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REVIEW ARTICLE

Nanocarriers for Targeted Breast Cancer Treatment: Liposomes, NLCs, Polymeric Nanoparticles

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Breast cancer is one of the most common malignancies in the world in the sense that it requires novel therapeutic interventions whose selectivity is enhanced and systemic toxicity is minimised. Drug delivery systems using nanocarriers have become a potent approach to deliver drug to breast cancer therapy as it improves the solubility, stability, bioavailability, and tumour localization of drugs by passive and active targeting. Liposomes, nanostructured lipid carriers (NLCs) and polymeric nanoparticles are among the various nanocarriers that have exhibited excellent therapeutic attributes in the delivery of chemotherapeutic agents, hormones, genes and biologicals. Doxorubicin and paclitaxel are biocompatible drugs whose platform can be delivered using liposomes and has been clinically approved. Compared to traditional lipid systems, NLCs can be loaded with drugs and released more effectively and be individually engineered with regard to surface functionality, whereas polymeric nanoparticles can be engineered with respect to stimuli-responsive drug release. This review summarises the current developments on nanocarrier-mediated targeted drug delivery of breast cancer, with respect to fabrication methods, targeting modes, treatment and adjetsments, and challenges in clinical translation. The prospective paths such as AI-based nanodesign, personalised nanomedicine and combinatorial nano-therapies are also addressed as the novel methods of breast cancer management.

Keywords: Breast Cancer; Nanocarriers; Liposomes; Polymeric Nanoparticles; Targeted Drug Delivery

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0.1 List of Abbreviations

Abbreviation	Full Form
AI	Artificial Intelligence
CD44	Cluster of Differentiation 44
EGFR	Epidermal Growth Factor Receptor
EPR	Enhanced Permeability and Retention
FDA	Food and Drug Administration
GMP	Good Manufacturing Practice
HER2	Human Epidermal Growth Factor Receptor 2
MCF-7	Michigan Cancer Foundation-7
MDA-MB-231	M.D. Anderson–Metastasis Breast Cancer-231
miRNA	MicroRNA
NLCs	Nanostructured Lipid Carriers
PCL	Polycaprolactone
PEG	Polyethylene Glycol
PLA	Polylactic Acid
PLGA	Poly(lactic-co-glycolic acid)
PNPs	Polymeric Nanoparticles
RES	Reticuloendothelial System
siRNA	Small Interfering RNA
SLNs	Solid Lipid Nanoparticles

0.1.1 Additional Scientific Terms and Symbols

Abbreviation / Symbol	Full Form
In vitro	Studies performed outside a living organism under controlled laboratory conditions
In vivo	Studies performed within a living organism
nm	Nanometre
pH	Potential of Hydrogen

1 Introduction

The most common type of cancer that has been diagnosed in women worldwide and is one of the major causes of cancer deaths is breast cancer[1, 2]. Even though there has been steady improvements in the diagnosis, surgical therapies, radiotherapy, chemotherapy, endocrine therapies as well as targeted biological therapies, various clinical issues are still evidenced, such as multidrug resistance, systemic toxicity, inadequate selectivity, and recurrence of the disease. Traditional chemotherapy is used to spread drugs and distribute the drug in the body without any selection, which leads to dose-limiting toxicities in healthy tissues, including the heart, liver, kidneys, and bone marrow[3, 4].

The use of targeted drug delivery has transformed cancer treatment whereby drugs can now be targeted to cancer tissues at a minimal off-target toxicity level[5, 6]. The concept of nanotechnology is in the middle of this change as it is possible to design nanoscale-based carriers that can encapsulate therapeutic drugs and manoeuvre complex biological surroundings. Nano carriers take advantage of passive targeting using the Enhanced Permeability and Retention (EPR) effect as well as active targeting based on ligand-receptor interactions to accumulate the tumour specifically[7, 8]. **Figure 1**

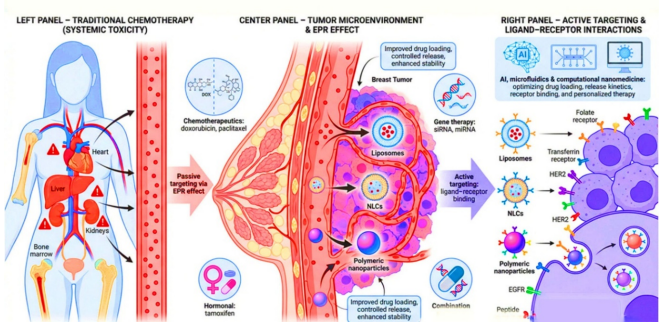

Fig. 1 Schematic comparing systemic chemotherapy toxicity with EPR-mediated passive accumulation and ligand-directed active targeting of nanocarriers, illustrating liposomes, NLCs, and polymeric nanoparticles for enhanced delivery, stability, and precision breast cancer therapy.

With the enormous variety of Nano carriers that have been studied, liposomes, nanostructured lipid carriers (NLCs), and polymeric nanoparticles have acquired incredible relevance due to their biocompatibility, versatility, and good clinical outcomes[9, 10] . The first nanosystems that were approved by FDA were used in treatment of cancer or cancer therapy which is still in the lead of clinical nanomedicine. NLCs are the more advanced versions of lipid-based carriers that address the shortcomings of the solid lipid nanoparticles in terms of leakage of drug and low loading. Instead, polymeric nanoparticles are better in terms of mechanical stability, tunable release properties, and surface engineering[11, 12].

Follic acid, transferrin, HER2 antibodies, epidermal growth factor (EGFR) ligands, and peptides are all ligands used as receptors in delivering nanoparticles to breast cancer cells[13, 14]. Such targeting approaches can be used to improve cellular uptake, intracellular trafficking, and anticancer efficacy and decrease adverse effects. Over the past couple of years, Nano carriers have been effectively used in the delivery of chemotherapeutic (doxorubicin, paclitaxel), hormonal (tamoxifen), gene (siRNA, miRNA) and combination regimens[15, 16].

