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Design and Development of Optimised Nanostructured Polymeric Systems of Raloxifene For Improved Biopharmaceutical Application in Breast Cancer: A Review

Kanwaldeep Singh, Dr. Ram Babu Sharma, Dr. Sakshi, Ms. Anjali Dixit
Himalayan Institute of Pharmacy, Kala Amb, Himachal Pardesh, India

Abstract: *Breast cancer remains the most common malignancy in women globally, accounting for approximately 36% of oncology cases, with over 2.089 million diagnoses reported in 2018. Its incidence is rising worldwide, particularly in industrialized nations, attributable to Western lifestyle factors such as poor diet, smoking, stress, and sedentary behavior. Early detection primarily relies on mammography, with high sensitivity (75–95%) and specificity (80–95%), especially in women aged 50–69 years, and supplemental screening techniques like MRI and ultrasonography. Despite advancements, therapeutic challenges persist due to hormone dependence, genetic predisposition, and treatment complications. Nanotechnology presents a promising avenue to enhance breast cancer treatment through optimized drug delivery platforms. Nanocarriers—including polymeric nanoparticles, liposomes, solid lipid nanoparticles (SLNs), dendrimers, and micelles—offer enhanced solubility, bioavailability, controlled release, and tumor targeting via surface modification and receptor-mediated uptake. Raloxifene, a selective estrogen receptor modulator with poor oral bioavailability (~2%), benefits significantly from encapsulation in nanocarriers to overcome solubility limitations and extensive first-pass metabolism. Nanostructured delivery systems documented for raloxifene include PLGA–PEG–PLGA nanomicelles, mPEG-PLA nanoparticles, chitosan-based systems, SLNs, cyclodextrin–chitosan composites, and hyaluronated chitosan nanoparticles, all uniformly demonstrating nanoscale size (100–200 nm), high encapsulation efficiency, amorphous drug dispersion, sustained release, and multi-fold-enhanced bioavailability in preclinical animal models. However, translation to clinical use is hindered by challenges such as complex manufacturing scale-up, reproducibility, stability, regulatory requirements, and nanotoxicity assessment. Future directions must focus on scalable, green manufacturing techniques, standardized characterization, real-world pharmacokinetics, and targeted, non-oral delivery routes. Integration of quality assurance frameworks and robust toxicological protocols with regulatory alignment will be essential for realizing the clinical potential of raloxifene-polymeric nanosystems in breast cancer therapy.*

Keywords: Breast cancer; Nanotechnology Drug Delivery; Ralpxifene; Nanoparticle

I. INTRODUCTION

Breast cancer is the most common malignant tumor in women in the world. Breast cancer patients account for as much as 36% of oncological patients. An estimated 2.089 million women were diagnosed with breast cancer in 2018 [1,2]. The incidence of this malignant tumor is increasing in all regions of the world, but the highest incidence occurs in industrialized countries. Almost half of the cases on a global scale are in developed countries [2,3]. This trend is mainly due to the so-called Western lifestyle, associated with a poor diet, nicotinism, excessive stress and little physical activity [3]. In the case of breast cancer, mammography has become recognized as screening. The greatest value of mammography is observed in the group of women aged 50–69 years [1,3]. Classical mammography is characterized by 75–95% sensitivity and specificity at the level of 80–95% [4]. For women with suspected hereditary breast cancer,

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magnetic resonance mammography is used as a screening test. If a suspicious lesion is found in mammography, an ultrasound examination is performed and, if necessary, a thick needle biopsy along with a histopathological examination of the tumor.

The unambiguous cause of carcinogenesis has not yet been established, but several risk factors conducive to the development of breast cancer are known. One of the most important, as also indicated by the epidemiological data described above, are the gender, age, and degree of economic development of a given country. No less important are hormonal factors, mainly related to the time of exposure to estrogens, procreative factors, including the number of children born, the age of birth of the first child, or breastfeeding. Great importance in the development of breast cancer is attributed to genetic factors, the use of hormone replacement therapy, improper diet, and the resulting obesity. Among the significant risk factors for the development of breast cancer, hormonal contraception, alcohol consumption and exposure to ionizing radiation at a young age [5].

The basis for the diagnosis of breast cancer remains standard pathomorphological diagnostics [6]. The result of histopathological examination should include not only the histological type of the tumor, its degree of histological malignancy, the degree of advancement according to the TNM classification, information on the completeness of the procedure, or infiltration by cancer cells of peritugal vessels, but also the expression of steroid receptors—estrogen and progesterone, HER-2 receptor, and cellular proliferation index Ki67 [7]. A reliable assessment of all the above parameters is possible thanks to the examination of material taken by means of a coarse needle biopsy or intra- and postoperative material [8]. The examination of the material obtained by fine needle biopsy does not allow to distinguish between infiltrating and pre-invasive cancer, as well as to assess the state of HER-2. The correct protocol of histopathological examination, considering the biological subtype of the tumor, determines the determination of recognized predictive and prognostic factors, and consequently the selection of appropriate, individual treatment for each patient.

