Review article
AMERICAN JOURNAL OF PHARMACY AND HEALTH RESEARCH
www.ajphr.com
2026, Volume 14, Issue 08
ISSN: 2321–3647(online)

Emerging Drug Delivery Systems for Exemestane: Enhancing Therapeutic Outcomes in Breast Cancer

Gurdeep Singh[1], Ashnoor Kaur[1], Prabha Kumari[1], Gurpreet Singh[1], Ashish Tangotra[1], Puneet Verma[1], Neena Bedi[1*]
Department of Pharmaceutical Sciences, Guru Nanak Dev University, Amritsar-143005, India

ABSTRACT

Breast cancer is a leading contributor of cancer-related death among women throughout the world. Exemestane (EXE), a third-generation irreversible aromatase inhibitor, is widely employed for the management of estrogen receptor-positive (ER^+) breast cancer. Although the clinical efficacy of EXE is well established, poor aqueous solubility, low oral bioavailability, short plasma half-life, and low permeability limit its therapeutic efficacy. Therefore, the advancement of drug delivery technologies which can improve the pharmacokinetics profile, therapeutic efficacy, and tumor specific accumulation becomes important. In light of the above, the current review summarizes various formulation strategies of EXE including lipid-based nanoparticles, nanoemulsion, lipid nanocapsules, nanoparticles, liposomes, to name a few. However, polymeric mixed micelles are emerging as an effective nanocarrier system because they can improve drug solubilization, enhance cellular uptake, prolong systemic circulation, and facilitate passive tumor targeting. This review discusses the advantages and characterization techniques of polymeric micelles as a drug delivery system with special emphasis on methods of preparation, micellar architecture, and selection of polymers. Furthermore, the review explores polymeric micelles currently approved for clinical usage and undergoing clinical trials for an effective management of cancer. Additionally, incorporating micellar formulations into injectable hydrogels has gained popularity among the research community as it facilitates localized drug delivery and reduces the off target side effects thereby, improve the overall therapeutic efficacy. These advantages underscore the need for EXE encapsulated polymeric micelles integrated *in situ* hydrogel system to ensure sustained release and maintain therapeutic concentration of EXE to improve the breast cancer treatment.

Keywords: polymeric micelles; exemestane; breast cancer; characterization; clinical trials

*Corresponding Author Name: Dr. Neena Bedi, neena.pharma@gndu.ac.in

Please cite this article as: Bedi N *et al*., Emerging Drug Delivery Systems for Exemestane: Enhancing Therapeutic Outcomes in Breast Cancer. American Journal of Pharmacy & Health Research 2026.

Received 10 June 2026, Accepted 13 July 2026

INTRODUCTION

Breast cancer is one of the most prevalent and lethal types of cancer that poses a critical global threat, as indicated by International Agency for Research on Cancer (IARC) in their January 2022 report. [1] Estrogen promotes cancer cell proliferation via estrogen receptor-mediated signaling pathway and is pivotal in the initiation and progression of tumor. [2] Therefore, endocrine therapy has become an integral part of management of hormone receptor-positive breast cancer. Exemestane is a potent steroidal aromatase enzyme inactivator that irreversibly binds to aromatase enzyme (CYP19A10) and reduces estrogen-dependent tumor growth. EXE is used as an adjuvant for the treatment of advanced hormone receptor- positive breast cancer because of its clinical efficacy and safety profile. [3] Prolonged treatments with conventional EXE delivery systems can lead to acquired drug resistance, reduced intracellular drug accumulation, increased cancer cell survival, and eventually failure of therapy. [4] Furthermore, long-term therapy leads to severe adverse effects like osteoporosis, arthralgia and musculoskeletal complications therefore, highlighting the need for advanced therapeutic approaches to promote the therapeutic outcomes and reduce the associated systemic side effects. [5] To augment the aqueous solubility and oral bioavailability of EXE, various research approaches including nanoparticles, nanoemulsion, lipid nanocapsules, and liposomes to name a few, have been previously explored. [6] However, the full potential of EXE has not been achieved which can be attributed to its limited therapeutic efficacy at the target tumor site.

Polymeric micelles have gained popularity because of their unique core-shell structure that permits efficient encapsulation of hydrophobic drugs, enhances aqueous solubility, improves pharmacokinetic behavior, prolong systemic circulation and better tumor accumulation through enhanced permeability retention (EPR) effect. Micellar formulations offer critical benefits for Exemestane over conventional oral and systemic strategies. [7] By encapsulating Exemestane in the hydrophobic core of a nanocarrier, micelles bypass its low water solubility, avoid harsh pre-systemic metabolism and improve targeted tumor delivery. In advancing technology, mixed micelles are formed using mixture of amphiphilic polymers which provide superior physicochemical stability, higher drug loading capacity, controlled drug release and improved formulation in comparison to conventional single polymer micelles. Due to their excellent biocompatibility, low toxicity, and regulatory acceptance, Pluronic block copolymers have been extremely investigated as micellar carriers; they also exhibit biological activity by inhibiting P- glycoprotein-mediated drug efflux, reducing intracellular ATP levels, modulating mitochondrial function, and sensitizing multidrug-resistant cancer cells to chemotherapy. For EXE delivery binary and ternary mixed micellar systems

based on Pluronic L121, Pluronic F127, and Gelucire 44/14 have established efficient micellar stability, improved drug encapsulation and better solubilization of hydrophobic anticancer agent. [8] While micelles are highly effective for delivering poorly water-soluble drugs, they have several distinct chemical and structural limitations like low physical stability, poor core capacity, rapid structure disruption, toxicity risks, and production scalability. Therefore, localized drug delivery strategies have emerged as a topic of interest for achieving sustained drug release and higher drug concentration at tumor site and reducing systemic exposure such as injectable-stimuli responsive *in situ* hydrogels, they undergo sol-to-gel transition under physiological conditions thereby forming biodegradable three-dimensional matrices that enable prolonged drug retention. [9] To overcome limitations with oral chemotherapy, addition of drug-loaded polymeric micelles into hydrogel matrices represents a two-step drug delivery technique with solubilization and targeting capabilities of nanocarriers, and sustained release properties of hydrogels.

To summarize, this review provides an overview of cancer, specifically breast cancer, and discusses notable breakthroughs in EXE-based drug delivery platforms for the treatment of estrogen-dependent breast cancer. Apart from this, a considerable emphasis has been given to the advantages and characterization techniques of polymeric micelles as a drug carrier approach with special emphasis on methods of preparation, micellar architecture, and selection of polymers. To improve therapeutic efficacy and patient outcomes, this review summarizes anticancer drugs based polymeric micelles and polymeric micelles currently approved for clinical application or undergoing clinical trials for an effective management of cancer. Lastly, the review focuses on the benefits of incorporating the micellar system into an injectable hydrogel to achieve better therapeutic outcomes while minimizing the off-target effects.

Cancer

Cancer is defined by the unregulated multiplication of normal cells, which can potentially metastasize to other areas of the body. Carcinogenesis, marked by six major hallmarks, can arise in any cell, tissue or organ, precipitating pathological changes that give rise to numerous types of cancer. [10] Tumors can be categorized by their location, such as breast, brain, lung and ovarian cancers. However, within these tumor categories, further subtypes can be distinguished through differences in their molecular profiles, morphology, and expression of specific markers. As reported in the IARC, GLOBOCAN 2022 update, cancer resulted in approximately 9.7 million deaths and 20 million new cases worldwide, compared to 9.96 million deaths and 19.6 million cases in 2020. [11] It is estimated that cancer will claim the lives of 1 in 9 men and 1 in 12 women over the course of their lifetime. As of the past decade, India ranked third in global cancer burden,

following China and the United States of America.[12] Apart from this, the metastatic process involves invasion, intravasation and extravasation. In the early invasive stages, tumor cells acquire aggressive properties, adopting a spindle-shaped morphology similar to stem cells or fibroblasts, enabling migration and invasion of the breast basement membrane through EMT network activation.[13] Tumor progression involves transitions between epithelial, mesenchymal, and squamous components. MBCs are typically large, poorly differentiated, node-negative and ER/PR/HER2-negative.[14] They have a low incidence rate of less than 0.02–5% of cases and are generally linked to a poorer prognosis compared to IDC patients.[15, 16]

Breast cancer

Earlier investigations revealed that early breast cancer detection, along with appropriate treatment and effective therapeutic strategies, plays a crucial role in significantly reducing long-term mortality rates. Nearly half of all the cases worldwide are reported in advanced economies. [17] This phenomenon is largely linked to a unhealthy lifestyle, marked by poor dietary habits, smoking, elevated stress levels, and insufficient physical activity. In 2018, the number of breast cancer cases reported was 234,087 in the United States (crude rate: 85/100,000), 55,439 in the United Kingdom (crude rate: 94/100,000), 56,162 in France (crude rate: 99/100,000), 71,888 in Germany (crude rate: 85.4/100,000), and 66,101 in Japan (crude rate: 58/100,000). [18] Despite the array of available therapies such as radiation, chemotherapy and surgery, effective treatment of cancer remains a significant challenge. The continued effectiveness of chemotherapy as a leading cancer treatment has driven the development of numerous potent anticancer drugs, such as doxorubicin and paclitaxel, which target rapidly dividing cancer cells by damaging their RNA or DNA. [19] Approximately one-third of human breast cancer cases are classified as hormone-dependent. [20] Estrogen is critically related to the occurrence and advancement of hormone-dependent breast cancer. Estrogen synthesis generally takes place in adipose tissues, ovaries, skin, and breast in postmenopausal women, making a radiological and surgical approach to ablation unworkable. [21]

Epidemiology of Breast Cancer

Breast cancer arises from the interplay of multiple interrelated factors. The precise mechanism underlying breast carcinogenesis remains unclear; however, various risk factors have been identified as contributing to its onset and progression. [22, 23] As evidenced by the aforementioned epidemiological data, key risk factors for breast cancer include advancing age, biological sex and the socioeconomic status of a given country. [24] The likelihood of developing breast cancer increases with early menarche, late menopause and the absence of childbirth. [25] Hormones are considered one of the most significant etiological factors that facilitate breast cancer progression.