The recent developments in artificial intelligence (AI), microfluidics, and computational nanomedicine have reinforced optimization of nanocarrier to personalised therapy[17, 18]. Predictions of drug loading with assistance of AI are now speeding up translational achievement by enabling release kinetics modelling and receptor-binding optimization.

This review aims at providing an in-depth comparison between liposomes, NLCs and polymeric nanoparticles as targeted drug delivery systems to breast cancer treatment with reference to formulation strategies, targeting modalities, therapeutic performance, clinical condition and future prospects[19, 20]. **Table 1**

Table 1 This table summarizes key nanocarrier systems used in breast cancer therapy, highlighting materials, targeting mechanisms, representative drugs, and primary advantages that contribute to improved efficacy, safety, and clinical translational potential.

S. No	Nanocarrier Type	Core Material	Targeting Approach	Key Drug Example	Major Advantage
1	Liposomes	Phospholipid bilayer	Passive & Active	Doxorubicin	High biocompatibility
2	NLCs	Solid–liquid lipids	Passive targeting	Paclitaxel	High drug loading
3	Polymeric NPs	Biodegradable polymers	Active targeting	Tamoxifen	Controlled release
4	Ligand-Modified NPs	Functionalized surface	Receptor-mediated	siRNA	High cellular uptake
5	Combination Nanocarriers	Hybrid systems	Dual targeting	Dox + PTX	Synergistic therapy
6	AI-Optimized Systems	Data-driven design	Precision targeting	Multi-drug	Personalized treatment

1.1 Liposomes in Breast Cancer Therapy

1.2 *Structural Design and Drug Encapsulation Mechanism*

Liposomes are bilayered, spherical vesicles, which are mainly made of phospholipids and cholesterol and have a structure that resembles closely that of biological cell membranes[21, 22]. Such special structural construction enables liposomes to carry the hydrophilic and lipophilic anticancer drugs into the various compartments of the vesicle. Drugs that have hydrophobic properties like doxorubicin and cisplatin are trapped in the aqueous core, but those that do not exhibit hydrophobicity like paclitaxel are integrated into the lipid bi-layer[23, 24]. To increase the rigidity of membrane, decrease permeability, and structural stability in circulation, cholesterol is commonly incorporated.

Vesicle size, lamellarity and encapsulation efficiency are optimised by a number of preparation methods, which are; thin-film hydration, reverse-phase evaporation, ethanol injection and microfluidic-based fabrication[25, 26]. The loading of the drugs involves physicochemical forces that include electrostatic attraction, hydrophobic partitioning and transmembrane pH gradients. Ammonium sulphate or pH gradient loading techniques are found to be more effective with regard to the efficiency of drug entrapment and stable retention, particularly when working with weakly basic drugs such as doxorubicin.

Passive tumour accumulation with Enhanced Permeability and Retention (EPR) effect is made accessible by the nanoscale of the liposomes (80-200 nm)[27, 28]. PEGylation PEGylation, which is surface modification with polyethylene glycol (PEG), also enhances circulation half-life by inhibiting opsonization and reticuloendothelial system (RES) clearance[29, 30]. Liposomal structural design is flexible,

which means that, liposomes can be easily targeted and controlled with regard to drug release kinetics, stability and efficiency, which makes them one of the most favoured choice of nanocarriers in the treatment of breast cancer. **Figure 2**

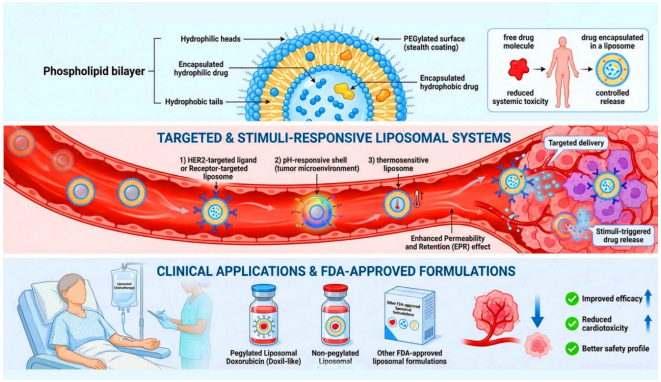

Fig. 2 This illustration demonstrates liposome structure, PEGylation, stimulus-responsive targeting, EPR-mediated tumor accumulation, and FDA-approved formulations, emphasizing controlled release, enhanced efficacy, and reduced systemic toxicity in precision breast cancer therapy via nanocarrier engineering.

1.3 *Targeted and Stimuli-Responsive Liposomal Systems*

Stimuli-responsive and targeted liposomal systems constitute a significant breakthrough in nanomedicine of breast cancer since they permit delivery of drugs to their destination sites and control intracellular release[31, 32]. This is done by active targeting of the surface of the ligands including folic acid, transferrin, peptides, aptamers as well as monoclonal antibodies (e.g., anti-HER2) which selectively bind overexpressed receptors on breast cancer cells. These ligand-receptor interactions facilitate receptor-mediated endocytosis, and thus, enhance drug accumulation in the cell and minimises off-target toxicity[33, 34].

Stimulus-responsive liposomes are designed to release their drug cargo in response to a certain tumour-associated stimulus such as pH, temperature, redox potential or enzyme activity[35, 36]. pH-sensitive liposomes use the acid microenvironment of tumours and endosomes to destabilise lipid bilayers and release its drug cargo. Phase changes in thermosensitive liposomes occur during mild hyperthermia (40-42 degC), and allow an external regulated drug release with localised heat. The redox-responsive liposomes are used to deliver drugs to cytosol which happens when there is a high concentration of glutathione in the cell and release drugs[37, 38].