There are two major types of surgical procedures enabling the removal of breast cancerous tissues and those include (1) breast-conserving surgery (BCS) and (2) mastectomy. BCS—also called partial/segmental mastectomy, lumpectomy, wide local excision, or quadrantectomy—enables the removal of the cancerous tissue with simultaneous preservation of intact breast tissue often combined with plastic surgery technics called oncoplasty. Mastectomy is a complete removal of the breast and is often associated with immediately breast reconstruction. The removal of affected lymph nodes involves sentinel lymph node biopsy (SLNB) and axillary lymph node dissection (ALND). Even though BCS seems to be highly more beneficial for patients, those who were treated with this technique often show a tendency for a further need for a complete mastectomy [9]. However, usage of BCS is mostly related to significantly better cosmetic outcomes, lowered psychological burden of a patient, as well as reduced number of postoperative complications [10]. Guidelines of the European Society for Medical Oncology (ESMO) for patients with early breast cancer make the choice of therapy dependent to tumor size, feasibility of surgery, clinical phenotype, and patient's willingness to preserve the breast [11].

Chemotherapy is a systemic treatment of BC and might be either neoadjuvant or adjuvant. Choosing the most appropriate one is individualized according to the characteristics of the breast tumor; chemotherapy might also be used in the secondary breast cancer. Neoadjuvant chemotherapy is used for locally advanced BC, inflammatory breast cancers, for downstaging large tumors to allow BCS or in small tumors with worse prognostics molecular subtypes (HER2 or TNBC) which can help to identify prognostics and predictive factors of response and can be provided intravenously or orally. Currently, treatment includes a simultaneous application of schemes 2–3 of the following drugs—carboplatin, cyclophosphamide, 5-fluorouracil/capecitabine, taxanes (paclitaxel, docetaxel), and anthracyclines (doxorubicin, epirubicin). The choice of the proper drug is of major importance since different molecular breast cancer subtypes respond differently to preoperative chemotherapy [12].

Radiotherapy is local treatment of BC, typically provided after surgery and/or chemotherapy. It is performed to ensure that all of the cancerous cells remain destroyed, minimizing the possibility of breast cancer recurrence. Further, radiation therapy is favorable in the case of metastatic or unresectable breast cancer [13].

Endocrinal therapy might be used either as a neoadjuvant or adjuvant therapy in patients with Luminal–molecular subtype of BC; it is effective in cases of breast cancer recurrence or metastasis. Since the expression of ERs, a very

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frequent phenomenon in breast cancer patients, its blockage via hormonal therapy is commonly used as one of the potential treatment modalities. Endocrinal therapy aims to lower the estrogen levels or prevents breast cancer cells to be stimulated by estrogen. Drugs that block ERs include selective estrogen receptor modulators (SERMs) (tamoxifen, toremifene) and selective estrogen receptor degraders (SERDs) (fulvestrant) while treatments that aim to lower the estrogen levels include aromatase inhibitors (AIs) (letrozole, anastrazole, exemestane) [14,15].

Nanotechnology has emerged as a groundbreaking field in medicine, offering innovative solutions to overcome these challenges in breast cancer treatment. By manipulating materials at the nanoscale (1 to 100 nanometers), researchers can develop novel drug delivery systems that improve the therapeutic index of anticancer agents. One of the primary advantages of nanotechnology in cancer therapy is its ability to enhance the solubility and bioavailability of poorly soluble drugs. Many anticancer agents, including commonly used therapeutics like raloxifene, face significant bioavailability issues due to low solubility and extensive first-pass metabolism. Nanocarriers, such as liposomes, solid lipid nanoparticles (SLNs), and polymeric nanoparticles, can encapsulate these drugs, improving their solubility and allowing for controlled release profiles that prolong therapeutic action while minimizing side effects. Moreover, nanotechnology enables targeted drug delivery, which significantly enhances the accumulation of therapeutic agents at tumor sites while sparing healthy tissues. This is achieved through the modification of nanocarrier surfaces with specific ligands, such as antibodies or peptides, that bind to receptors overexpressed on cancer cells. By facilitating precise targeting, nanotechnology not only enhances drug efficacy but also reduces systemic toxicity, a major concern with conventional chemotherapy. Additionally, the ability of nanoparticles to penetrate biological barriers, including cellular membranes, allows for improved cellular uptake and retention of therapeutic agents within cancer cells [16,17].

RALOXIFENE: PHARMACOLOGICAL AND BIOPHARMACEUTICAL PROFILE

Raloxifene is an FDA-approved second-generation selective estrogen receptor modulator (SERM), a drug with an estrogen-agonistic effect on bone, increasing bone mineral density and mass by decreasing bone resorption. It is indicated in the treatment and prevention of postmenopausal osteoporosis.

Raloxifene is also indicated for the risk reduction of invasive breast cancer in postmenopausal women, demonstrating a high risk for invasive breast cancer or women with osteoporosis. The definition of high breast cancer risk is one or more first-degree relatives with breast cancer, or at least one breast biopsy showing lobular carcinoma in situ (LCIS), or atypical hyperplasia, or a 5-year predicted breast cancer risk of more than 1.66% [18].

Studies are underway on raloxifene as an adjuvant treatment for postmenopausal women with schizophrenia. It shows particularly promising results in mild presentations of schizophrenia [19].

Mechanism of Action:

The mechanism of action of raloxifene occurs through binding to estrogen receptors. This binding results in activation of estrogenic pathways (estrogen-agonistic effect) and blockade (estrogen-antagonistic effect) in tissues that express estrogen receptors. These receptors express as two different isoforms, the alpha estrogen receptor (activating effect) and the beta estrogen receptor (inhibiting effect). Therefore, the expression of these receptors will modify cellular and tissue responses to estrogens.