[26, 27] Atypical lobular or ductal hyperplasia, along with localized estrogen production in the breast, is instrumental in the development of symptoms associated with benign breast changes, previously termed "breast disease". [28] Breast cancer development is significantly affected by genetic predisposition, hormone replacement therapy, unhealthy eating patterns, and obesity. Additional key risk factors include the consumption of hormonal contraceptives, alcohol, and early-age exposure to the ionizing radiations. Modern scientific approaches illuminate the pathology and molecular traits of breast cancer, offering insights into its classification based on its occurrence in different regions of the breast (Figure 1). Therefore, breast cancers are typically classified as either sarcomas or carcinomas, depending on the specific type of cell from which they originate. [29]

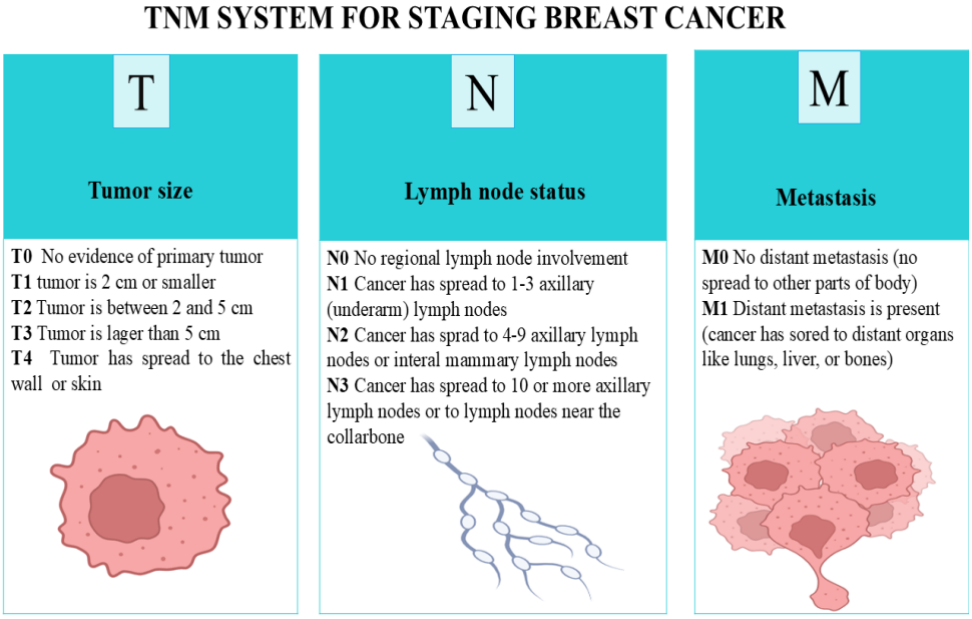

Figure 1: Tumor, node and metastasis (TNM) staging of breast cancer (T: Tumor; N: Lymph node; M: Metastasis)

Breast cancer subtypes based on pathology and invasiveness

Non-invasive (*In situ*) breast cancer

Breast ductal carcinoma *in situ* (DCIS) is a non-obligate, pre-invasive form of malignancy that remains strictly localized. It remains restricted to the basal membrane of the milk ducts and is recognized as a common precancerous condition across all tissue types, consisting of a diverse group of lesions with the potential to develop into invasive cancer. Clinically, DCIS can manifest as a palpable mass, nipple discharge, or Paget's disease. [30, 31] Nevertheless, as a precursor, most DCIS cases do not progress to an invasive stage, while active screening programs have contributed to a rise in invasive BC diagnoses. [32]

Invasive breast cancer

Invasive breast cancer (IBC) comprises of a diverse groups of tumors that vary in characteristics of clinical, behavioral, and morphological origins. The World Health Organization (WHO) identifies approximately 18 distinct histological types of breast cancer. Invasive breast cancer of no-special type (NST), previously referred to as invasive ductal carcinoma, accounting for 40–80% of cases, and frequently encountered subtype. [33] This subtype is diagnosed by default when a tumor cannot be particularly classified into any established histological categories. Around 25 % of invasive breast cancers display distinct growth patterns and cytological features, leading to their classification as separate subtypes (*e.g.,* invasive lobular carcinoma, tubular, mucinous A, mucinous B, neuroendocrine) *etc*. [34] Invasive lobular carcinoma (ILC) is the second most prevalent form of invasive breast cancer, representing about 5–15% of all diagnosed cases. It predominantly occurs in older women, with a higher incidence among postmenopausal women. ILC is marked by loss of cellular cohesion of epithelial cells accumulating within the terminal duct lobular units, largely resulting from the loss of E-cadherin expression, a key cell-adhesion molecule, in 60-90% of cases. From an evolutionary standpoint, ILC originates from precursor lesions such as atypical lobular hyperplasia and lobular carcinoma *in situ.* Furthermore, the aforementioned types of tumors are associated with a strong tendency to develop ER/PR-positive and HER2-negative profiles. [35, 36]

EXEMESTANE IN BREAST CANCER

Mechanism of action

Exemestane (EXE) is a third-generation, Type-I steroidal irreversible aromatase inhibitor that selectively inhibits aromatase. [37] It has been approved by the United States Food and Drug Administration (US-FDA) for estrogen receptor-positive breast cancer treatment in post-menopausal women. [38] It binds irreversibly to the active site of the aromatase enzyme, mimicking a natural substrate and resulting in permanent enzyme inactivation (Figure 2). [39] The therapeutic potential of EXE has not been fully exploited, due to its low oral bioavailability (5%), poor water solubility (80 µg/mL), and poor permeability (BCS IV). [40] Its high lipophilic nature makes it susceptible to p-glycoprotein efflux pumps, in addition, the high metabolic clearance and extensive first-pass metabolism of exemestane collectively reduce its bioavailability at the tumor site. [41] Also, lack of a tumor-targeting approach leads to patients remaining non-adherent to prescribed therapy, which eventually stretches the treatment duration and exhibits drug resistance as a result of p-gp efflux pump overexpression on tumor cells. [42] Moreover, increased dosage has resulted in serious long-term adverse effects such as osteoporosis, thus limits its therapeutic potential. [43]

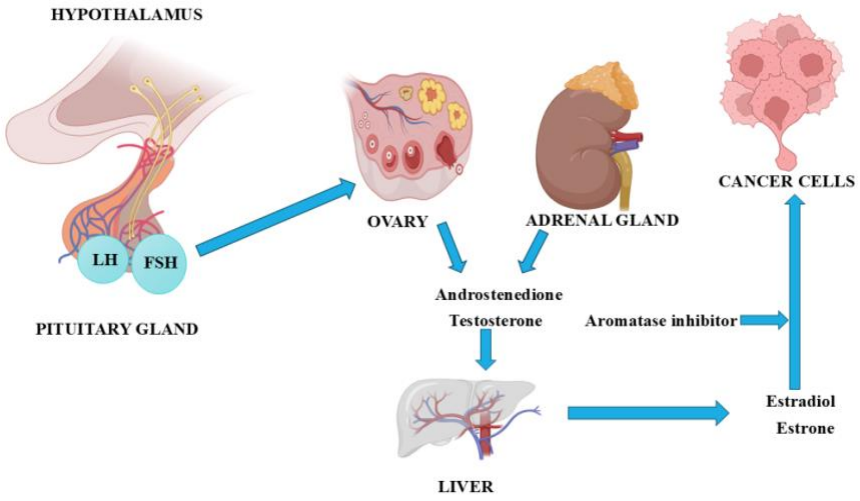

Figure 2: Illustration of mechanism of action of aromatase inhibitors in cancer therapy (Dowsett and Howell 2004) (LH: Luteinizing Hormone; FSH: Follicle-Stimulating Hormone)

Formulation strategies of exemestane

Developing an efficient nanocarrier-based system is crucial to facilitate effective delivery of EXE and enhancement of its therapeutic efficacy. In the last decade, substantial advancements have been made in development of innovative formulations to enhance the systemic availability of EXE (endocrine therapy) and improve its therapeutic effectiveness in treating EDBC (estrogen-dependent breast cancer). [44, 45] These innovative delivery systems encompass lipid-based nanoparticles (LPN), polymeric nanoparticles, nanosuspensions, solid dispersion, carbon nanotubes and co-crystallization approaches *etc.* [46, 47] Moreover, breast cancer cells are reported to develop resistance to endocrine therapies due to the overexpression of P-glycoprotein efflux pumps. [48]