Dual-targeted and multifunctional liposomes combine ligand-based targeting and stimuli-responsive release which enable improved therapeutic specificity[39, 40]. These superior liposomal systems have shown to have better tumour regression, less systemic toxicity and better survival in preclinical model of breast cancer. The incorporation of imaging agents into these systems has also made it possible to do theranostic applications where cancer diagnosis and treatment monitoring is performed simultaneously. Therefore, selective and stimuli-reactive liposomes are one of the pillars of diversity in precision nanotherapy of breast cancer.

1.4 *Clinical Applications and FDA-Approved Liposomal Formulations*

The most clinically developed nanocarrier in oncology is the liposomes, and a number of these FDA approved formulations are being used in the treatment of breast cancer[41, 42]. The most notable one is pegylated liposomal doxorubicin (PEGylated liposomal doxorubicin (Doxil(r)/Caelyx(r)) which is characterised by considerably lower cardiotoxicity levels than traditional doxorubicin and high anticancer activity. PEG coating offers long circulation time and high tumour accumulation by the EPR effect. This formula has demonstrated great results in the metastatic breast cancer especially when the patient has been subjected to anthracycline previously[43, 44].

The other notable clinical formulation is the liposomal paclitaxel which was created to address poor aqueous solubility and hypersensitivity side effects linked to other paclitaxel formulations[45, 46]. The liposomal encapsulation removes the use of toxic solvents like Cremophor EL, hence enhancing tolerability and safety of patients. Both liposomal vincristine and cisplatin preparations were shown to show greater therapeutic indices and lesser neuro- and nephrotoxicity, respectively.

The clinical findings are always showing better pharmacokinetics, reduced systemic toxicity, and better tumour selectivity of liposomal drugs as compared to their free drug equivalents[47, 48]. Nonetheless, the issues of batch-to-batch reproducibility, high scale of production, long term stability, and cost are all obstacles to universal access. Nevertheless, the liposomes have remained the gold standard of nanocarrier-based breast cancer drug delivery, which can be used as a strong clinical basis of the next-generation of targeted and personalised nanotherapies[49, 50]. **Table 2**

Table 2 This table summarises major structural designs, targeting approaches, stimuli-responsive mechanisms, therapeutic benefits, and clinical translation status of liposomal systems developed for efficient and safe breast cancer drug delivery.

Aspect	Structural Feature	Targeting Strategy	Stimulus Type	Therapeutic Benefit	Clinical Status
Conventional Liposomes	Phospholipid bilayer vesicles	Passive (EPR effect)	None	Enhanced tumour accumulation	Preclinical
PEGylated Liposomes	PEG surface coating	Passive + prolonged circulation	None	Reduced RES clearance	FDA Approved
Targeted Liposomes	Ligand-modified surface	HER2, folate, transferrin	None	Improved cellular uptake	Preclinical
pH-Responsive Liposomes	Acid-sensitive lipids	Passive + active	Tumour pH	Controlled endosomal drug release	Preclinical
Thermosensitive Liposomes	Phase-change lipids	Passive	Hyperthermia	Heat-triggered drug release	Clinical trials
FDA-Approved Liposomes	Optimised lipid composition	EPR-based targeting	None	Reduced cardiotoxicity, improved safety	Approved

1.5 Nanostructured Lipid Carriers (NLCs)

1.6 *Design and Structural Benefits of Nanostructured lipid carriers (NLCs)*

Nanostructured lipid carriers (NLCs) are the next generation of lipid-based nanocarriers that have been designed to address the drawbacks of solid lipid nanoparticles (SLNs) that are low drug-loading capacity, crystal drug expulsion, and instability with time[9, 51]. The NLCs structurally consist of a well-balanced blend of solid lipids and liquid lipids (oils) to form an imperfect and less organised lipid matrix. Such intentional misaligned crystal structure provides more spaces in the core of the lipid, which allows an increase in the amount of drug entrapped and reduces the chances of drug leakage during storage.

NLCs can be divided into three type's imperfect type, amorphous type and multiple type NLCs on the basis of their internal structure[52, 53]. The imperfect one has spatial distortions permitting greater drug accommodation; the amorphous type does not crystallise at all, reducing the expulsion of the drug and the multiple type has oil Nano compartments that are distributed within a solid lipid matrix and offers a better solubilization of the drug. These carrier designs enhance a lot the physical stability and performance of the carrier system.

NLCs have got good biocompatibility, biodegradability and low systemic toxicity because of the use of physiological lipids. Their small size of nanoscale enables passive targeting through the Enhanced Permeability and Retention (EPR) effect that promotes selective concentration in the tumour tissues[8, 54]. Also, the lipid composition enables the surface modification with polymers and targeting ligands with ease. All of these structural capabilities contribute to NLCs as a better and more flexible delivery system to breast cancer therapeutics. **Figure 3**

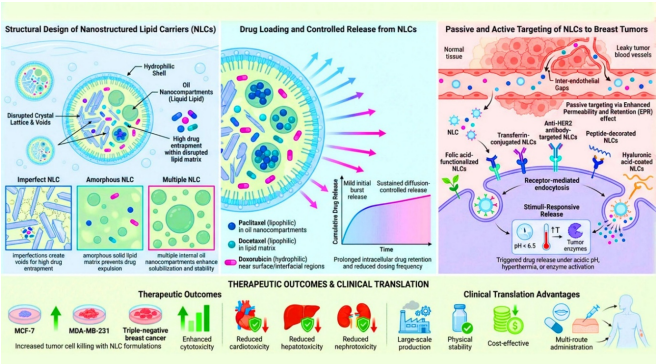

Fig. 3 Schematic illustrates NLC structure, drug entrapment, burst and sustained release, EPR-mediated passive targeting, ligand-driven active uptake, stimulus-responsive release, and resulting therapeutic benefits with improved efficacy and reduced systemic toxicities profile.