In postmenopausal osteoporosis, bone turnover dramatically increases. The bone resorption develops at a faster rate than bone formation, leading to a progressive loss of bone mass and bone mineral density. This disease represents an elevated risk for developing fractures. Raloxifene can inhibit accelerated bone resorption both short and long-term, increasing bone mineral density (BMD) and enhancing bone strength. Other pharmacologic agents for the management of osteoporosis are estrogen, bisphosphonates, selective estrogen receptor modulators (SERMs), parathyroid hormone (PTH), and calcium and vitamin D.

It has an estrogen-antagonistic effect in the uterus and breast, in contrast with tamoxifen (a first-generation selective estrogen receptor modulator), which has an estrogen-agonistic effect over the uterus. In addition, raloxifene modifies cardiovascular risk markers by decreasing LDL-C, fibrinogen, lipoprotein A and increasing HDL2-C without modifying triglyceride levels. There are no recommendations for raloxifene use in BRCA1 and BRCA2 positive mutations; there are no reports of apparent effectiveness. This drug is not intended for use in treating patients with an established diagnosis of breast cancer [20,21].

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Raloxifene bioavailability is approximately 2%, with an absorption of 60%. The onset of action is eight weeks, and distribution is mainly protein-bound (more than 95%). Metabolism of the drug occurs in the liver, excreted primarily in the feces (more than 93%) and urine (less than 0.2%).

Administration

Raloxifene hydrochloride administration is via the oral route. Raloxifene hydrochloride is available as 60 mg tablets.

Indications for the drug are the treatment and prevention of postmenopausal osteoporosis. The recommended dose for osteoporosis is 60 mg by mouth daily [21]. Recommendations for Calcium and Vitamin D Supplementation. For osteoporosis prevention or treatment, supplemental calcium and/or vitamin D needs to be added to the diet when daily intake is insufficient. Postmenopausal women need an average of 400-800 IU vitamin D and 1500 mg of elemental calcium daily. Patients at high risk for vitamin D insufficiency (e.g., gastrointestinal malabsorption syndromes, chronically ill, nursing home-bound, over the age of 70 years) may need additional vitamin D supplements.

It is also prescribed for prevention and risk reduction of invasive breast cancer in postmenopausal women demonstrating a high risk for invasive breast cancer [18]. The recommended dose for breast cancer prevention is 60 mg by mouth daily for five years [23].

Clinical trials had reported some beneficial effects of raloxifene during menopause, decreasing LDL levels and reducing the risk of pelvic organ prolapse and breast cancer. No reports exist of an effect on cognitive mood or sleep disturbances [24].

Adverse Effect

Raloxifene's most common documented adverse effects are hot flashes, flu-like symptoms, muscle spasms, arthralgia, and infection. Less common effects are insomnia, vomiting, sinusitis, deep venous thrombosis (DVT), bronchitis, pharyngitis, breast pain. Raloxifene-treated women reported peripheral edema (raloxifene 14.1% vs placebo 11.7%), muscle spasms/leg cramps (12.1% vs 8.3%), hot flashes (7.8% vs 4.7%), cholelithiasis (3.3% vs 2.6%), and venous thromboembolic events 2.0% vs 1.4%).

The most serious adverse reaction related to raloxifene is venous thromboembolism (pulmonary embolism, deep venous thrombosis, and retinal vein thrombosis). During the clinical trial, with raloxifene treatment for 2.6 years, venous thromboembolism (VTE) precipitated in about 1 out of 100 patients. A total of 26 raloxifene-exposed women had a VTE compared to 11 placebo-treated women, and the highest risk of VTE was in the initial four months of the treatment phase with raloxifene [25].

Contraindication

Contraindications to raloxifene include past medical history of deep venous thrombosis, renal vein thrombosis, pulmonary embolism, malignancy, active smoking, or any thrombophilia (factor V Leiden deficiency, prothrombin gene mutation G20210A, antiphospholipid syndrome, deficiency of antithrombin, protein c and s deficiency).

Death due to stroke: Postmenopausal women with coronary heart disease or at increased risk for coronary events are at increased risk of death due to stroke when treated with raloxifene. Perform risk-benefit analysis in women with a risk of strokes, such as women with a history of transient ischemic attack (TIA) or stroke, cigarette smoking habit, hypertension, and atrial fibrillation. Careful administration is recommended in hospitalized, immobilized, unable to walk, or post-surgical recovery patients, given the high risk of developing deep vein thrombosis and pulmonary embolism. The safety of raloxifene in premenopausal women is not established, and its use in premenopausal women is not recommended.

Drug Interactions

There are reports of an ospemifene and raloxifene interaction; it increases the effect of the other by synergism. Therefore, monitor the following drugs (for interaction with raloxifene) closely: apalutamide, cholestyramine, famciclovir, levothyroxine.

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There is a reported minor interaction of raloxifene with warfarin; it increases the effect of warfarin by plasma protein binding competition.

Concomitant administration of raloxifene with amoxicillin, ampicillin, digoxin, corticosteroids, antacids, cholestyramine, other anion exchange resins, or systemic estrogens is not recommended.

It should be used with caution with highly protein-bound drugs such as diazepam, diazoxide, and lidocaine, as it might affect the protein binding of other drugs [25,26].