In order to bypass first-pass metabolism associated with oral delivery, a nanoemulsion (NE) encapsulating EXE was formulated for transdermal administration. The formulation optimization was conducted using the Box-Behnken experimental design, which assessed the impact of key formulation variables, including drug concentration, oil phase content, and surfactant–cosurfactant (S_{mix}) ratio. The optimized nanoemulsion (OE-NE) comprised 10% linoleic acid, 10 mg of EXE, and 45.73% S_{mix}, attaining an overall desirability index of 0.782. The findings highlight the successful development of a stable formulation with improved skin permeation and retention, devoid of dermal irritation, indicating its feasibility as an alternative therapeutic approach for estrogen receptor-positive breast cancer. [44] Methotrexate-lactoferrin (Lf)-targeted EXE cubosome-based formulation exhibited an average droplet size of 143.6±3.24 nm, an encapsulation efficiency >90% for EXE, and a conjugation efficiency of 33.3% for methotrexate (MTX). The co-delivery of EXE and MTX revealed synergistic cytotoxicity against MCF-7 breast cancer cells with a

combination index (CI) of 0.342. Cellular uptake studies confirmed that Lf-targeted liquid crystalline nanoparticles (LCNPs) exhibited significantly higher internalization in MCF-7 cells relative to non-targeted LCNPs at both 4 and 24 h. Collectively, the dual drug-loaded, receptor-targeted LCNPs offer a promising strategy for synergistic hormonal therapy and chemotherapy in breast cancer management. [49] Lipidic nanocapsules (LNCs) were formulated utilizing a quality by design (*QbD*) approach to increase the antiestrogenic activity of EXE in breast cancer therapy. The developed LNCs exhibited significant cytotoxic effects against MCF-7 cancer cell line and demonstrated increased anticancer activity while mitigating cardiotoxicity in a dimethylbenz[a]anthracene (DMBA)-induced breast cancer model, compared to EXE alone. Furthermore, the pharmacokinetic studies *in vivo* indicated a 4.2-fold increase in oral systemic availability compared to the EXE suspension. This work emphasizes the potential of EXE-loaded LNCs as an effective oral delivery strategy system for optimizing the antiestrogenic effects of EXE in BC treatment. [50] A liquid crystalline formulation of EXE was developed for targeted drug delivery. The influence of varying concentrations of oil, surfactant–cosurfactant mixture (S_{mix}), and EXE on the lattice parameter, rheological properties, and drug release profile was systematically investigated across different formulation combinations. The optimized gel formulation exhibited thermo-responsive behavior, maintaining a gel-like consistency while transitioning into a free-flowing liquid at 37 °C. *In vitro* experimentation indicated a 38% release rate at physiological temperature. This system presented a significant potential for hyperthermia-induced drug release with improved EXE bioavailability, attributed to increased solubility, permeability, and absorption. [51] EXE was formulated using the nano-precipitation technique and optimized through a Box-Behnken design approach to achieve minimal particle size, low PDI, and high encapsulation efficiency. The developed nanoparticles exhibited an average particle size of 136.3±3.2 nm, a polydispersity index (PDI) of 0.110±0.013, and an entrapment efficiency of 88.56± 2.15%. *In vitro* evaluations conducted in simulated gastrointestinal fluids showed an initial fast release phase followed by a sustained drug release up to 24 h. Moreover, the synthesized nanoparticles demonstrated increased cellular uptake and dose-dependent cytotoxicity against MCF-7 breast cancer cells relative to free EXE. These results indicate that the synthesized PLHNs may be used for controlled release of EXE, which may improve its therapeutic efficiency against estrogen receptor-positive breast cancer. [52] An EXE nanosuspension was developed by using the Box-Behnken design for improved dissolution and oral bioavailability. The optimization results demonstrated that the variations in critical formulation parameters substantially affected the average particle size of the EXE nanosuspension. *In vitro* studies showed a substantial

improvement in the rate of dissolution whereas, *in vivo* results from pharmacokinetic study indicated a 2.7-folds increase in the oral relative bioavailability, suggesting the potential of the nanosuspension over pure EXE. [53] EXE PEGylated liposomes were developed *via* the thin-film hydration method, and then freeze-dried using trehalose to impart long-term stability. Intracellular uptake and *ex vivo* intestinal permeation studies revealed superior cellular internalization and enhanced intestinal permeability of PEGylated liposomes. *In vivo* pharmacokinetic analysis demonstrated a marked increase in the oral bioavailability of EXE over both conventional liposomes as well as EXE suspension. These findings indicated that PEGylation protected against acidic and enzymatic degradation within the gastrointestinal tract, and thereby served as a favorable approach for improving the oral bioavailability of hydrophobic drugs. [54] EXE-loaded nanostructured lipid carriers (NLCs) were successfully formulated using the ultrasonication method. X-ray diffraction (XRD) and differential scanning calorimetry (DSC) analyses confirmed a reduction in the crystalline nature of EXE, indicating its successful encapsulation within the lipid matrix of the NLCs. *Ex vivo* permeation studies demonstrated a significantly enhanced apparent permeability coefficient (P_{app}) of 3.15×10^{-4} cm/min compared to 0.8×10^{-4} cm/min for the EXE suspension. This improvement in permeability was attributed to the increased solubility of EXE within the lipid core, the submicron size of the NLCs, and the inhibition of P-glycoprotein-mediated efflux by Tween 80 and Poloxamer 188. Confocal laser scanning microscopy (CLSM) studies further corroborated increased permeation of EXE through enterocytes, as evidenced by fluorescent-labelled NLCs penetrating to a depth of 154.9 µm, compared to 64.9 µm for the EXE solution. Pharmacokinetic evaluation in rats demonstrated a 3.4-fold increase in the bioavailability on oral administration of EXE-NLCs compared to the EXE suspension, highlighting the potential of NLCs for maximizing the therapeutic efficacy of EXE. [55] Liquid crystalline gels (LCGs) of EXE were formulated for transdermal drug delivery that exhibited an %EE ranging from 85-92%, with vesicles size in the range of 119.9-466.2 nm. Histopathological study also revealed epidermal thinning, which confirmed the penetration of formulations into the intercellular region of squamous cells. These results indicate the potential of EXE-loaded LCGs as a viable transdermal delivery system for enhanced therapeutic efficacy in breast cancer treatment. [56] Similarly, EXE-loaded vitamin E-TPGS polymeric nanoparticles (TPGS–PCLNPs) were successfully prepared by the nanoprecipitation method. The combined effect of critical formulation and process variables on physicochemical properties of the nanoparticles was investigated using 2^3 factorial design. Characterization studies confirmed encapsulation of EXE in amorphous form in spherical TPGS–PCLNPs with no detectable drug–polymer interactions. In vitro cytotoxicity assays on MCF-7

breast cancer cells showed that EXE encapsulated in TPGS–PCLNPs exhibited a much stronger cytotoxic effect than pure EXE. These findings support TPGS–PCLNPs as a feasible EXE delivery platform, providing improved anticancer effectiveness in breast cancer. [57] However, the prior art does not reveal any investigation pertaining to the development of a formulation containing EXE encapsulated within a polymeric nanocarrier system such as mixed micelles.

POLYMERIC MICELLES AS DRUG NANOCARRIER SYSTEMS

Polymeric micelles (PM) are versatile drug carrier systems produced from amphiphilic copolymers, as its self-assembled nanostructure (≈10 to 200 nm) capable of carrying a payload, owing to varying functions and clinical utility. [58] The polymer science has emerged as a potential design system for these colloidal-based drug deliveries that can be selectively targeted with improved loading capability. This polymer self-assembles into nanostructure in an aqueous medium above their critical micelle concentration (CMC), embedded with hydrophilic and hydrophobic portions. In aqueous environments, the hydrophilic segment forms the core, while the hydrophobic segment facilitates the formation of the corona of micelles. [59] The hydrophobic portion serves as a drug-retaining Reservoir, whereas the hydrophilic portion stabilizes the carrier. The micellar corona plays a crucial function by reducing protein adsorption and combined with their nanoscale dimensions, facilitates their accumulation in tissues having leaky vasculature *via* the EPR effect. Prolonged circulation of polymeric micelles may be reduced due to rapid glomerular filtration. [60]

Fabrication of amphiphilic copolymer micelles

Polymeric micelles were initially formulated by employing conventional methods such as solvent evaporation, thin-film hydration, direct solubilization and oil-in-water emulsion techniques. [61] Moreover, conjugate-based polymeric micelles or polymer modifications, such as block and graft copolymerization, were typically carried out in solution phase, involving initiators and solvents, and characterized by complex mechanisms and poorly controlled reaction parameters. [62] The fabrication of amphiphilic copolymer micelles was initially conducted using conventional organic solvent-mediated approaches, which raised concerns about residual by-products and consequently limited their suitability for clinical evaluation. Utilizing toxic redox initiators to produce free radicals can result in their uneven incorporation along the polymer backbone, potentially leading to the unintended homopolymer impurities. [63] Subsequent methods included living radical polymerization, enzymatic reactions using oxidoreductases and radiation-induced polymerization. [64] Thus, the simplest available methods that are considered suitable for effective drug loading and reproducibility include solvent evaporation and oil-in-water solvent evaporation methods.

