crosslinking[58].

3.12.3 Toxicity and Immunogenicity

Even while many nanocarrier components are biocompatible on their own, composite systems may cause unanticipated toxicities, complement activation, or immunogenic reactions. Because of their potential for long-term accumulation and oxidative stress, inorganic and carbon-based nanomaterials are particularly concerning, requiring careful dose selection and long-term safety investigations. Before clinical progress, regulatory bodies are increasingly demanding thorough nano-specific toxicity assessment (Cern et al., 2017).

3.12.4 Cost and Scalability Issues

It can be difficult and expensive to produce sophisticated nanocarriers on a large scale with precise control over size, polydispersity, and surface properties. The clinical translation of several advanced 5-FU nanoplatforms has been hindered by the need for scale-up procedures to guarantee batch-to-batch reproducibility and adhere to good manufacturing principles. Whether or not improved formulations can be widely used in a variety of healthcare settings will depend on economic factors (Ahmed et al., 2021).

3.13 Future Perspectives and Emerging Trends

3.13.1 Personalized Nanomedicine

Personalized therapy plans based on each patient's unique breast cancer biology are being made possible by the integration of nanocarrier-based 5-FU administration with genomic, proteomic, and imaging indicators. By identifying patients who can benefit from particular targeted ligands or stimuli-responsive designs, companion diagnostics might enhance treatment indices and reduce needless exposure. Dosage and schedule customisation could be further improved with adaptive trial designs and real-time monitoring of nanocarrier biodistribution (Singh et al., 2025).

3.13.2 AI-Driven Nanocarrier Design

To anticipate pharmacokinetics, optimize nanocarrier composition, and link structural characteristics to biological function, artificial intelligence and machine learning are being used. Formulation screening can be sped up and the need for labor-intensive empirical methods can be decreased by using in silico modeling based on experimental datasets, such as those describing 5-FU-loaded systems. These techniques could be especially useful for creating multi-component, stimuli-responsive nanoplatforms with a wide range of adjustable characteristics (Jain et al., 2024).

3.13.3 Biomimetic and Exosome-Based Delivery Systems

The goal of biomimetic techniques is to take advantage of endogenous trafficking pathways and immune evasion mechanisms. Examples of these techniques include employing exosomes and extracellular vesicles as natural delivery vehicles or covering nanocarriers with cell membranes. Similar strategies for 5-FU could improve targeting of breast cancer and metastatic areas while lowering immunogenicity. Exosome-based delivery of chemotherapeutics has demonstrated promise in preclinical cancer models. Standardization, large-scale isolation, and safety characterisation, however, continue to be major obstacles (Yan et al., 2020).

3.13.4 Translational and Clinical Outlook

Numerous 5-FU nanotheranostic platforms have shown enhanced safety and efficacy in preclinical models of different malignancies, including breast cancer, according to systematic studies. However, because to translational bottlenecks in manufacturing, regulatory, and clinical trial design, only a small percentage have progressed into early-phase clinical trials and none have yet established the standard of care for breast cancer. Realizing the clinical potential of nanocarrier-based 5-FU delivery will require interdisciplinary cooperation between chemists, engineers, oncologists, and regulatory scientists (Milewska et al., 2021).

4. Conclusion

The pharmacological restrictions and resistance mechanisms that limit traditional 5-FU therapy in breast cancer can be effectively addressed by using nanocarrier-based 5-FU delivery. In preclinical models, lipid-based, polymeric, inorganic, and hybrid platforms which frequently include stimuli-responsive components and active targeting have all shown improved antitumor activity and decreased systemic toxicity, especially when set up for logical combination or theranostic applications. In order to incorporate these cutting-edge formulations into standard breast cancer care, future advancements will require overcoming biological obstacles and translational difficulties, incorporating personalized and AI-guided design principles, and thoroughly verifying safety and efficacy in carefully monitored clinical trials.

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6. Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this review.

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