1.7 *Kinetics of Drug loading, release and targeting of NLCs*

The high capacity of nanostructured lipid carriers to load drugs is one of the greatest benefits of the given structures over the traditional ones[51, 55]. The presences of the liquid lipids into the solid lipid matrix enhances the solubility of the hydrophilic and lipophilic anticancer drugs, which facilitates the encapsulation of chemotherapeutics drugs in paclitaxel, doxorubicins, docetaxel, and natural anticancer drugs. The loading efficacy of the drug is regulated precisely by balancing lipid composition, concentration of surfactant and preparation method.

NLCs demonstrate sustained and regulated profiles of drug release which are important in terms of retaining therapeutic levels of drugs at the tumour site with minimal exposure to systems. The behaviour of release is mostly biphasic with an initial burst release of mild intensity and diffusion-controlled lasting release of the compound[56, 57]. This sustained release has the advantage of increasing the intracellular retention of drugs, tumour penetration, and decreases the frequency of dosing.

NLCs take advantage of passive and active targeting in terms of targeting potential. They have a small size (typically less than 200 nm) because of which they can be passively accumulated in tumour tissues due to the EPR effect[58, 59]. In addition, active targeting could be done by functionalizing the surface of the cells with ligands including folic acid, transferrin, HER2 antibodies, peptides, and CD44-binding hyaluronic acid. These alterations greatly promote the process of receptor meditated endocytosis and drug delivery to the intracellular levels in breast cancer cells [60, 61]. Also, the site-specific targeting and therapeutic accuracy is further enhanced by the use of stimulus-responsive NLCs, which release drugs in response to pH, temperature, or activity of enzymes.

1.8 *Therapeutic Efficacy and Clinical Relevance of NLCs in Breast Cancer*

Nanostructured lipid carriers have been found to show significant therapeutic effects in breast cancer models in the preclinical stage with a significant enhancement in drug bioavailability, tumour concentration, and anticancer effect besides a reduction in systemic toxicity. Experiments conducted on paclitaxel-loaded and docetaxel-loaded NLCs have demonstrated to have better cytotoxicity against MCF-7, MDA-MB-231 and triple-negative breast cancer models than the conventional formulations[62, 63]. Enhanced cellular uptake by endocytosis and increased retention of the drug within the tumour cells will help to increase the degree of induction of apoptosis and prevent tumour proliferation.

In vivo studies also indicate that NLC-based drug delivery regimes result in significant tumour growth inhibition at a low dose of cardiotoxicity, hepatotoxicity and nephrotoxicity compared to the administration of free drugs[64, 65]. This is due to the selective accumulation and controlled release characteristics of NLCs that resulted in higher safety profile. In addition, combination chemotherapy and chemosensitizers through co-delivery by NLCs have demonstrated positive results overcoming multidrug resistance in breast cancer.

In a clinical translation point of view, NLCs have a few advantages, such as, simple large scale production, high physical stability, affordability and ability to be combined with various administration methods, such as oral, transdermal and parenteral. In spite of the fact that most of the NLC formulations remain in experimental and preclinical phases, their good preclinical outcome and good safety profiles prove their future clinical promotion[66, 67]. As the field of lipid engineering and lipid targeting approaches continues to evolve, NLCs appear as clinically useful nanocarriers with a great potential to enhance targeted breast cancer therapy. **Table 3**

Table 3 This table summarizes the application of deep learning models in predicting breast cancer treatment outcomes, with a focus on chemotherapy response, recurrence prediction, survival analysis, and multi-omics integration. It highlights the types of data used, algorithm types, and the accuracy of the models, demonstrating their potential in personalized treatment and decision-making in clinical practice.

Feature/Model	Application	Data Type	Algorithm Type	Accuracy	Outcome
Response Prediction	Chemotherapy Response	Imaging, Clinical	CNN, LSTM	85 %	Early Intervention
Recurrence Prediction	Tumor Recurrence	Clinical, Genomic	ANN, SVM	90 %	Personalized Care
Survival Prediction	Survival Analysis	Multi-Omics, Imaging	CNN, XGBoost	92 %	Risk Stratification
Multi-Omics Integration	Cancer Biomarkers	Genomic, Proteomic	CNN, RF	88 %	Treatment Optimization
Predictive Models	Chemotherapy Outcome	Imaging, Genomic	CNN, RNN	87 %	Personalized Therapy
Case Study Example	Chemotherapy Response	Imaging, Clinical	CNN, ANN	89 %	Improved Prognosis

1.9 Polymeric Nanoparticles

1.9.1 Polymer Selection and Nanoparticle Fabrication Strategies

Polymeric nanoparticles (PNPs) are made of biocompatible and biodegradable polymers which determine their physicochemical stability, drug carrying capacity and in vivo destiny[68, 69]. Common synthetic polymers are poly (lactic-co-glycolic acid) (PLGA), poly (lactic acid) (PLA), polycaprolactone (PCL), and polyethylene glycol (PEG) and natural polymers like chitosan, alginate, gelatin and dextran have more biocompatibility and mucoadhesive ability. The reason that PLA is regarded as the gold standard is because of its controllable degradation rate, predictable drug release, and excellent acceptance by the regulatory authority. PEGylation has been commonly used to enhance hydrophilicity, enhance systemic blood circulation and inhibit opsonization by the reticuloendothelial system[70, 71] . The optimization of mechanical stability, surface charge, degradation kinetics, and therapeutic payload compatibility can be realised through rational design of the polymer type to be used in targeted therapy of breast cancer.