Micellar architecture

Polymeric micelles constitute exceptional properties, including low critical micelle concentration (CMC), increased stability and reduced dissociation rate, improved site-specific accumulation and higher drug encapsulation. [65] The architecture of polymeric micelle confers its superior applicability as compared to other polymer-based carriers especially drug-polymer conjugates, which show precipitation, low water solubility, and issues in injecting hydrophobic drugs in systemic circulation. Additionally, the composition, size, and properties of micelles are key determinants in achieving their optimal design. The ideal size of micelles is mostly in the range of ≈10–200 nm, providing an effective tissue penetration, reducing uptake by mononuclear phagocyte system for prolonged circulation and enhanced delivery at tumor site, improved pharmacokinetics, pharmacodynamic profiles, higher drug-loading efficiency, reproducibility, and cost-effective synthesis. [66] Most polymeric micelles are composed of di-block or tri-block copolymers or graft polymers with a hydrophobic/hydrophilic segment or ionic copolymers. Block copolymer micelles can be classified as per the type of intermolecular forces driving the separation of the inner core from the surrounding aqueous phase, including amphiphilic micelles (governed by hydrophobic interactions), polyion complex micelles (PICMs; formed through electrostatic interactions), and micelles generated *via* metal complexation. [60] Comprehensive research has been conducted on the use of poly(ethylene glycol) (PEG), an FDA-approved functional excipient for oral administration, to construct the hydrophilic shell of most polymeric micelles. Polymeric micelles with multiple compartments within their hydrophobic core, encased by a single hydrophilic shell, are referred to as multi-compartment micelles. Such structures provide key attributes that are extensively utilized in nanomedicine, biotechnology, catalysis, and nanopatterning. This strategy is suitable for the encapsulation and controlled release of incompatible drugs within a single formulation. The hydrophilic shell of the micellar structure imparts colloidal stability by preventing aggregation in aqueous environments. [67]

Selection of polymer

The physical and biological attributes of polymeric micelles are mainly defined by the co-polymer or starting material employed for the preparation of micelles. [68] Therefore, the selection of suitable polymers is an important step required in successful delivery. Also, the clinical attributes such as biodistribution, pharmacokinetic parameters, and toxicity are influenced by the physicochemical properties of mixed micelles. [69] In addition to these aspects, effective solubilization of hydrophobic or hydrophilic drugs and controlled release from the core-shell structure depend on the selection of an appropriate polymer for the delivery system. [70] Conversely, the molecular weight and chemical

characteristics of the inner core and outer shell formed by copolymers dictate the systemic circulation kinetics of the micelles. [71] Encapsulation of hydrophobic/ hydrophilic drugs inside the core/ corona units is mainly governed by the compatibility of these moieties with co-polymers of the carrier system. [72] Additionally, effective drug encapsulation largely depends on the hydrophilic-lipophilic balance (HLB) of the block copolymer and the polymer-to-drug ratio. [73] Pluronics® have attracted research interest as potential nanocarriers because they can self-assemble into micelles for therapeutic agent delivery once their critical micelle concentration (CMC) is exceeded. [74] Pluronics are non-ionic, non-toxic, highly biocompatible copolymers approved by the US-FDA, exhibiting core and corona-forming units, respectively. [75] The spontaneous self-assembly behavior of copolymers in an aqueous environment leads to the formation of nanocarrier micelles which can incorporate hydrophobic drug molecules within their core. [76] Such structures have a key role in improving drug solvency and bioavailability (Table 1). Also, nano-scaled polymeric micelles offer advantages including enhanced drug circulation and drug accumulation at the site of action due to increased drug permeation. [77] These classical characteristics of polymeric micelles confer a significant advantage in the design of nanocarrier systems. Consequently, polymeric micelles continue to represent one of the most extensively investigated nanocarrier platforms for breast cancer therapy and other solid malignancies, with several formulations advancing toward clinical evaluation (Table 2).

Table 1: Polymeric micelles as drug delivery systems for the breast cancer treatment

Polymeric micelles	Pluronic polymer	Drug loaded	Key features	Ref.
Genexol-PM	Pluronic P105	Paclitaxel	Improved solubility, Reduced toxicity, Cremophor-free formulation	78, 79
Mixed micelles	Pluronic F127 and Pluronic P123	Paclitaxel	Enhanced solubility, stability, sustained release, *in vitro* apoptosis induction	80
Multifunctional polymeric micelles	Pluronic F127 and Pluronic P123	Paclitaxel	Folate receptor-mediated endocytosis effect, *in vitro* cytotoxicity, cell apoptosis and cell cycle arrest studies also revealed that FPF-PTX, improved *in vivo* bioavailability and anticancer activity	81
Mixed micelles	Pluronic F127 and 188	Paclitaxel	Dialysis method was used for preparation of mixed polymeric micelles. Low MW heparin-all-trans-retinoid acid conjugates were developed, improved cell cytotoxicity and *in vivo* anticancer activity	82

Micelles	Pluronic® F127 grafted poly (methyl vinyl ether-alt-maleic acid) copolyme r	Doxorubicin	A Pluronic-grafted poly(methyl vinyl ether-maleic acid) copolymer was synthesized and used to encapsulate the antineoplastic drug doxorubicin into micelles for BC treatment. Drug-loaded micelles formulation exhibited improved cytotoxicity with *in vitro* sustained release profile	83
Mixed micelles	Pluronic P105 and Pluronic F127	Doxorubicin and Paclitaxel	A Pluronic P105–DOX conjugate was synthesized and utilized as a hydrophobic core to encapsulate an additional anticancer drug, paclitaxel, in combination with Pluronic F127, resulting in dual drug-loaded mixed micelles. *In vitro* studies demonstrated enhanced cytotoxicity, induction of apoptosis, and cell cycle arrest. Furthermore, increased intracellular drug accumulation was observed, leading to a synergistic therapeutic effect	84
Micelles	Pluronic127	Paclitaxel (PTX)-Lapatinib (LPT)	LPT enhances the intracellular levels of PTX by inhibiting efflux pumps. Micelles formulation exhibited *in vitro* sustained release profile with improved cytotoxicity	85
Pluronic P123 Micelles	Pluronic P123	Curcumin, Paclitaxel	Sustained release, Enhanced solubility, Tumor accumulation	86
Mixed Micelles	Vitamin E TPGS, Pluronic F127 and Pluronic P123	Curcumin	Improved solubility, stability, sustained release, *in vitro* apoptosis, drug accumulation and *in vivo* anticancer activity	87
Micelles	Pluronic P123	Curcumin	Enhancing solubility and developing a gel formulation with the Mucoadhesive polymer κ-Carrageenan, along with *in vitro* apoptosis evaluation in MCF-7 cells	88
Mixed Micelles	Pluronic F127 and P123	Curcumin	Improved anticancer, antioxidant, antimicrobial and α-amylase inhibitory activity	89
Mixed micelles	Pluronic P123 and 407 with D-α-tocopherol	Quercetin	Improved solubilization of Quercetin, *in vitro* sustained release from micelles formulation and improved *in vitro*	90

	polyethylene glycol succinate		cytotoxicity as compared to pure Quercetin	
Micelles	Pluronic127 (PF)-folic acid conjugated polymer	Fisetin	Improved solubility, bioavailability and targetability of prepared micelles formulation loaded with Fisetin	91
Mixed micelles	Pluronic L61 and Pluronic F127	Doxorubicin	Doxorubicin micelles formulation exhibited enhanced colony formation, migration, and invasion *in vitro*, as well as greater tumorigenicity *in vivo*, compared to the parental and non-CSC counterparts.	92
Pluronic F127 Micelles	Pluronic F127	Docetaxel, Doxorubicin	Enhanced stability, Prolonged circulation, Targeted drug delivery	93
Pluronic micelles F127 and P123	Pluronic F127 and Pluronic P123	Paclitaxel and Curcumin	Targeted drug delivery, improved *in vitro* anticancer activity in MCF-7 cells	94
Micelles	D-α-tocopherol polyethylene glycol 1000 succinate and Pluronic F127	Baicalein	In comparison to pure baicalein, the developed formulation markedly improved cellular uptake and cytotoxicity in MDA-MB-231 cell lines. ROS (reactive oxygen species) and MMP (mitochondrial membrane potential) assays indicated that the formulation suppresses cell proliferation through a ROS-dependent, mitochondria-mediated apoptotic pathway	95

Table 2: **Polymeric micelles currently approved for clinical application and undergoing clinical trials**

S. No	Polymer micelles	Polymer used	Release of drug	Therapeutic agent used	Disease type	NCT number and clinical phase status
1.	Genexol-PM	PEG-b-PLA	Controlled drug release was achieved without the need for any specific triggering mechanism	Paclitaxel	Breast cancer	NCT00876486/Phase III (Completed)
				Paclitaxel and Doxorubicin	Metastatic Breast cancer	NCT01784120/Phase II (Unknown)
				Paclitaxel	Recurrent breast cancer	NCT00912639/Phase IV (Unknown)

				Paclitaxel with carboplatin	Ovarian cancer	NCT00877253/Phase I (Completed)
				Paclitaxel	Breast cancer	NCT01169870/Phase II (withdrawn)
2.	NK105	PEG-b-PPBA	A sustained release profile was achieved, delivering an equivalent dose of under 1 µg/ml without the need for a specific triggering mechanism	Paclitaxel	Metastatic recurrent breast cancer	NCT01644890/ Phase III (Completed)
3.	Nanoxel-PM	PEG-PDLLA	Docetaxel was rapidly released from the micelles, allowing it to bind with plasma proteins, and exhibited pharmacokinetics similar to Taxotere®.	Docetaxel	Breast cancer, Non-small Cell Lung cancer	NCT04066335/(Recruiting)
			Absence of a specific activation trigger	Paclitaxel	Advanced breast cancer	NCT00915369/Phase (unknown)
4.	Docecal	XR-17 Block polymer	Controlled release with no specific triggering mechanism	Docetaxel	Breast cancer	2012-005161-12 (EudraCT)/Phase III (results not published)
5.	NK012	PEG-b-poly(glutamate)	SN-38 is released under neutral conditions even in the absence of a hydrolytic enzyme	SN-38 An active metabolite of irinotecan hydrochloride (CPT-11)	Triple-negative breast cancer	NCT00951054/Phase II/ Completed
			Releases SN-38 under neutral conditions	NK012 and Carboplatin	Metastatic triple-negative breast cancer	NCT01238952/Phase 1/ Completed

*NCT: National Clinical Trial

Characterization of Polymeric Micelles

Determination of Critical Micelle Concentration (CMC) of Polymeric Micelles

The thermodynamic stability of the micellar carrier system is described through the CMC of amphiphilic polymers, where a lower value of CMC indicates greater system stability. [96] At times, critical association concentration (CAC) is employed in place of critical micelle concentration (CMC) to distinguish polymeric micelles from conventional surfactants. [97] Methods reported for CMC determination are interfacial tension measurement, conductivity, osmotic pressure, and viscosity. [98] Given the extremely low CMC values of polymeric micelles, traditional methods lack accuracy and necessitate the use of advanced techniques such as fluorescence spectroscopy, gel permeation chromatography (GPC) and light scattering. [99, 100, 101] Dynamic light scattering may have difficulty distinguishing the contributions from a single population in multi-component media especially when polymeric micelles aggregate, thus resulting in misleading CMC determinations. [102] Lower CMC values are essential for ensuring the *in vivo* stability of the developed micellar system. Micelles prepared using polymers with extremely low CMC prevent the micellar disassembly by dilution in the blood circulation. [72, 103] However, CMC of polymeric micellar solutions can be tailored by modifying its chemical properties and length of the hydrophobic segment of amphiphilic copolymers. [104] Hydrophobic drug encapsulation is generally involved in the decrease of CMC of the carrier system. The MW of copolymer also influences the CMC; the higher is the MW of the hydrophobic segment of the polymer, the lower will be the CMC of the system. Pluronic polymers used in micelle preparation of anticancer agents show lower CMC. However, polymer concentration and mixing of these polymers with another polymer decrease the CMC of the polymeric mixture as compared to individual polymer. Such as, Pluronic L121 in combination with Pluronic F127 reduces the polymeric mixture CMC by ten-folds as compared to the original CMC of individual polymers.