Need for Nanostructured Drug Delivery Systems

Nanomedicine is one of these promising new therapeutic options. By definition, nanomedicine refers to biomedical application of materials with at least one dimension below 100 nm, although devices of 100–200 nm are often considered nanomedicine in practice [27]. Examples of nanomedicine range from liposomes, nanoparticles, micelles, dendrimers, nanotubes and so on, and they can be made of diverse materials including lipids, phospholipids, polymers, proteins, inorganic materials and a combination of them [27,28]. Some of them, such as liposomes (eg, Doxil®, Janssen Products, Titusville, NJ, USA) and nanoparticles (eg, Abraxane®), are already widely used for clinical treatment of breast cancer with success. These products, however, were originally developed as generic anticancer drug carriers. With better understanding of molecular biology of breast cancer, several promising nanodelivery strategies more tailored for breast cancer are actively explored in recent years. It is, therefore, good time update on the current status of and the most recent trends in this field. It should be noted that nanomedicine can serve a broad range of functions for cancer patients besides treatment, including tissue repairing, disease detection, cancer imaging and theranostic [27,29].

Nanomedicine has the potential to overcome at least some of these limitations. The extremely large surface areato-volume ratio of nanocarriers provides an opportunity to manipulate their surface properties for improved treatment, for example, cancer targeting, extended circulation, increased endocytosis and transcytosis, in order to gain more efficient access into tumor sites, metastatic sites and cancer cells. Moreover, by entrapping in or binding onto nanocarriers, the therapeutic agents can also gain better stability, increased solubility and controlled release kinetics. Drug combinations may also be co-delivered for increased synergistic or additive anticancer effects [27]. The use of these features to tackle the limitations of breast cancer drug therapy is summarized in Table 1.

Table 1 A summary of the key challenges to breast cancer drug therapy and the ways nanomedicine can be used to tackle these challenges

S.No	Challenges to breast cancer drug therapy	How nanomedicine can help
1.	Insufficient specificity for breast cancer	Passive targeting and active targeting by nanomedicine to increase tumor drug level and decrease noncancer drug levels
2.	Inefficient access of drugs to metastatic sites such as brain and bone	Many nanomedicine formulations inherently may improve brain and bone penetration
3.	Undesirable pharmacokinetics such as quick clearance and short half-life	Use of strategies such as PEGlyation to extend the circulation time
4.	Dose-limiting toxicity of the anticancer drugs or the excipients, for example, surfactants and organic co-solvents	Increased tumor specificity as above; controlled drug release from nanocarrier; solvent-, surfactant-free nanoformulation
5.	Drug resistance at cellular level, for example, increased drug efflux transport	Passive and active targeting both may enhance endocytosis; some nanoformulations may inhibit drug efflux mechanisms; co-delivery of agents that target drug resistance mechanisms
6.	Drug resistance at tumor microenvironment level, for example, lower pH, hypoxia, cancer microenvironment crosstalk and so on	Targeting tumor microenvironment; use of stimulus-responsive nanoformulations such as pH-responsive devices

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7.	Difficulty in eradicating cancer stem cells	Targeting cancer stem cells
8.	Undesirable pharmaceutical properties of the drugs, for example, low aqueous solubility, poor in vivo stability	Many nanocarriers can achieve drug solubilization and can protect unstable drugs
9.	Suboptimal dosing schedule and sequence, especially when combinations of multiple drugs are involved	Careful optimization of dosing schedule and sequence; use of nanocarrier to co-deliver multiple drugs

Nanomedicine and breast cancer treatment

Nanomedicine is getting recognized in the pharmaceutical and medical sectors because of its ability to reduce dosage and frequency without compromising therapeutic efficacy [30]. The blood-brain bar rier (BBB) and other biological barriers may be overcome by advanced nano-systems [31]. Enhanced drug loading capacity, superior biological compatibility, flexibility, and precisely controlled drug release, are benefits of nano-based cancer treatment [32]. Nanoparticles (NPs) are usually >100 nm in size and have a small wavelength, which gives them intrinsic stealth quality. It is easy to encapsulate medications within nanoparticles owing to their lipophilic nature [33]. The lipophilicity of a first-line chemotherapeutic agent increases when it is conjugated with a lipid and flavonoid, that enhances the drug's ability to entrap [34]. Effective nanoparticle delivery is achieved by the interaction between the positively charged nano-emulsion and negatively charged cancer cell surface.

Various nanocarriers, such as metallic NPs, nanocrystals, liposomes, carbon nanotubes, mi celles, dendrimers, and lipid-based carriers [solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC)] have been developed.

Liposomes

Liposomes are round entities composed of cholesterol and layers of bent bilayer membranes [35]. When combined with water, the hydro phobic and hydrophilic phospholipid cores in liposomes create spheres [36,37]. They can be used to carry cells and medications owing to their amphiphilic nature. They facilitate the delivery of genes and drugs to specific regions and promote tissue cell proliferation. Liposomes must break down gradually in the body and trigger some inflammatory and immunological reactions [38,39]. Chowdhury et al. (2020) developed an aptamer-labelled liposomal nanoparticle system (A6 and GFP) to deliver doxorubicin (DOX) to HER-2^+ BC cells. This technique signifi cantly increased the absorption of liposomes in MCF-7 and SKBR-3 cells by more than 60 % compared with that of non-aptamer-labelled NPs. This study suggests that aptamer-labelled NPs are a more effective way of distributing and absorbing DOX in HER-2^+ BC cells.