The choice of different fabrication strategies varies with physicochemical characteristics of the drug and polymer system[72, 73]. The most popular technique of hydrophobic drugs has been emulsion-solvent evaporation because it is simpler and its encapsulation of drugs is high. Nanoprecipitation has the advantage of providing a swift production of particles with low size dispersion and can be used on hydrophobic anticancer drugs. Natural polymers such as chitosan have a preference in ionic gelation in the encapsulation of hydrophilic molecules and genetic material. Recent manufacturing methods like microfluidics, supercritical fluid processing and spray drying allow control of the reproducible particle size and scalable production. Sensitive control of the fabrication conditions including polymer concentration, stirring rate, surfactant nature, and solvent system is essential towards realisation of nanoparticles with best size, stability, and therapeutic action[74, 75]. Figure 4

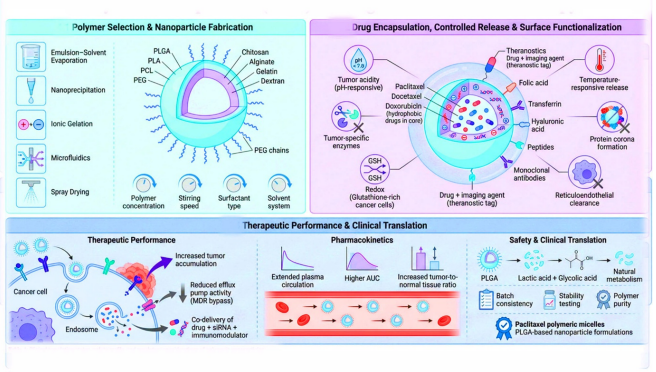

Fig. 4 Schematic depicts polymeric nanoparticle fabrication, drug encapsulation, stimulus-responsive release, surface functionalization, tumor targeting, enhanced pharmacokinetics, MDR bypass, co-delivery strategies, and safety advantages, highlighting translational potential of polymeric nanocarriers for precision breast cancer therapy.

1.10 *Drug Encapsulation, Controlled Release and Surface Functionalization*

According to the polymer-drug compatibility, the entrapment of the drug in the polymer nanoparticle could be done through physical encapsulation, adsorption, or chemical conjugation. Hydrophobic anticancer agents (paclitaxel, docetaxel and doxorubicin) have been readily incorporated into the polymer matrices through hydrophobic interactions, whereas hydrophilic drugs and nucleic acids have been encapsulated by means of electrostatic interactions or by crosslinking polymer. Excellent encapsulation efficiency and long term maintenance of the payload reduces early drug leakage in the systemic circulation[76, 77]. Polymer degradation, diffusion processes and environmental factors are the most dominant factors that determine release kinetics. Stimuli responsive polymers that can be pH-responsive, redox-responsive, enzyme responsive or temperature responsive give site selective drug release in the acid microenvironment of tumours or in cancer cells.

The further functionalization of the surface of polymeric nanoparticles is known to improve the targeting and therapeutic performance of these nanoparticles[78, 79]. The targeting can be actively realised by conjugation of ligands, including folic acid, transferrin, hyaluronic acid, peptides, and monoclonal antibodies, in order to identify overexpressed receptors present on the breast cancer cells. PEGylation gives stealth properties steering off the formation of protein corona and extending the circulation time[80, 81]. Targeting with imaging agents can be used in dual functionalization of targeting ligands which will enable real-time monitoring of tumour and theranostics. Also, charge modifying coats enhance cellular internalisation and endosomal escape, particularly when used in gene delivery. The surface engineered polymeric systems have a significant effect on boosting cellular uptake, intracellular drug accumulation, and therapeutic selectivity and minimising off-target toxicity.

1.11 *Therapeutic Performance and Safety Profile and Clinical Translation*

Polymeric nanoparticles have shown impressive therapeutic effects of breast cancer therapy with better uptake and better tumour retention of the particle in cells and by increasing the drug retention[82, 83]. In vitro experiments are always associated with a high level of cytotoxicity against cancer cell lines in the breast cancer where receptor-mediated endocytosis and controlled intracellular discharge of the drug occur. In vivo pharmacokinetic findings indicate sustained plasma concentrations of the drug, increased area under the curve as well as increase in tumour to normal tissue ratio. These nanoparticles overcome the multidrug resistance with high efficacy because they can avoid efflux transporters and eliminate the hypoxic and drug resistant tumour sites[84]. In addition, polymeric carriers allow the synergistic anticancer action of chemotherapeutic agents, gene therapy molecules, siRNA, or immunomodulators to be delivered at the same time.

Considering safety, polymeric nanoparticles are less toxic to the body when there is limited exposure of the drug to normal body tissues. Biodegradable polymers like PLGA are broken down by predictable metabolic processes to lactic and glycolic acids which are expelled through the physiological processes[85]. Nevertheless, the large-scale reproducibility, batch-to-batch consistency, and long-term stability are some of the main challenges in translational research. The regulatory passing has a high assessment of purity of the polymer, degradation products, and manufacturing reproducibility. A number of polymeric nanoparticle formulations including paclitaxel-polymeric micelles and polymeric nanoparticles made of PLGA have undergone advanced clinical trials[86]. As scalable manufacturing, ligand engineering, and individually relevant models of medicine display further improvements, polymeric nanoparticles will assume a paradigm shift in the treatment of breast cancer. **Table 4**

Table 4 The table outlines the key challenges in the application of deep learning for breast cancer diagnosis and treatment prediction, including data quality, size, diversity, interpretability, regulatory hurdles, and ethical concerns. It provides potential solutions and examples to illustrate how these challenges manifest in clinical practice.

Challenge	Description	Impact on Diagnosis	Impact on Treatment Prediction	Solutions	Example Case
Data Quality	Inconsistent, noisy, and low-quality data affecting training models.	Reduced accuracy in cancer detection.	Inaccurate predictions for treatment outcomes.	Better data-sharing and standardization.	Imaging data quality issues.
Data Size	Insufficient large datasets for training robust models.	Difficulty in model generalization.	Limited scope for treatment response analysis.	Collect diverse, large datasets.	Limited dataset from specific regions.
Data Diversity	Lack of representation from diverse populations in datasets.	Bias towards majority groups.	Suboptimal model performance for minority groups.	Include multi-ethnic, global data.	Disparity in model predictions for different ethnicities.
Interpretability	Black-box nature of DL models, reducing trust.	Clinicians uncertain of model rationale.	Difficulty in justifying treatment decisions.	Develop Explainable AI (XAI) methods.	Lack of transparency in CNNs.
Regulatory Hurdles	Slow regulatory approval processes and unclear AI guidelines.	Delayed adoption in clinical settings.	Hindered integration of AI models in treatment protocols.	Streamline approval, improve guidelines.	FDA approval delays for AI diagnostics.
Ethical Concerns	Potential bias in models, privacy issues, and accountability gaps.	Unfair diagnosis, unequal treatment access.	Misuse of AI predictions affecting patient care.	Ethical AI development and regulations.	Privacy concerns with patient data.