Structural and Morphological Evaluation of Polymeric Micelles

Static light scattering, dynamic light scattering (DLS), atomic force microscopy (AFM), and cryogenic transmission electron microscopy (Cryo-TEM) provide important details regarding the shape, size, and distribution of micelles. Notably, Cryo-TEM holds an advantage over traditional transmission electron microscopy (TEM) for micellar morphological studies because it preserves the native structure of the micelles. [105] The size and morphology of micelles is an important step to understand drug loading into micellar formulations that are necessary for successful pharmaceutical applications. [106] The shape, size, and behavior of polymeric carrier systems in aqueous solutions have been extensively investigated using small-angle neutron scattering (SANS) and small-angle X-ray scattering (SAXS). [107] The physical stability of micellar dispersions is evaluated using techniques such as zeta potential analysis, Förster resonance energy transfer

(FRET), resonance energy transfer (RET) and electronic energy transfer (EET). For instance, Lu and colleagues utilized FRET analysis to assess micellar stability using 3′-dioctadecyloxacarbocyanine perchlorates as a donor and 1,1′-dioctadecyl-3,3,3′,3′-tetramethyl indocarbocyanine perchlorate as an acceptor in the presence of serum proteins. [108] Furthermore, atomic force microscopy (AFM) is employed to analyze the morphology and structural stability of micelles by measuring microcosmic forces, including covalent bonding, π-π interactions, host-guest recognition, intercalating forces and hydrogen bonding. [109] These comprehensive evaluations are crucial for rationally designing and optimizing the micelles-based drug delivery systems for cancer therapy.

TARGETED DRUG DELIVERY SYSTEMS FOR LOCALIZED DELIVERY OF ANTICANCER DRUGS

Medicines administered orally or parenterally are distributed throughout the body, resulting in minimal drug accumulation at the tumor area. [110] Targeted drug delivery systems have emerged as a promising intervention for the breast cancer management. These approaches are designed to enable targeted delivery to malignant cells thereby, improve safety by enhancing treatment selectivity. [111] The targeted drug delivery systems for breast cancer employs multiple mechanisms to enhance treatment efficacy while reducing the off-target side effects. [112] The ligand-targeted approach involves employing monoclonal antibodies, such as trastuzumab, which specifically bind to HER2-positive breast cancer cells, ensuring precise drug delivery. [113] Additionally, aptamers and peptides act as selective targeting agents that recognize and bind to cancer cells, further improving drug localization. Nanoparticle-based delivery systems offer another promising strategy. Liposomes, spherical vesicles capable of encapsulating drugs, provide stable delivery with controlled release at the tumor site. [114] Similarly, polymeric nanoparticles, composed of biodegradable polymers, facilitate sustained drug release, improving treatment outcomes. Gold nanoparticles, due to their ability to undergo surface modifications, enable targeted and precise drug delivery. [115]

Furthermore, stimuli-responsive systems enhance drug release specificity. pH-sensitive drug carriers exploit the acidic tumor microenvironment, triggering drug release precisely at the cancer site. [116] These advanced delivery systems collectively contribute to improving breast cancer treatment by improving tumor-specific drug delivery while reducing systemic side effects. [117] Temperature-sensitive drug delivery systems are crucial for improving the targeted delivery of anticancer agents. Hyperthermia induces significant changes in the tumor microenvironment by increasing blood flow, oxygenation, and vascular permeability, thereby enabling drug penetration.

[118] Studies have shown that most delivery systems, with diameters of up to 400 nm, can successfully penetrate tumor cells when exposed to a temperature of 42 °C *in vitro*. Incorporating thermosensitive components into drug carriers further improves site-specific release, as these materials undergo structural changes in response to elevated temperatures. [119] Thermosensitive polymers with a lower critical solution temperature (LCST) at around 40 °C have been extensively developed; they remain water-soluble below this threshold but become insoluble above it, triggering drug release. [120] In addition to temperature-sensitive systems, external stimuli-responsive mechanisms, such as magnetic and ultrasound-triggered delivery, offer precise control over drug release at the target site. [121] These advanced strategies enhance the efficacy of targeted drug delivery by facilitating controlled and localized release of therapeutic agents. The targeted approach offers substantial benefits by enabling higher accumulation of drug at the tumor site while reducing systemic exposure and associated toxicity. [122] This reduces adverse effects, including nausea, hair loss, and immunosuppression, commonly associated with chemotherapy. Additionally, encapsulating drugs within nanoparticles protects them from premature degradation, ensuring effective delivery to the tumor.

However, challenges remain in implementing targeted therapies. Tumor heterogeneity can influence treatment efficacy, as cancer cells may develop resistance, necessitating combination therapies. Furthermore, physiological barriers, such as the dense extracellular matrix in tumors, can hinder drug penetration, limiting therapeutic outcomes. Overcoming the aforementioned drawbacks necessitates the need for further research and innovation in the field of novel drug delivery systems.

CONCLUSION AND FUTURE DIRECTIONS

Breast Cancer is a major reason for cancer-related mortality amongst women, which necessitates the need for more efficacious and safer therapeutic drug delivery systems. Exemestane is a 3rd generation aromatase inhibitor used in the management of hormone receptor-positive breast cancer, however, its therapeutic potential is reduced due to poor aqueous solubility, low oral bioavailability, extensive first-pass metabolism and dose-related side effects. As a result, substantial research efforts are being made to focus on developing superior drug delivery systems having the ability to overcome these pharmacokinetics and pharmacodynamics limitations. This review thoroughly sums up the recent progress in EXE delivery system, including cyclodextrin complexes, SMEDDS, nanoemulsions, nanosuspensions, polymeric nanoparticles, lipid-based nanocarriers, liposomes, nanostructured lipid carriers, liquid crystalline systems, cubosomes and polymeric micelles. Even with the remarkable progress achieved in the field of nanomedicine,

there are several challenges that restrict the advancements in EXE delivery system such as formulation stability, large-scale production, drug loading efficiency, biological barriers and regulatory requirements. Amidst the available nanocarriers, polymeric micelles have emerged as enticing delivery systems as a result of their unmatched shell structure, high drug loading capacity, excellent colloidal stability, low critical micellar concentration, prolonged circulation and ability to harness the enhanced permeability and retention (EPR) effect for passive tumor targeting. These physicochemical properties can be promptly modified through proper polymer selection and structural changes, enabling controlled drug release, improved pharmacokinetic performance and addition of targeting ligands. Latest progress in mixed polymeric micelles have demonstrated synergistic improvements in drug solubilization, encapsulation efficiency, stability and therapeutic performance, focusing on their potential as next-generation nanocarriers for therapy of breast cancer. Among various polymers, Pluronic block copolymers have been extensively investigated as micellar carriers because of their excellent biocompatibility, low toxicity, and regulatory acceptance. Beyond their carrier function, they also exhibit biological activity by inhibiting P-glycoprotein-mediated drug efflux, reducing intracellular ATP levels, modulating mitochondrial function, and sensitizing multidrug-resistant cancer cells to chemotherapy. Despite these advantages, Pluronic polymers also have some limitations such as limit the drug retention at tumor site and causes premature drug release, therefore highlighting the need of localized delivery approaches.

Stimuli-responsive targeted delivery systems have shown significant potential in improving selectivity of tumor while reducing the systemic toxicity. Incorporation of polymeric micelles with injectable hydrogels enhance the direct drug release at the site of tumor, therefore enhances drug retention, reduce dose related toxicities, reduce systemic exposure and improve therapeutic effects. Therefore, future research should focus on the advancement of multifunctional or personalized treatment for breast cancer. Overall, the continuous interdisciplinary research will be pivotal for expanding the therapeutic possibilities of EXE in breast cancer management. Furthermore, successful future clinical translation of these formulations will need harmonized manufacturing processes, consistent quality of product and precise regulatory standards in order to ensure the safety, efficacy, quality and reproducibility of nanotechnology-based EXE formulations.

REFERENCES

1. Singh G, Singh S, Singh A, Singh SK, Mehra A, Mahajan M, Singh AP, Bedi N. Chitosan Based Thermosensitive *In Situ* Hydrogel for Localized Delivery of Exemestane Loaded Micelles: A Novel Strategy for Enhanced Breast Cancer Therapy. J Pharm Innov 2026; 21(3): 314.