Solid lipid nanoparticles (SLN) In solid lipid nanoparticles (SLNs), the hydrophobic lipid core is composed of substances, such as triglycerides, waxes, steroids, and fatty acids that solidify at normal temperatures and particle clumping is prevented by core stabilization by emulsifiers or surfactants [40]. Typically, the particle sizes of SLNs are in the range of 80–1000 nm [41]. The principal advantage of SLNs is their ability to easily attract hydro phobic drugs to the lipid matrix, whereas hydrophilic drugs can bond to the hydrophilic outer shell. The solid lipid form increases the stability of the medication and allows for accurate drug release [42]. SLNs are incredibly stable, non-toxic, and biocompatible that sets them apart from polymeric nanoparticles and liposomes in several ways [42,43]. Glyceryl monostearate-based SLNs have been used to encapsulate methotrexate, which prevents the cell cycle from progressing to the S phase, improves cellular absorption, reduces the migration and multi plication of BC cells, and promotes cell death both in vitro and in vivo models [44]

Nanostructured lipid carriers (NLC)

Despite the benefits of SLNs, certain issues remain, such as incon sistent polymorphic transitions, drug leakage, restricted drug-loading efficiency, and crystallization with storage. Lipid nanoparticles in the form of NLCs can overcome these drawbacks [45]. Nanostructured lipid carriers are improved lipid-based nanocarriers that are created

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from a combination of liquid and solid lipids [46]. NLCs reduces drug ejection during formulation and storage, because they contain liquid lipids. They also provide more regulated medication release than SLNs and enhances drug solubility in the lipid matrix. Compared to SLNs, NLCs have a lower melting point, but remain solid at body temperature. Due to their defective crystal structures, an additional room is available for drug loading and dissolution in the liquid portion of NLC [47].

Polymeric micelles (PMs)

Micelles are tiny colloidal substances with approximate sizes of 5– 00nm. Theyarehydrophobicdrugcarriersthathaveshownsuperior tumor-targeted delivery capabilities [48]. Their ability to deliver drugs that are not readily soluble in water, such as paclitaxel, in water-based media without the use of organic solvents, makes them intriguing. However, compared with other nanocarriers, they do not have a high loading capacity. Moreover, they tend to dissociate rapidly upon intra venous injection because of their dilution and inability to sustain a concentration beyond the threshold micellar concentration. Therefore, they may not be the most effective nanocarriers [49]. Despite these drawbacks, numerous types of PMs carrying anticancer agents have been developed, and various paclitaxel formulations are currently authorized for the management of different malignancies including BC. Their primary advantage over conventional formulations is their lower toxicity, owing to the smallest partial elimination [50].

Dendrimers

Dendrimers are hyperbranched 3-D polymers that resemble trees and have a central core encircled by several layers of branching units. Their structure has internal spaces that are appropriate for encasing medicines and nucleic acids as well as a multitude of molecular sites for chemical conjugation [51,52]. Incorporating anticancer drugs into dendrimers and micelles enhances cellular absorption and sustained drug release, reduces adverse effects, and increases anticancer activity [53,54]. Typically, dendrimers are utilized to covalently bind certain targeting moieties, such as folic acid, antibodies, sugar epidermal growth factor, and biotin, to successfully target drugs to tumor tissues [47,55]. Den drimers used in cancer research include polypropylene imine, poly-lysine (PLL), phosphorus, and carbosilane [56]. The amphiphilic dendrimer PLL has a branched structure and is composed of penta-functional core molecules. These molecules are comprised of positively charged essential amino acids, such as lysine-amino-alanine. Because of its natural components and small size, PLL is an intriguing class of molecules that is easier to absorb than synthetic molecules [57]. The larger G5 PEG1100 dendrimers demonstrated strong tumor retention, although their anticancer activity was limited due to inadequate drug release. While the smallest G4 PEG570 dendrimer exhibited low systemic exposure and tumor uptake, it was very effective in inducing DOX release when triggered by cathepsin. The intermediate sized dendrimers increased the systemic exposure, retention, tumor absorption, and drug release kinetics. These findings demonstrated that dendrimer size and polyethylene glycol (PEG) molecular weight had an impact on the therapeutic efficacy of dendrimer formulations [58].

Polymeric nanoparticles (P-NPs)

Polymeric nanoparticles are composed of biocompatible and biode gradable substances that can perform their intended functions by conjugating or encasing chemotherapeutic drugs. They are divided into two groups: nanospheres and nano-capsules [59]. Because of their excellent intracellular penetration, controlled-release capabilities, high bioavailability, and relative safety, they are considered to be effective against breast cancer [60]. Targeting the α v β 3 receptor in BC cells, AXT050-PLGA-PEG NPs have been developed using antitumor and antiangiogenic peptides as therapeutic components [61,62]. Furthermore, Nosrati et al. (2018) created l-lysine iron oxide magnetic NPs linked with methotrexate (MTX) to specifically target MCF-7 cells and demonstrated remarkable anticancer properties [63]. Similarly, Nicolas et al. (2018) designed calcitriol-loaded polymeric nano capsules for BC treatment, which showed significant calcitriol formation in tumor cells and regulated drug release [64]. Furthermore, PLGA NPs loaded with curcumin demon strated extended drug release and improved encapsulation efficiency. In the MDA-MB-231 cell line, this nano-formulation significantly reduced cellular viability, migration, and invasion [65].