1.12 Targeting Strategies in Breast Cancer Nano therapy

1.13 *Passive Targeting: improved Permeability and Retention (EPR) Effect*

Passive targeting is mainly founded on enhanced permeability and retention (EPR) effect a unique attribute of solid tumours that have abnormal vascular structures and lack lymphatic drainage[87]. Tumour blood vessels have massive fenestration with the range between 100 and 800 nm diameter, which enables Nano carriers to extravasate in tumour tissues selectively. When amassed, the absence of an effective lymphatic clearance promotes tumour micro environmental retention of nanoparticles. Surface ligands are not required in this phenomenon because of the non-specific but effective accumulation of Nano carriers in breast tumours. The size range of between 50-200 nm comprising liposomes, polymeric nanoparticles, and lipid-based Nano carriers has shown the most EPR-based accumulation of both preclinical and clinical models of breast cancer[88].

The EPR effect, although simple and highly successful, has contradictory reliability between patients and tumour types. Interstitial fluid pressure, the density of the vascularity, tumour size, stromal composition and heterogeneity are some of the factors, which affect the extent of nanoparticle accumulation. This can be hindered by dense stromal barriers and hypoxic areas in aggressive forms of breast cancer like triple-negative ones in the presence of EPR. Moreover, the clinical translation of EPR-based targeting is a problem because of the lack of reproducibility of animal models and human tumours[89]. To address these limitations and boost the efficacy of passive targeting, strategies like tumour priming, normalisation of the vasculature and combined with active targeting ligands are currently under investigation as an effort to improve the passive targeting delivery in breast cancer Nano therapy. **Figure 5**

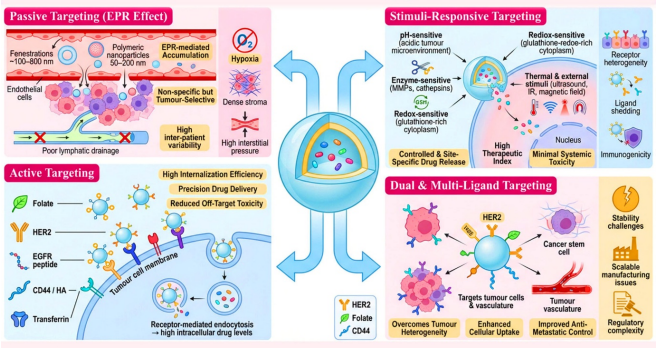

Fig. 5 Overview illustrates passive EPR-based accumulation, active ligand-mediated targeting, stimulus-responsive release, and dual-ligand strategies in breast cancer nanotherapy, highlighting enhanced cellular uptake, site-specific delivery, reduced toxicity, and improved antimetastatic therapeutic efficacy.

1.14 *Active Targeting: Folate, HER2, EGFR, CD44, transferrin*

Active targeting is the use of ligand-receptor interactions to optimise the selective uptake of nanoparticles by breast cancer cells[90]. Nano carrier surfaces are usually conjugated with ligands like folic acid, transferrin, hyaluronic acid and monoclonal antibodies directed against the HER2 and EGFR. The folate receptors are also overexpressed in most cancer cells in the breast leading to receptor-mediated endocytosis of folate-conjugated nanoparticles. Nano-carriers which target the HER2/neu receptors, especially antibody-conjugated carriers, have demonstrated impressive effectiveness in the treatment of breast cancer that has the HER2/neu receptor in that the system has been shown to deliver drugs to the intracellular environment in a more effective manner and could lower the off-target toxicity[91]. Equally, EGFR- and transferrin-targeted systems improve the uptake in cells of highly proliferative tumour cells.

A hyaluronic acid receptor known as CD44 is also found in high amounts in breast cancer stem cells and metastatic tumours, and it is a useful target in preventing recurrence and resistance[92]. Active targeting increases the internalisation efficiency, optimal intracellular drug concentration, and allows the delivery precision with minimum systemic exposure. Targeting efficiency can however be influenced by receptor heterogeneity, receptor saturation and shedding of the ligand[93]. Also, big molecules like antibodies can cause immunogenicity increase and reduce nanoparticle circulation. To overcome these challenges, small peptides, aptamers, and two-ligand approaches have gained more and more popularity among the researchers in order to enhance receptor binding and reduce biological variability in targeting active breast cancer.

1.15 *Active Targeting: Folate, HER2, EGFR, CD44, transferrin*

The Nano carriers are stimuli-responsible and give drugs to be released in a controlled and site-specific manner by taking advantage of pathological variations between tumour and normal tissues. Selective release of drugs within cancer cells is also possible in the acidic extracellular tumour pH environment and endosomal/lysosomal environment by using pH-sensitive Nano carriers[94]. The enzymes that are overexpressed in tumour-associated enzyme-responsive systems are matrix metalloproteinases and cathepsins, which are used to cause carrier degradation and drug release. The high levels of glutathione ions in the intracellular environment trigger the redox-sensitive Nano carriers to release selectively into the intracellular environment, but remain stable at the extracellular environment.