2. Yaşar P, Ayaz G, User SD, Güpür G, Muyan M. Molecular mechanism of estrogen–estrogen receptor signaling. Reprod Med Biol 2017; 16(1): 4-20.
3. Amaral C, Correia-da-Silva G, Almeida CF, Valente MJ, Varela C, Tavares-da-Silva E, Vinggaard AM, Teixeira N, Roleira FM. An exemestane derivative, oxymestane-D1, as a new multi-target steroidal aromatase inhibitor for estrogen receptor-positive (ER+) breast cancer: effects on sensitive and resistant cell lines. Molecules 2023; 28(2): 789.
4. Zhu J, Lv L, Yan Y, Wang S, Lu X, Ma X, Sun X, Qin Y, Wu H, Yu G, Wang Q. Role of autophagy in tumorigenesis and drug resistance: molecular mechanisms and therapeutic targets. Mol Biomed 2026; 7(1): 28.
5. Sarti S, Viansone AA, Serra O, Casadei C, Cecconetto L, Di Menna G, Farolfi A, Gianni C, Mariotti M, Merloni F, Palleschi M. Pharmacological Prevention in Breast Cancer: Current Evidence, Challenges, and Future Directions. Cancers 2025; 17(22): 3597.
6. Talebibidhendi N, Pourmadadi M, Yazdian F, Rashedi H, Rahdar A, Ghotekar S. Advancements in Exemestane-Loaded Nanocarriers For Targeted Breast Cancer Therapy: A Comprehensive Review. BioNanoSci 2025; 15(4): 558.
7. Singh G, Kaur K, Bhalla V, Singh A, Singh SK, Kumar S, Aswal VK, Bedi N. Pluronic L121-Chrysin conjugated polymeric micelles of exemestane: improved synergistic effect, *in vitro* and *in vivo* anticancer activity Colloids Surf. A: Physicochem Eng Asp 2024; 698: 134458.
8. Singh G, Singh D, Choudhari M, Kaur SD, Dubey SK, Arora S, Bedi N. Exemestane encapsulated copolymers L121/F127/GL44 based mixed micelles: solubility enhancement and in vitro cytotoxicity evaluation using MCF-7 breast cancer cells. J Pharm Investig 2021;51(6):701-14
9. Carballo-Pedrares N, Giménez VM, Alonso MJ. Clinical translation of injectable hydrogels: from bioactive polymers to long-acting drug delivery systems. Drug Deliv Transl Res 2026; 22: 1-24.
10. Malarkey DE, Hoenerhoff, MJ and Maronpot, RR. Carcinogenesis: manifestation and mechanisms. Toxicol Pathol 2018; 83-104.
11. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: CA Cancer J Clin 2024; 74(3): 229-63.

12. Arnold M, Morgan E, Rumgay H, Mafra A, Singh D, Laversanne M, Vignat J, Gralow JR, Cardoso F, Siesling S, Soerjomataram I. Current and future burden of breast cancer: Global statistics for 2020 and 2040. Breast J 2022; 66: 15-23.
13. Agrawal A, Javanmardi Y, Watson SA, Serwinski B, Djordjevic B, Li W, Aref AR, Jenkins RW, Moeendarbary E. Mechanical signatures in cancer metastasis. NPJ Biol Phys Mech 2025; 2(1): 3.
14. Liu Z, Chen J, Ren Y, Liu S, Ba Y, Zuo A, Luo P, Cheng Q, Xu H, Han X. Multi-stage mechanisms of tumor metastasis and therapeutic strategies. Signal Transduct Target Ther 2024; 9(1): 270.
15. Wu SG, Yang SP, Zhang WW, Wang J, Lian CL, Chen YX, He ZY. The longitudinal risk of mortality between invasive ductal carcinoma and metaplastic breast carcinoma. Sci Rep 2020; 10(1): 22070.
16. Niveria K, Yadav M, Dangi K, Verma AK. Overcoming challenges to enable targeting of metastatic breast cancer tumour microenvironment with nano-therapeutics: current status and future perspectives. OpenNano 2022; 8: 100083.
17. Bellanger M, Zeinomar N, Tehranifar P, Terry MB. Are global breast cancer incidence and mortality patterns related to country-specific economic development and prevention strategies. J Glob Oncol 2018; 4: 1-6.
18. Duggan C, Trapani D, Ilbawi AM, Fidarova E, Laversanne M, Curigliano G, Bray F, Anderson BO. National health system characteristics, breast cancer stage at diagnosis, and breast cancer mortality: a population-based analysis. Lancet Oncol 2021; 22(11): 1632-42.
19. Kashifa Fathima J, Lavanya V, Jamal S, Ahmed N. The effectiveness of various chemotherapeutic agents in cancer treatment. Curr Pharmacol Re 2022; 8(4): 236-52.
20. Al-Shami K, Awadi S, Khamees AA, Alsheikh AM, Al-Sharif S, Ala'Bereshy R, Al-Eitan SF, Banikhaled SH, Al-Qudimat AR, Al-Zoubi RM, Al Zoubi MS. Estrogens and the risk of breast cancer: A narrative review of literature. Heliyon 2023; 9(9).
21. Chumsri S, Howes T, Bao T, Sabnis G, Brodie A. Aromatase, aromatase inhibitors, and breast cancer. J Steroid Biochem Mol Biol 2011; 125(1-2): 13-22.
22. Swaminathan H, Saravanamurali K, Yadav SA. Extensive review on breast cancer its etiology, progression, prognostic markers, and treatment. Oncol 2023; 40(8): 238.
23. Xiong X, Zheng LW, Ding Y, Chen YF, Cai YW, Wang LP, Huang L, Liu CC, Shao ZM, Yu KD. Breast cancer: pathogenesis and treatments. Signal Transduct Target Ther 2025; 10(1): 49.

24. Kamińska M, Ciszewski T, Łopacka-Szatan K, Miotła P, Starosławska E. Breast cancer risk factors. Prz Menopauzalny 2015; 14(3): 196-202.
25. Coombs NJ, Taylor R, Wilcken N, Boyages J. HRT and breast cancer: impact on population risk and incidence. Eur J Cancer 2005; 41(12): 1775-1781.
26. Russo IH, Russo J. Role of hormones in mammary cancer initiation and progression. J Mammary Gland Biol Neoplasia 1998; 3(1): 49-61.
27. Hankinson SE, Colditz GA, Willett WC. Towards an integrated model for breast cancer etiology: the lifelong interplay of genes, lifestyle, and hormones. Breast Cancer Res 2004; 6(5): 213-218.
28. Harris L, Batist G, Belt R, Rovira D, Navari R, Azarnia N, Welles L, Winer E, TLC D-99 Study Group. Liposome-encapsulated doxorubicin compared with conventional doxorubicin in a randomized multicenter trial as first-line therapy of metastatic breast carcinoma. Cancer 2002; 94(1): 25-36.
29. Barba D, Leon-Sosa A, Lugo P, Suquillo D, Torres F, Surre F, Trojman L, Caicedo A. Breast cancer, screening and diagnostic tools: All you need to know. Crit Rev Oncol Hematol 2021; 157: 103174.
30. Strand SH, Rivero-Gutiérrez B, Houlahan KE, Seoane JA, King LM, Risom T, Simpson LA, Vennam S, Khan A, Cisneros L, Hardman T. Molecular classification and biomarkers of clinical outcome in breast ductal carcinoma in situ: Analysis of TBCRC 038 and RAHBT cohorts. Cancer cell 2022; 40(12): 1521-36.
31. Hammood ZD, Salih AM, Salih RQ, Mohammed SH, Sharif HM, Salih KM. Metaplastic breast carcinoma with invasive and high-grade ductal carcinoma in situ; a rare case with review of literature. Int J Surg Open 2022; 40: 100447.
32. Zheng L, Gökmen-Polar Y, Badve SS. Is conservative management of ductal carcinoma in situ risky. NPJ Breast Cancer 2022; 8(1): 55.
33. Weigelt B, Horlings HM, Kreike B, Hayes MM, Hauptmann M, Wessels LF, De Jong D, Van de Vijver MJ, Veer LV, Peterse JL. Refinement of breast cancer classification by molecular characterization of histological special types. J Patho 2008; 216(2): 141-50.
34. Erber R, Hartmann A. Histology of luminal breast cancer. Breast Care 2020 ; 15(4): 327-36.
35. McCart Reed AE, Kalinowski L, Simpson PT, Lakhani SR. Invasive lobular carcinoma of the breast: the increasing importance of this special subtype. Breast Cancer Res 2021; 23(1): 6.

