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Review

Targeted and Localized Therapeutic Delivery for Breast Cancer: Current Technologies, Translational Challenges, and Future Innovations

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Abstract

Breast cancer is among the most common cancers globally. While several advancements have been made to improve breast cancer management, there is still a need to find innovative ways to deliver drug therapy to improve efficacy and side effects associated with treatment. Among these methods, local and targeted drug delivery is particularly promising. The current review highlights localized polymer-based methods to effectively deliver breast cancer therapy, with a specific focus on the strengths and limitations of these systems. Injectable and surgically implanted scaffolds, microneedles, topical patches, liquid and semisolid topical drug carriers are amongst some of the delivery systems discussed. Highlighted in the discussion is how physiological changes that occur during breast cancer should be considered and utilized when developing drug formulations, by specifically exploiting the tumor microenvironment. Remaining gaps and future areas for drug delivery research are highlighted including personalized medicine and insights into novel drug delivery systems like nanomedicines and three-dimensional drug printing.

Keywords: breast cancer; polymers; localized drug delivery; targeted drug delivery; polymeric drug delivery; polymeric biomaterials

1. Introduction

Breast cancer is a global issue that occurs in every country of the world. In 2022, it was estimated that 2.3 million women were diagnosed with breast cancer and 670,000 died from it [1]. Besides skin cancer, breast cancer is the most common cancer [2]. Due to the higher exposure of estrogen and progesterone, being born female is the biggest risk factor for breast cancer. Though, breast cancer still affects men, with 0.5–1% of breast cancers occurring in men. In the United States, the overall lifetime risk of a woman developing breast cancer is one in eight [2]. While the rate of deaths from breast cancer is decreasing, there is still a need for innovative prevention, screening, and treatment options to eliminate breast cancer [1,2].

The female breast is comprised mainly of adipose tissue which contains lobes, lobules, and mammary ducts [3]. In the lobules, there are glands that produce milk which is then carried by the mammary ducts to the nipple. Most breast cancers originate from the epithelial cells lining the mammary ducts or lobules and are histologically classified as

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carcinomas. Carcinomas can be further divided into carcinoma in situ and invasive cancer. In addition to the pathology of breast cancer, the hormone receptor and human epidermal growth factor receptor 2 (HER2) status are both significant for prognosis and treatment strategies [4]. Hormone receptors are nuclear transcription factors that promote cell growth by activating signal transduction pathways. They include estrogen receptors (ERs) and progesterone receptors (PRs). The *HER2* gene is located on chromosome 17q21 and encodes a transmembrane tyrosine kinase growth factor receptor responsible for normal cell growth. Overexpression of the *HER2* gene is associated with increased tumor aggressiveness and mortality [5]. The type of breast cancer is important for understanding the management and can be utilized when developing new treatments.

Unlike some cancers, often there are few or no symptoms at all in the early stages of breast cancer. Examples of symptoms that people may experience include a breast lump or thickening, changes in the size or appearance of the breast, and changes in the nipple appearance or areola [1]. In addition to being female, other risk factors for breast cancer include increasing age, family history, obesity, age of menarche, age of first pregnancy, and tobacco use [6]. Additionally, 5 to 10% of breast cancers can be characterized as having a genetic mutation, with *Breast Cancer* gene (*BRCA*) 1 and 2 being the most common [7]. Broadly, management of breast cancer consists of surgical treatment, radiation, chemotherapy, hormonal therapy, immunotherapy, and other targeted drug therapy [8].

A recent and rapidly developing focus for cancer treatment is the use of polymeric drug delivery systems. Polymeric drug delivery is broadly described as a formulation that introduces a biologically active substance into the body, but is unique in that the rate, time, and site of drug delivery in the body can be modified [9]. The polymeric excipients used for the synthesis of these drug carriers can be systematically chosen to optimize or create a desired effect, including increased drug efficacy or a reduction in side effects. Additionally, they can be used to increase drug solubility or bioavailability of the drug at the desired site of action. Some examples of polymeric drug delivery systems include nanoparticles, liposomes, dendrimers, hydrogels, and implants [10]. These innovative systems offer a potential solution for the localized delivery of therapeutic molecules to a specific area of the body, for example the breast tissue in the case of breast cancer [11].