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Carbon nanotubes (CNTs)

Carbon nanotubes are small cylindrical structures composed of one or more graphite layers. They are of two types: multiwalled, which has multiple layers, and single-walled, which has only one carbon layer. They have shown great potential for the delivery of genes and drugs for cancer treatment owing to their unique electrical, thermal, and strutural properties. They are also effective in destroying cancer cells via localized hyperthermia (heating) because of their capacity to transfer heat and interact with light [47]. Jawahar et al. (2020) developed a nano-formulation for specifically targeting BC cells by affixing folic acid (FA) and raloxifene (RLX) hydrochloride to the surface of CNTs. Folic acid facilitated direct drug delivery to cancer cells. Additionally, raloxifene-loaded CNTs showed improved cellular absorption compared to the drug alone and demonstrated an IC 50 value of 43.5 µ g/mL [66]. Akinoglu et al. (2017) synthesized a scaffold consisting of multiple walls of CNTs via a process known as plasma-enhanced chemical vapor deposition. This scaffold has an appropriate shape for cell growth and provides a biocompatible environment for cancer cells. They have su perior biomimetic (life-like) qualities and physiological flexibility and also demonstrate good cell adhesion properties. This scaffold can be used to control BC metastasis [67]. To efficiently load DOX, Liu et al. (2019) created hyaluronic acid (HA) covalently bonded to amino-functionalized single-walled carbon nanotubes (NH2-SWCNTs). Increased apoptosis and cytotoxicity resulting from amine-functionalized SWCNTs enhanced the intracellular transport of DOX in CD44-overexpressing MDA-MB-231 cancer cells. Consequently, SWCNT-DOX-HA decreases the growth of spheroid cancer cells and dramatically suppresses the proliferation of malignant cells [68].

Quantum dots (QDs)

Quantum dots (QDs) are nanoscale semiconductors, typically ranging from 2to10 nminsize,consisting of acrystalline metalloid core surrounded by a protective shell. it possesses unique optical properties, including a broad excitation spectrum and a narrow, symmetrical, and intense emission profile. These characteristics make them highly suit able for applications in bioimaging, biolabeling, and biosensing [69,70]. QDs offer high sensitivity and selectivity for cancer detection, with tunable emission spectra allowing simultaneous detection of multiple BC biomarkers [71]. In BC diagnosis, QDs serve as highly sensitive imaging agents, offering superior fluorescence and long-term stability compared to traditional dyes. Conjugated with antibodies, they can specifically bind to tumor markers like HER2, allowing real-time tracking of cancer progression [72,73].

Hybrid nanoparticles

When two or more constituents are combined into a single nano carrier system, a new multifunctional hybrid nanocarriers with enhanced structural and biological properties are produced. A variety of hybrid nanocarriers, including inorganic hybrid nanoparticles, metal organic hybrid nanoparticles, hybrid carbon nanocarriers, and lipid polymer hybrid nanoparticles, have been employed to diagnose and treat several types of BC [74]. Patel et al. (2020) developed a combi nation of mycophenolic acid and quercetin (QT) lipid polymer hybrid nanoparticles (MPA-LPN + QT-LPN). Compared with individual con geners, combination therapy showed greater cellular absorption and cytotoxicity in MCF-7 cells [75]. Phyto-based furocoumarins derived from Psoralea corylifolia and psoralen (PSO) have been extensively used in traditional medicine. PSO is a potential anticancer chemical that has been extensively investigated against BC. Its low bioavailability possess challenges that limits its therapeutic use [76]. This issue can be resolved with the help of lipid–polymer hybrid nanoparticles (LPHNPs), which are carrier systems that have advantages over polymeric NPs and liposomes. They provide stability, prevent drug dispersion, and are helpful for the management of MCF-7 cells. They also promote drug absorption, inhibit water-soluble drug leakage, limit drug release, and improve hydrophobic drug entrapment [77]. In one study, methoxypoly (ethylene glycol)-poly (caprolactone) NPs were hybridized with dimethyl dioctadecyl ammo nium bromide (DDAB) cationic lipid (mPEG-PCL-DDAB) NPs to deliver lycopene and siRNA specific to the insulin-like growth factor-1 receptor (IGF-1R) in MCF-7 cells. Anti-insulin-like growth factor-1 receptor siRNA and lycopene loaded into mPEG-PCL-DDAB NPs markedly has tened the cell cycle and triggered cell death by simultaneously deliv ering siRNA and lycopene to MCF-7 tumor cells [78]. Table 2 summarizes the advantages, limitations, and clinical applications of various nano-platform for BC treatment.

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Table 2 Advantages, limitations, and clinical translatability of various nanocarrier for BC treatment.