36. Davey MG, Keelan S, Lowery AJ, Kerin MJ. The impact of chemotherapy prescription on long-term survival outcomes in early-stage invasive lobular carcinoma–a systematic review and meta-analysis. Clin Breast Cancer 2022; 22(8): e843-9.
37. Sayyad NB, Sabale PM, Umare MD, Bajaj KK. Aromatase inhibitors: development and current perspectives. Indian J Pharm Educ Res 2022; 56: 311-20.
38. Brueggemeier RW. Overview of the pharmacology of the aromatase inactivator exemestane. Breast Cancer Res Treat 2002; 74(2): 177-85.
39. Lønning PE. Exemestane: a review of its clinical efficacy and safety. The breast 2001; 10(3): 198-208.
40. Chaturvedi S, Garg A. A comprehensive review on novel delivery approaches for exemestane. J Drug Deliv Sci Technol 2022; 75: 103655.
41. Jayapal JJ, Dhanaraj S. Exemestane loaded alginate nanoparticles for cancer treatment: formulation and *in vitro* evaluation. Int J Biol Macromol 2017; 105: 416-21.
42. Waghray D, Zhang Q. Inhibit or evade multidrug resistance P-Glycoprotein in cancer treatment : Miniperspective. J **Med Chem** 2017; 61(12): 5108–21.
43. Hirano A, Inoue H, Ogura K, Hattori A, Yukawa H, Sakaguchi S, Matsuoka A, Tanaka N, Kodera A, Kamimura M, Naritaka Y. Long-term effect of exemestane therapy on bone mineral density supported by bisphosphonates: Results of 5-year adjuvant treatment in postmenopausal women with early-stage breast cancer. Asia-Pac J Clin Oncol 2018; 14(5): 238-42.
44. Chaturvedi S, Garg A. Development and optimization of nanoemulsion containing exemestane using box-behnken design. J Drug Deliv Sci Technol 2023; 80: 104151.
45. Prajapati BG, Patel P, Paliwal H, Khunt D. Enhancing exemestane delivery: Solid lipid nanoparticles formulation and pharmacokinetic evaluation. Nano-Struct Nano-Objects 2024; 40: 101388.
46. Elzoghby AO, El-Lakany SA, Helmy MW, Abu-Serie MM, Elgindy NA. Shell-crosslinked zein nanocapsules for oral codelivery of exemestane and resveratrol in breast cancer therapy. Nanomedicine 2017; 12(24): 2785-805.
47. Kaur S, Jena SK, Samal SK, Saini V, Sangamwar AT. Freeze dried solid dispersion of exemestane: A way to negate an aqueous solubility and oral bioavailability problems. Eur J Pharm Sci 2017; 107: 54-61.
48. Chen T, Wang C, Liu Q, Meng Q, Sun H, Huo X, Sun P, Peng J, Liu Z, Yang X, Liu K. Dasatinib reverses the multidrug resistance of breast cancer MCF-7 cells to doxorubicin by

downregulating P-gp expression via inhibiting the activation of ERK signaling pathway. Cancer Biol Ther 2015; 16(1): 106-14.

49. Mokhtar S, Khattab SN, Elkhodairy KA, Teleb M, Bekhit AA, Elzoghby AO, Sallam MA. Methotrexate-lactoferrin targeted exemestane cubosomes for synergistic breast cancer therapy. Front Chem 2022; 10: 847573.
50. Singh P, Alka, Maurya P, Nisha R, Singh N, Parashar P, Mishra N, Pal RR, Saraf SA. QbD-assisted development of lipidic nanocapsules for antiestrogenic activity of exemestane in breast cancer. J Liposome Res 2023; 33(2): 154-69.
51. Shah V, Bharatiya B, Gawali S, Hassan PA, Shukla AD, Khandelwal A, Bhatt H, Vasu V, Shah DO. Thermoresponsive liquid crystalline formulation of exemestane: design and structural characterization. Colloids Surf B Biointerfaces 2021; 202: 111683.
52. Rizwanullah M, Perwez A, Mir SR, Alam Rizvi MM, Amin S. Exemestane encapsulated polymer-lipid hybrid nanoparticles for improved efficacy against breast cancer: Optimization, *in vitro* characterization and cell culture studies. Nanotech 2021; 32(41): 415101.
53. Parmar K, Shah J. Optimization of performance variables of exemestane nanosuspension using box-behnken design to improve dissolution and oral bioavailability. Curr Drug Deliv 2021; 18(8): 1160-73.
54. Singh A, Neupane YR, Shafi S, Mangla B, Kohli K. PEGylated liposomes as an emerging therapeutic platform for oral nanomedicine in cancer therapy: in vitro and in vivo assessment. J Mol Liq 2020; 303: 112649.
55. Singh A, Neupane YR, Mangla B, Kohli K. Nanostructured lipid carriers for oral bioavailability enhancement of exemestane: formulation design, in vitro, ex vivo, and in vivo studies. J Pharm Sci 2019; 108(10): 3382-95.
56. Musa MN, David SR, Zulkipli IN, Mahadi AH, Chakravarthi S, Rajabalaya R. Development and evaluation of exemestane-loaded lyotropic liquid crystalline gel formulations. BioImpacts 2017; 7(4): 227-239.
57. Mishra B, Padaliya R, Patel RR. Exemestane encapsulated vitamin E-TPGS–polymeric nanoparticles: preparation, optimization, characterization, and in vitro cytotoxicity assessment. Artif Cells Nanomed Biotechnol 2017; 45(3): 522-34.
58. Tang Z, He C, Tian H, Ding J, Hsiao BS, Chu B, Chen X. Polymeric nanostructured materials for biomedical applications. Prog Polym Sci 2016; 60: 86-128.

59. Odrobińska J, Neugebauer D. Micellar carriers based on amphiphilic PEG/PCL graft copolymers for delivery of active substances. Polymers 2020; 30 12(12): 2876.
60. Kang N, Perron MÈ, Prud'Homme RE, Zhang Y, Gaucher G, Leroux JC. Stereocomplex block copolymer micelles: Core− shell nanostructures with enhanced stability. Nano Lett 2005; 5(2): 315-9.
61. Gaucher G, Satturwar P, Jones MC, Furtos A, Leroux JC. Polymeric micelles for oral drug delivery. Eur J Pharm Biopharm 2010; 76(2): 147-58.
62. Singh V, Kumar P, Sanghi R. Use of microwave irradiation in the grafting modification of the polysaccharides–A review. Prog Polym Sci 2012; 37(2): 340-64.
63. Shi HY, Zhang LM. New grafted polysaccharides based on O-carboxymethyl-O-hydroxypropyl guar gum and N-isopropylacrylamide: Synthesis and phase transition behavior in aqueous media. Carbohydr Polym 2007; 67(3): 337-42.
64. Wang X, Shen L, An Z. Dispersion polymerization in environmentally benign solvents via reversible deactivation radical polymerization. Prog Polym Sci 2018; 83: 1-27.
65. Manna K, Roy A, Dey S, Ghosh S, Pradhan P, Pal S. A review on the culmination of rational development of stimuli-responsive polymeric micelles as vehicles for site-specific hydrophobic therapeutics. J Macromol Sci, Part A 2024; 61(6): 349-75.
66. Mahmud A, Xiong XB, Aliabadi HM, Lavasanifar A. Polymeric micelles for drug targeting. J Drug Target 2007; 15(9): 553-84.
67. Lodge TP, Rasdal A, Li Z, Hillmyer MA. Simultaneous, segregated storage of two agents in a multicompartment micelle. J Am Chem Soc 2005; 127(50): 17608-9.
68. Kotta S, Aldawsari HM, Badr-Eldin SM, Nair AB, Yt K. Progress in polymeric micelles for drug delivery applications. Pharmaceutics 2022; 14(8): 1636.
69. Ghezzi M, Pescina S, Padula C, Santi P, Del Favero E, Cantù L, Nicoli S. Polymeric micelles in drug delivery: An insight of the techniques for their characterization and assessment in biorelevant conditions. J Control Release 2021; 332: 312-36.
70. Kulthe SS, Choudhari YM, Inamdar NN, Mourya V. Polymeric micelles: authoritative aspects for drug delivery. Des Monomers Polym 2012; 15(5): 465-521.
71. Cabral H, Miyata K, Osada K, Kataoka K. Block copolymer micelles in nanomedicine applications. Chem Rev 2018; 118(14): 6844-92.
72. Torchilin VP. Structure and design of polymeric surfactant-based drug delivery systems. J Control Release 2001; 73(2-3): 137-72.

73. Deshmukh AS, Chauhan PN, Noolvi MN, Chaturvedi K, Ganguly K, Shukla SS, Nadagouda MN, Aminabhavi TM. Polymeric micelles: Basic research to clinical practice. Int J Pharm 2017; 532(1): 249-68.
74. Dalgakiran EA, Ergin AD, Kacar G. Properties of Pluronic F68 and F127 micelles interacting furosemide from coarse-grained molecular simulations as validated by experiments. Colloids Surf A: Physicochem Eng Asp 2023; 666: 131352.
75. Khaliq NU, Lee J, Kim S, Sung D, Kim H. Pluronic F-68 and F-127 based nanomedicines for advancing combination cancer therapy. Pharmaceutics 2023; 15: 1-25.
76. Kaur J, Mishra V, Singh SK, Gulati M, Kapoor B, Chellappan DK, Gupta G, Dureja H, Anand K, Dua K, Khatik GL. Harnessing amphiphilic polymeric micelles for diagnostic and therapeutic applications: Breakthroughs and bottlenecks. J Control Release 2021; 334: 64-95.
77. Liu Q, Song L, Chen S, Gao J, Zhao P, Du J. A superparamagnetic polymersome with extremely high T2 relaxivity for MRI and cancer-targeted drug delivery. Biomaterials 2017; 114: 23-33.
78. Kim TY, Kim DW, Chung JY, Shin SG, Kim SC, Heo DS, Kim NK, Bang YJ. Phase I and pharmacokinetic study of Genexol-PM, a cremophor-free, polymeric micelle-formulated paclitaxel, in patients with advanced malignancies. Clin Cancer Res 2004; 10(11): 3708-16.
79. Gradishar WJ, Tjulandin S, Davidson N, Shaw H, Desai N, Bhar P, Hawkins M, O'Shaughnessy, J. Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil–based paclitaxel in women with breast cancer. J Clin Oncol 2005; 23(31): 7794-7803.
80. Wei Z, Hao J, Yuan S, Li Y, Juan W, Sha X, Fang X. Paclitaxel-loaded Pluronic P123/F127 mixed polymeric micelles: formulation, optimization and in vitro characterization. Int J Pharm 2009; 376(1-2): 176-85.
81. Zhang W, Shi Y, Chen Y, Ye J, Sha X, Fang X. Multifunctional Pluronic P123/F127 mixed polymeric micelles loaded with paclitaxel for the treatment of multidrug resistant tumors. Biomater 2011; 32(11): 2894-906.
82. Dahmani FZ, Yang H, Zhou J, Yao J, Zhang T, Zhang Q. Enhanced oral bioavailability of paclitaxel in pluronic/LHR mixed polymeric micelles: preparation, in vitro and in vivo evaluation. Eur J Pharma Sci 2012; 47(1): 179-89.