Nano carriers are thermo-responsive and the external stimuli utilised include ultrasound, infrared radiation, or magnetic fields to create localised hyperthermia[95]. These systems show temperature induced structural changes resulting in high speed release of drugs within the hot tumour site. The important benefit of stimuli-responsive targeting is excellent spatiotemporal control of drugs which greatly increases therapeutic index and reduces systemic toxicity. Nonetheless, common to the clinical translation are difficulties with generating consistent stimulus delivery within the tumors, and recapitulating strong responsiveness in the physiological conditions. The future of stimulus-responsive breast cancer Nano therapy is steadily on the rise as more developments in polymer chemistry, hybrid nanomaterials, and externally controllable delivery technologies are made.

1.16 *Dual-Targeted and Multi-Ligand Nano carriers*

In order to counter tumour heterogeneity and to enhance specific cell recognition, dual-targeted Nano carriers incorporate two distinct targeting ligands on the same nanoparticle surface. Indicatively, HER2 folate, EGFR transferrin or CD44 integrin-targeting peptide systems have shown excellent cellular uptake than single-ligand systems. The practise resolves the variability of receptors in various tumour subpopulations and optimises the overall treatment efficacy[96]. Multi-ligand systems extend the same approach by using three or more targeting moieties in order to treat both cancer cells, tumour vasculature, and the tumour microenvironment.

These new targeting systems have great enhancement of accumulation of tumours, intracellular delivery and response to treatment and limit resistance of drug. Dual and multi-ligand Nano carriers can be of special use in aggressive and metastatic breast cancer where single-pathway targeting is not effective to produce a long-lasting effect. More surface complexity may however change the nanoparticle stability, pharmacokinetics, and large-scale manufacturability[97]. Control of regulatory approval is also difficult as a result of the complexity of the formulation and the reproducibility of the ligands. Nevertheless, in spite of these challenges, multi-targeted Nano carriers are the future of precision nanomedicine, and are able to provide the true personalised cancer treatment approaches in breast cancer. **Table 5**

2 Clinical Translation & Limitations

2.1 *Barriers of Regulations and Manufacturing*

The advanced regulatory and manufacturing requirements put serious limitations on the clinical translation of Nano carrier-based breast cancer therapeutics. Nanomedicines in contrast to the traditional pharmaceuticals possess a multifactorial nature through such properties as particle size distribution, surface charge, morphology, drug loading efficiency, and release kinetics, which are critical determinants of safety and efficacy[98]. These attributes, including regulatory agencies, must be characterised and reproducible in a strict manner, but internationally recognised regulatory standards in nanomedicine are rare. Lack of universally recognised standards on the classification or bioequivalence testing of nanoparticle and long-term safety evaluation makes it difficult to approve. Also, laboratory-to-industrial manufacturing requires significant challenges to be overcome in terms of scale-up. Most solvent-intensive multistep fabrication-based polymeric and lipid-based Nano carriers are hard to scale to Good Manufacturing Practise (GMP)-manufacturable large-scale synthesis. Batches to batch variability, sterility and solvent residue and storage stability also make manufacturing processes more difficult. In addition, further surface functionalization and active conjugation of ligand enhance the complexity and cost of production. Real time monitoring of nanoparticle characteristics at the industrial level is yet to be developed using analysis tools[99]. To the effect of these regulatory uncertainties and manufacturing inefficiencies, the approvals of clinical facilities and industrial investments will be postponed. The barriers discussed above need to be overcome by standard regulatory frameworks, scalable green manufacturing strategies, real-time quality control technologies, and more intensive interaction between researchers, industries, and regulatory organisations. **Figure 6**

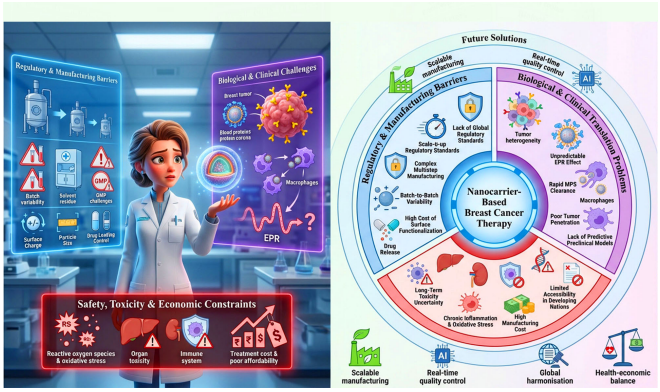

Fig. 6 Conceptual overview depicting regulatory, manufacturing, biological, safety, and economic barriers limiting nanocarrier-based breast cancer therapy clinical translation, alongside integrated future solutions including scalable production, real-time quality control, global harmonization, and AI-enabled predictive modeling.

2.2 *Problems in Biological and Clinical Translation*

Although the biological complexity of breast cancer is promising in preclinical performance, there are tremendous challenges faced when trying to translate Nano carriers-based therapies into the clinical setting. The heterogeneity of tumour, lack of consistency in receptor expression, and variation in the microenvironment of the tumour have a drastic influence on the nanoparticle accumulation, penetration, and treatment response. Enhanced permeability and retention (EPR) effect that was long believed to be the foundation of passive targeting is characterised by high interpatient variability and a low degree of predictability in human tumours as opposed to the case of animals[100]. Also, biological obstacles include formation of protein coronas, rapid clearance by mononuclear phagocytic system and poor penetration of tumours, which limit the delivery of drugs. Active targeting modalities, despite their appearance to work well in vitro, do not necessarily translate into a consistent clinical outcome as they are prone to downregulation of receptor, off-target interactions as well as immune sensitization. Also, translational discrepancies between laboratory success and clinical outcomes are caused by the absence of predictive preclinical models, which correctly recapitulate human breast cancer physiology. Nano carriers Pharmacokinetic profiles, bio distribution patterns and long-term fate of Nano carriers in humans are poorly understood[101]. Immunological, genetic polymorphisms, previous exposure to chemotherapy and metabolic differences are other clinically specific factors that complicate therapeutic predictability. These biological confusions warrant the creation of sophisticated humanised tumour models, patient-derived xenografts and image-guided nanomedicine tracking in order to enhance translational efficacy.