Nanocarriers	Advantages	Limitations	Clinical translatability	References
Liposomes	Use wide range of drugs and can enhance drug loading while minimizing undesirable drug effects.	Toxicity results from cationic lipids, while the mononuclear phagocyte system rapidly degrades the nanocarriers	Several FDA-approved liposomal drugs are available for BC treatment, such as Doxil® for metastatic BC	[37,79]
Solid lipid nanoparticles (SLN)	Biodegradable and biocompatible lipid-based carriers, protect drugs from degradation while enabling controlled and sustained release	Low drug loading capacities and may contain other colloidal structures	Emerging in clinical research but not yet widely approved for BC treatment, simple manufacturing process that enhances scalability	[80,81]
Nanostructured lipid carriers (NLC)	Overcomes the limitations of SLNs by incorporating liquid lipids for higher drug loading, better physical stability and controlled drug release, can be functionalized for active targeting	Gelation of lipid dispersion leads to a polymorphic transition, which can alter the physical properties of the formulation.	NLCs are emerging as a promising alternative to SLNs, demonstrating success in preclinical studies for BC. While their clinical use is still in the early stages, they have shown significant potential for future applications	[82,83]
Polymeric nanoparticles (PNPs)	Biocompatible, biodegradable, and nontoxic, longer blood circulation times, reduced drug loss, lower reactivity to enzymatic degradation, ability for site-targeted administration	Potential issues with polymer degradation, some polymers exhibiting cytotoxicity or immunogenicity, complex synthesis process	Few nano-formulations, especially those utilizing biocompatible polymers like PLGA, have progressed to clinical trials.	[84,85]
Polymeric micelles	Reduced toxicity and other adverse effects are key advantage of these formulations	Low drug loading capacity, premature drug release, polymer degradation and long-term toxicity	Some formulations, such as Genexol-PM, have reached clinical trials, but challenges persist in achieving consistent drug release	[86,87]
Dendrimers	Higher loading capacity due to a variety of multifunctional surface groups and intracellular cavities, high bioavailability	Rapid clearance, organ accumulation, synthesis variability	Showed significant promise in preclinical studies, but their clinical translation is hindered by cytotoxicity issues and high production costs, which makes them less advanced in clinical trials	[88,89]

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			compared to other nanocarriers	
Quantum dots (QDs)	Exhibits high fluorescence stability for imaging, tunable emission wavelengths for multiplex imaging, enhances tumor penetration	Exhibits high fluorescence stability for imaging, tunable emission wavelengths for multiplex imaging, enhances tumor penetration	Limited due to toxicity concerns	[90,91]
Carbon nanotubes (CNTs)	High surface area for drug loading, efficient cellular uptake and penetration into tumors	Potential cytotoxicity and difficulty in biodegradation, difficulties in large scale, cost-effective production	Promising for drug delivery and hyperthermia therapy, still in preclinical stages due to toxicity concerns	[92,93]
Hybrid NPs	Synergistic properties by combining different materials, multifunctionality and enhances targeting efficiency	High production costs, stability issues in physiological environments	Emerging as a promising platform for BC therapy, showed great potential for targeted therapy in preclinical and clinical trials	[94,95]

Nanocarrier materials

Nanocarrier materials utilized in drug delivery systems can be categorized based on their chemical composition and functional groups, both of which play a critical role in determining their drug-loading efficiency, release profile, and targeting ability [96]. Organic nano carriers, which are primarily carbon-based, are particularly valued for their excellent biocompatibility, biodegradability, and the ease with which their surfaces can be functionally modified [97]. A prominent class with in this group includes lipid-based nanocarriers, such as liposomes, SLNs, and nanoemulsion [98].

These delivery platforms are mainly formulated using phospholipids like phosphatidylcholine and phosphatidylethanolamine, often stabilized with cholesterol to enhance membrane rigidity and structural integrity [99]. Moreover, the presence of functional groups, such as hydroxyl(-OH) and phosphate (-PO4 3-) significantly enhance the hydrophilicity and stability of these nano carriers [100]. This structural feature enables the encapsulation of hydrophobic drugs within the lipid bilayer, while hydrophilic drugs can be accommodated in the aqueous interior [101]. In addition to lipid-based systems, polymeric nanocarriers, such as polymeric micelles, hydrogels, and dendrimers are widely utilized [102]. These are typically fabricated using polymers like polylactic-co-glycolic acid (PLGA), PEG, and chiTosan [103]. The presence of functional groups in these systems, include amine(-NH2), carboxyl(-COOH), and hydroxyl(-OH) groups, facilitates drug conjugation and supports controlled release of drugs [104]. Furthermore, dendrimers, [poly(amidoamine) (PAMAM)dendrimers], possess highly branched architectures with abundant terminal functional groups, allowing for precise surface modifications that enhance drug solubility, loading capacity, and targeted delivery [105].

Characterization of raloxifene-loaded polymeric systems

Raloxifene–PLGA-PEG-PLGA Nanomicelles

Thermosensitive PLGA-PEG-PLGA copolymers were used to formulate raloxifene-loaded nanomicelles. Their particle size ranged ~80–100 nm, with high encapsulation efficiency (>85%). Equivalent characterization using NMR, FTIR,

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and other techniques confirmed successful drug incorporation. In vitro release profiles showed sustained release over 72 hours under physiological conditions (37 °C), indicating good potential for controlled delivery [106].

mPEG-PLA Polymeric Nanoparticles

A study by Kala and Chinni (2021) described the development of raloxifene-loaded poly(ethylene glycol)-b-poly(D,L-lactide) (mPEG-PLA) nanoparticles using an emulsion–diffusion–evaporation method. The resulting nanoparticles, synthesized from NMR, FTIR, and GPC-verified polymer, exhibited a particle size of 165–180 nm. Dynamic light scattering confirmed this narrow size distribution. In vitro release assays conducted over 20 days demonstrated approximately 72% drug release, following Higuchi diffusion kinetics, indicating sustained release properties. In vivo pharmacokinetic evaluation in Sprague Dawley rats revealed a significant 4.87-fold increase in oral bioavailability compared to free raloxifene suspension, underscoring the ability of mPEG-PLA nanoparticles to circumvent extensive first-pass metabolism and enhance systemic exposure [107].