83. Varshosaz J, Hassanzadeh F, Sadeghi-Aliabadi H, Larian Z, Rostami M. Synthesis of Pluronic® F127-poly (methyl vinyl ether-alt-maleic acid) copolymer and production of its micelles for doxorubicin delivery in breast cancer. Chem Eng J 2014; 240: 133-46.
84. Chen Y, Zhang W, Huang Y, Gao F, Sha X, Fang X. Pluronic-based functional polymeric mixed micelles for co-delivery of doxorubicin and paclitaxel to multidrug resistant tumor. Int J Pharm 2015; 488(1-2): 44-58.
85. Dehghan Kelishady P, Saadat E, Ravar F, Akbari H, Dorkoosh F. Pluronic F127 polymeric micelles for co-delivery of paclitaxel and lapatinib against metastatic breast cancer: preparation, optimization and in vitro evaluation. Pharm Dev Technol 2015; 20(8): 1009-17.
86. Su K, Yang Y, Wu Q, Mao Y, Hu Y. Preparation of Polymeric Micelles of Curcumin with Pluronic P123 and Assessment of. Adv Pharmacoepidemiol Drug Saf 2016; 5(3).
87. Wang J, Liu Q, Yang L, Xia X, Zhu R, Chen S, Wang M, Cheng L, Wu X, Wang S. Curcumin-loaded TPGS/F127/P123 mixed polymeric micelles for cervical cancer therapy: formulation, characterization, and in vitro and in vivo evaluation. J Biomed Nanotechnol 2017; 13(12): 1631-46.
88. Ganguly R, Kunwar A, Dutta B, Kumar S, Barick KC, Ballal A, Aswal VK, Hassan PA. Heat-induced solubilization of curcumin in kinetically stable pluronic P123 micelles and vesicles: An exploit of slow dynamics of the micellar restructuring processes in the aqueous pluronic system. Colloids Surf B Biointerfaces 2017; 152: 176-82.
89. Akbar MU, Zia KM, Nazir A, Iqbal J, Ejaz SA, Akash MS. Pluronic-based mixed polymeric micelles enhance the therapeutic potential of curcumin. AAPS PharmSciTech 2018; 19(6): 2719-39.
90. Patra A, Satpathy S, Shenoy AK, Bush JA, Kazi M, Hussain MD. Formulation and evaluation of mixed polymeric micelles of quercetin for treatment of breast, ovarian, and multidrug resistant cancers. Int J Nanomedicine 2018; 13: 2869-81.
91. Pawar A, Singh S, Rajalakshmi S, Shaikh K, Bothiraja C. Development of fisetin-loaded folate functionalized pluronic micelles for breast cancer targeting. Artif Cells Nanomed Biotechnol 2018; 46(sup1): 347-61.
92. Zhao Y, Alakhova DY, Zhao X, Band V, Batrakova EV, Kabanov AV. Eradication of cancer stem cells in triple negative breast cancer using doxorubicin/pluronic polymeric micelles. Nanomedicine 2020; 24: 102124.

93. Bholakant R, Dong B, Zhou X, Huang X, Zhao C, Huang D, Zhong Y, Qian H, Chen W, Feijen J. Multi-functional polymeric micelles for chemotherapy-based combined cancer therapy. J Mater Chem B 2021; 9(42): 8718-38.
94. Anirudhan TS, Varghese S, Manjusha V. Hyaluronic acid coated Pluronic F127/Pluronic P123 mixed micelle for targeted delivery of Paclitaxel and Curcumin. Int J Biol Macromol 2021; 192: 950-7.
95. Srivastava S, Kumar A, Yadav PK, Kumar M, Mathew J, Pandey AC, Chourasia MK. Formulation and performance evaluation of polymeric mixed micelles encapsulated with baicalein for breast cancer treatment. Drug Dev Ind Pharm 2021; 47(9): 1512-22.
96. Negut I, Bita B. Polymeric micellar systems-a special emphasis on "smart" drug delivery. Pharmaceutics 2023; 15(3): 976.
97. Mabrouk MM, Hamed NA, Mansour FR. Spectroscopic methods for determination of critical micelle concentrations of surfactants; a comprehensive review. Appl Spectrosc Rev 2023; 58(3): 206-34.
98. Pawlik A, Cox PW, Norton IT. Food grade duplex emulsions designed and stabilised with different osmotic pressures. J Colloid Interface Sci 2010; 352(1): 59-67.
99. Kedar U, Phutane P, Shidhaye S, Kadam V. Advances in polymeric micelles for drug delivery and tumor targeting. Nanomedicine 2010; 6(6): 714-29.
100. Aminabhavi TM, Munk P. Excess polarizability and volume of mixing and their effect on the partial specific volume and the refractive increment of polymers in mixed solvents. Macromol 1979; 12(6): 1186-94.
101. Qiu LY, Bae YH. Self-assembled polyethylenimine-graft-poly (ε-caprolactone) micelles as potential dual carriers of genes and anticancer drugs. Biomater 2007; 28(28): 4132-42.
102. Xu JP, Ji J, Chen WD, Shen JC. Novel biomimetic surfactant: Synthesis and micellar characteristics. Macromol Biosci 2005; 5(2): 164-71.
103. Owen SC, Chan DP, Shoichet MS. Polymeric micelle stability. Nano today 2012; 7(1): 53-65.
104. Trivedi R, Kompella UB. Nanomicellar formulations for sustained drug delivery: strategies and underlying principles. Nanomedicine 2010; 5(3): 485-505.
105. Haikola M, Hirvonen J, Medina OP, Simpura I, Kairemo K, Peltonen L. Stability and CMC determinations of amphiphilic (DSPEPEG (3400)-CTT2) peptide constructs by microtensiometry. J Drug Deliv Sci Technol 2011; 21(2): 183-8.

106. Narang AS, Delmarre D, Gao D. Stable drug encapsulation in micelles and microemulsions. Int J Pharm 2007; 345(1-2): 9-36.
107. Gapinski J, Szymanski J, Wilk A, Kohlbrecher J, Patkowski A, Hołyst R. Size and Shape of Micelles Studied by Means of SANS, PCS, and FCS. Langmuir 2010; 26(12): 9304-14.
108. Lu J, Owen SC, Shoichet MS. Stability of self-assembled polymeric micelles in serum. Macromolecules 2011; 44(15): 6002-8.
109. Yu G, Jie K, Huang F. Supramolecular amphiphiles based on host–guest molecular recognition motifs. Chem Rev 2015; 115(15): 7240-303.
110. Hörmann K, Zimmer A Drug delivery and drug targeting with parenteral lipid nano-emulsions-A review. J Control Release 2016; 223: 85-98.
111. Li J, Wang Q, Xia G, Adilijiang N, Li Y, Hou Z, Fan Z, Li J. Recent advances in targeted drug delivery strategy for enhancing oncotherapy. Pharmaceutics 2023; 15(9): 2233.
112. Wang B, Rosano JM, Cheheltani RE, Achary MP, Kiani MF. Towards a targeted multi-drug delivery approach to improve therapeutic efficacy in breast cancer. Expert Opin Drug Deliv 2010; 7(10): 1159-73.
113. Dhritlahre RK, Saneja A. Recent advances in HER2-targeted delivery for cancer therapy. Drug Discov Today 2021; 26(5): 1319-29.
114. Sultana A, Zare M, Thomas V, Kumar TS, Ramakrishna S. Nano-based drug delivery systems: Conventional drug delivery routes, recent developments and future prospects. Med Drug Discov 2022; 15: 100134.
115. Gholipourmalekabadi M, Mobaraki M, Ghaffari M, Zarebkohan A, Omrani VF, Urbanska AM, Seifalian A. Targeted drug delivery based on gold nanoparticle derivatives. Curr Pharm Des 2017; 23(20): 2918-29.
116. Karimi M, Eslami M, Sahandi-Zangabad P, Mirab F, Farajisafiloo N, Shafaei Z, Ghosh D, Bozorgomid M, Dashkhaneh F, Hamblin MR. pH-Sensitive stimulus-responsive nanocarriers for targeted delivery of therapeutic agents. Wiley Interdiscip Rev Nanomed Nanobiotechnol 2016; 8(5): 696-716.
117. Ahmadzada T, Reid G, McKenzie DR. Fundamentals of siRNA and miRNA therapeutics and A Review of targeted nanoparticle delivery systems in breast cancer. Biophys Rev 2018; 10(1): 69-86.
118. Yang S, Gao H. Nanoparticles for modulating tumor microenvironment to improve drug delivery and tumor therapy. Pharmacol Res 2017;126: 97-108.

119. Karimi M, Sahandi Zangabad P, Ghasemi A, Amiri M, Bahrami M, Malekzad H, Ghahramanzadeh Asl H, Mahdieh Z, Bozorgomid M, Ghasemi A, Rahmani Taji Boyuk MR. Temperature-responsive smart nanocarriers for delivery of therapeutic agents: applications and recent advances. ACS Appl Mater Interfaces 2016; 8(33): 21107-33.
120. Taylor MJ, Tomlins P, Sahota TS. Thermoresponsive gels. Gels 2017;3(1): 4.
121. Hu H, Busa P, Zhao Y, Zhao C. Externally Triggered Drug Delivery Systems. Smart Mater Med 2024; 5(3): 386-408.
122. Lammers T, Kiessling F, Hennink WE, Storm G. Drug targeting to tumors: principles, pitfalls and (pre-) clinical progress. J Control Release 2012; 161(2): 175-187.