2.3 *Safety, Toxicity and Economic Constraints*

Long-term toxicity and safety are key issues that have curtailed the globally used clinical implementation of the Nano carrier-based breast cancer therapeutics[102]. Even though much of the current eyelid polymeric and lipid Nano carriers are made of biodegradable materials, the degradation products, the accumulation behaviour, and immune interactions in the long run are not characterised. The impact of nanoparticles can be oxidative stress, inflammation, immunogenicity, and organ-target toxicity with regards to the size, surface chemistry, and frequency of their administration. The risks of chronic exposure, reproductive toxicity and genotoxic potential seldom appear in the conventional short-term preclinical study. Moreover, interactions of nanoparticles with the blood components are likely to change the coagulation pathways and cause pseudo allergy through complement activation. Other than biological risks, economic sustainability is also a big limitation. Nano carrier manufacturing process is a complex instrumentation process, requires high purity of raw materials, and is a multi-step process, which significantly increases the manufacturing cost of the Nano carriers[103]. A further increase in costs is that personalised nanomedicine practises though clinically appealing, require personalised formulations. In developing nations, Nano therapeutics are expensive, and this factor limits their access and equal healthcare provision. Also, uncertainties about reimbursement and insufficient insurance of advanced nanomedicine-based treatment are some of the factors that will not facilitate the adoption of these treatments in clinical practises. To mitigate these safety and economic obstacles, it is needed to utilise long-term toxicological surveillance, scalable cost-effective production technologies, and health-economic analyses to guarantee health and financial sustainability of the patients. **Table 6**

3 Future Directions

The Nano carrier-based targeted therapy of breast cancer in the future is in the intersection between nanotechnology and precision medicine, artificial intelligence, and new biomaterials. Nanostructured lipid carriers and next-generation liposomes and polymeric nanoparticles are likely to be further developed as multidrug that can belong to different categories and include chemotherapeutics, gene therapies, immunomodulators, and imaging agents in a single platform. PH, redox potential, enzyme, ultrasound, or external magnetic field-stimulable nanocarriers will be even more useful in site-targeted drug delivery and reduce systemic toxicity. It is expected that the combination of artificial intelligence and machine learning in formulation optimization, pharmacokinetic prediction, and patient stratification will help fasten the success of translational applications. Nanomedicine can be customised to allow unique methods of drug delivery to the various subtypes of breast cancer through personalised nanomedicine using tumour genomics and receptor profiling. In addition, an environmentally friendly synthesis methods, scalable manufacturing methods and regulatory-based quality-by-design will play a pivotal role in augmenting the industrial viability. Organ-on-chip models, advanced in vitro tumour models and patient-derived xenografts are also anticipated to fill the gap between the preclinical performance and clinical outcomes. All of these innovations make nanocarriers the key to the future of precision therapeutics of breast cancer.

4 Discussion

Targeted drug delivery via Nano carriers has revolutionised the treatment of the breast cancer disease by significantly overcoming critical challenges of traditional pharmacotherapy that include low solubility, systemic toxicity, quick clearance, and multidrug resistance. Liposomes are better in terms of biocompatibility and clinical validation, nanostructured lipid carriers offer better drug loading and stability and polymeric nanoparticles give better control and stimuli-responsive release at precise targeting. However, their clinical in vivo application is only inconsistent with tumour heterogeneity, variability in the enhanced permeability and retention effect, biological clearance, and regulatory complexities despite their strong preclinical efficacy. Ligand conjugation as an active targeting approach has had promise but has not consistently been translated into better clinical efficacy. More so, the issues of large-scale production, reproducibility, and uncertainty regarding long-term safety, remain to limit the large-scale clinical use. The cost of production of the advanced nanotherapeutics is economically high, which limits its accessibility, especially in low and middle income areas where the burden of breast cancer is increasing at a high rate. However, ongoing optimization of nanoparticles design, as well as molecular oncology, computational modelling and biomarker-mediated patient selection, are increasingly reinforcing reliability in translational research. Therefore, nanocarrier-based systems are a promising and developing treatment modality that must be multidisciplinary in its implementation to have a consistent clinical success.

5 Conclusion

Nanocarriers including liposomes, nanostructured lipid carrier and polymeric nanoparticles have recently become one of the most promising vehicles to targeted breast cancer therapy which provides a significant enhancement in drug solubility, pharmacokinetics, tumour selectivity, and therapeutic index. Such systems facilitate accurate control over drug administration, increase in tumour concentration and decrease in systemic toxicity thus overcome a number of inherent shortcomings of traditional chemotherapy. Although liposomes have also been characterised with high clinical promise, NLCs and polymeric nanoparticles are still expanding the parameter of controlled and multifunctional drug delivery. Nonetheless, the route to common clinical use is still problematic by the regulatory uncertainty, biological heterogeneity, long-term safety and financial limitations regardless of the impressive preclinical success. Standardised manufacturing, strong quality control, predictable translational worldview, and long-term toxicological validation all rely on the final outcome of clinical success of nanocarrier-based therapeutics. The next-generation nanomedicine will be redefined with the future incorporation of technological advancements of artificial intelligence, customised oncology, and green manufacturing. To sum up, nanocarriers can be qualified as a potential breakthrough in the area of breast cancer treatment as the full potential of this technology will assist in precision therapy, assuming that the issues of translation and regulation are carefully handled.

Author Contribution

5.1 CRediT Author Statement

Punniyakoti Veeraveedu Thanikachalam conceptualization of the study, drafted the manuscript and Joel Mart Elias, Vijayakumar Murugesan, Kommu Pradeep designed the figures, manuscript review and editing. All authors reviewed the manuscript.

5.2 Ethical Statement

This study did not involve human participants, animals, or biological materials, and therefore, ethics approval and consent to participate were not applicable.

5.3 Declaration Statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Conflicts of Interest

All authors declare that there are no conflicts of interest associated with the publication of this manuscript.

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