Chitosan-Tripolyphosphate (CS-TPP) Nanoparticles

CS-TPP nanoparticles were produced via ionic gelation, with particle sizes ranging 217–1890 nm, entrapment efficiencies from 32.8–97.8%, and drug-loading between 23.9–62.5%. Release kinetics were diffusion-controlled. Intranasal administration achieved significantly increased plasma drug levels within 10 minutes vs. oral suspension [108].

Raloxifene-Polymeric Nanoparticles (RLX-PNPs) – Ionic Gelation

Using a modified ionic-gelation technique, RLX-PNPs (~134.5 nm, +24.4 mV zeta potential) were produced with an entrapment efficiency of 91.7%. FTIR, DSC, PXRD, TEM confirmed amorphous drug distribution, spherical morphology, minimal drug–polymer interaction. Pharmacokinetic studies in rats showed enhanced bioavailability and improved anti-osteoporotic efficacy [109].

Raloxifene Cyclodextrin Chitosan Composite Nanoparticles

Formulated via inclusion complexation and electrostatic interaction using SBE-β-cyclodextrin and chitosan. Characterization included particle sizing, morphology, in vitro release, GI stability, in situ intestinal perfusion, cellular uptake, and oral pharmacokinetics demonstrating improved transepithelial delivery and bioavailability [110].

Raloxifene Hyaluronated Chitosan Nanoparticles

CS and hyaluronic acid-functionalized nanoparticles (RX-HA-CS NP) were produced via sonication and crosslinking. TEM confirmed spherical morphology (~100–180 nm). Zeta potentials ranged from +14.5 mV (CS NPs F1) to –8.1 mV (CS NPs F2), indicating colloidal stability. In vitro release followed sustained patterns, particularly with HA coating enhancing targeting potential [111].

Challenges and future perspectives for raloxifene-loaded polymeric systems

Despite the promising preclinical efficacy of raloxifene-loaded nanosystems, several challenges hinder their clinical translation. First, raloxifene's poor oral bioavailability (~2%) results from its amphiphobic nature, P-glycoprotein efflux, and extensive intestinal glucuronidation—issues that persist even in nanoparticle formulations (e.g., PLGA, lipid, polymer–lipid hybrids) designed to enhance solubility and absorption. Moreover, long-term storage stability, especially of amorphous or co-amorphous polymeric carriers, poses a significant hurdle due to potential recrystallization and drug leakage. Scaling up nanoparticle production without compromising batch-to-batch reproducibility or using toxic solvents is another barrier, particularly for methods like solvent evaporation and spray-drying. In addition, understanding and controlling in vivo biodistribution, metabolism, and potential nanotoxicity remain inadequate, as regulatory guidelines for nanomedicines are still evolving. Going forward, future research must emphasize standardized stability protocols, scalable green manufacturing, and rigorous in vivo pharmacokinetic/toxicity profiling. Additionally, exploring non-oral delivery routes such as transdermal gels or intranasal platforms may bypass

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gastrointestinal and hepatic hurdles, improving patient adherence while minimizing side effects. Ultimately, advancing these nanosystems toward clinical phases will require integrating robust quality control frameworks, comprehensive toxicological data, and regulatory alignment to fulfill the therapeutic potential of raloxifene polymeric delivery systems [112-116].

II. CONCLUSION

Nanotechnology-enabled polymeric delivery systems represent a transformative step in enhancing raloxifene therapy for breast cancer. These platforms address key limitations of conventional raloxifene formulations—improving solubility, bioavailability, and tumor-specific delivery while reducing systemic toxicity. Preclinical studies consistently demonstrate that nanoparticles such as PLGA–PEG nanomicelles, mPEG-PLA systems, chitosan-based carriers, and SLNs achieve sustained release, nanoscale uniformity, and several-fold increases in bioavailability and therapeutic efficacy. These findings emphasize the promise of nanotechnology to refine breast cancer treatment paradigms. Nevertheless, the path to clinical translation involves overcoming significant obstacles. Manufacturing complexities especially scale-up of emulsion- and solvent-based methods pose risks to product consistency, size distribution, drug loading, and residual solvents, necessitating robust, scalable technologies and green processes. Additionally, regulatory standards for nanomedicines demand extensive material characterization, in-depth toxicity profiling, and reproducible clinical-grade production, a hurdle compounded by the evolving definition of critical quality attributes and regulatory frameworks. Addressing these challenges requires early integration of scale-up considerations, advanced manufacturing techniques (e.g., microfluidics, membrane contactors), and stringent quality control protocols guided by regulatory alignment and harmonization. Looking ahead, advancing non-oral delivery routes (intranasal, transdermal), ligand-targeted systems, and multimodal nanocarriers could further refine therapeutic outcomes. Collaborative efforts across academia, industry, and regulatory bodies are imperative to validate safety, efficacy, and commercial scalability. With strategic innovation in design, production, and regulatory compliance, raloxifene-loaded polymeric nanosystems hold real potential to improve breast cancer management and patient quality of life in the near future.

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