The focus of this review will be on how recent advancements in polymeric drug delivery are being utilized to improve breast cancer management. Specifically, there are advantages and limitations of innovative localized polymer-based drug therapies compared to conventional management strategies in both the neoadjuvant and adjuvant chemotherapy setting. Through a detailed literature search, a comprehensive analysis will be conducted to identify recent advancements in localized polymeric drug delivery systems that have been targeted to improve breast cancer treatment outcomes. This up-to-date review will serve as a summary of the literature in this area and will provide emphasis on applications for future research and investigations. Compared to previously reported breast cancer drug delivery reviews and literature, this manuscript emphasizes the role of localized polymeric drug delivery strategies, how they target previous gaps in breast cancer treatment, and provides recommendations for next steps. To identify the literature, Google Scholar, PubMed, and the Cochrane Library were searched up to February 2026. Research performed in the last 10 years was prioritized and only English-language studies were included. Keywords in the search strategy included “cancer,” “breast cancer,” “cancer of the breast,” “mammary cancer,” “drug delivery,” “medication,” “dosage forms,” “pharmaceutical formulations”, “polymeric drug delivery”, “small molecule drugs for breast cancer”, biologic drugs for breast cancer”, and “drug technologies.” Search results were screened by publication title by the reviewers, and articles with titles and abstracts that included relevant keywords were further screened for inclusion, using the full text,

based on relevancy to the review topic. Formulation development studies and preclinical trials were considered the best evidence, and review articles were used to supplement evidence and identify other primary literature. The literature included was managed using reference management software.

2. Barriers to Historic Breast Cancer Treatment

2.1. Surgical Removal

Surgical removal of cancerous tissue is a common therapy option used for breast cancer treatment. It can be used both for curative intent and to improve quality of life. There are various types of surgeries depending on the stage and goals of treatments [8]. For example, a lumpectomy is done to remove just the tumor and surrounding tissue and is considered for early-stage breast cancers [12]. Mastectomy is another surgical option for breast cancer and generally involves the removal of all of the breast tissue, although there are different types [12]. This surgery may be chosen for larger tumors, advanced disease, or recurrence. While surgery is a first line therapy option for breast cancer, there are limitations. In patients of poor health who are frail, the elderly, or individuals with multiple comorbidities, surgery may not be an option due to the associated risks. There are also complications of surgery which include bleeding, infections, nerve pain, and mental health implications [13]. It is possible that undetected microscopic disease remains following surgery, which is why surgery is often concurrent with other treatments like chemotherapy and radiation therapy [14]. In one retrospective cohort study, breast conserving surgery (BCS) alone was compared with BCS plus adjuvant radiation therapy. It was found that the hazard ratio was higher for patients who did not receive radiation therapy for recurrence or death [14].

2.2. Radiation Therapy

Radiation therapy is another non-drug treatment option for breast cancer. Broadly, this therapy uses high-frequency radiation that causes damage to cell deoxyribonucleic acid (DNA), which results in cell death and tumor shrinkage [15]. It can be provided as an external (external beam radiotherapy (EBRT)) or internal source (brachytherapy) therapy [16]. Radiation therapy is often used as an adjuvant therapy, following BCS, to reduce the risk of local recurrence [17]. It is also used in instances where the tumor is unresectable or in instances of metastatic disease. It is associated with side effects like fatigue, skin changes, swelling, and tenderness [18]. Radiation itself can also be associated with secondary malignancies, with an absolute risk between 0.2% and 1% per year [18]. For breast cancer, lung cancer, leukemia, and the cancer of the opposite breast are associated secondary malignancies.

2.3. Chemotherapy

Chemotherapy is a group of drugs used to kill or slow the growth of cancerous cells. It can be given before surgery (neoadjuvant) or after surgery (adjuvant) and is used to shrink the tumor prior to surgery or kill an of the remaining cancers cells, respectively [19]. In the case of metastatic disease, it may be used to prolong survival and improve quality of life [19]. There are many different drugs used for breast cancer management, and these include anthracyclines (doxorubicin, epirubicin), taxanes (paclitaxel, docetaxel), 5-fluorouracil, cyclophosphamide, capecitabine, and gemcitabine [20]. Most chemotherapy agents used for breast cancer treatment must be given intravenously and administered frequently, often every 2 to 3 weeks. Traditional chemotherapy is limited by the extensive side effect profile, due to its lack of specificity to cancer cells. For example, in mice it was found that after 24 h, less than 0.5% of the total dose administered intravenously was available at the target

tumor site (Figure 1) [21]. Additionally, chemotherapy agents often show higher efficacy at higher doses, thus increasing the risk of adverse reactions [10]. Most chemotherapeutic agents have low aqueous solubility, limiting intravenous administration. Accordingly, the drugs are often modified, and these modifications can increase side effects like hypersensitivity reactions [22]. The side effects depend on the specific agent, but generally include heart damage, nausea and vomiting, hypertension, nerve damage, fatigue, hair loss, and increased risk of secondary cancer like leukemias [23]. Chemotherapy can also impact ovarian function and fertility, with 33% to 76% of women 50 years and older experiencing persistent post-treatment amenorrhea after systemic treatment for breast cancer [24]. Resistance to chemotherapy, the failure of a drug to produce a beneficial response, is another major concern for chemotherapy [25]. Other limitations of traditional chemotherapy include cost on the health care system associated with clinic visits to administer the medication and monitor the patient [26]. Futhermore, there is a burden on the patient to be able to get a facility where the medication can be administered, and the time required [27].

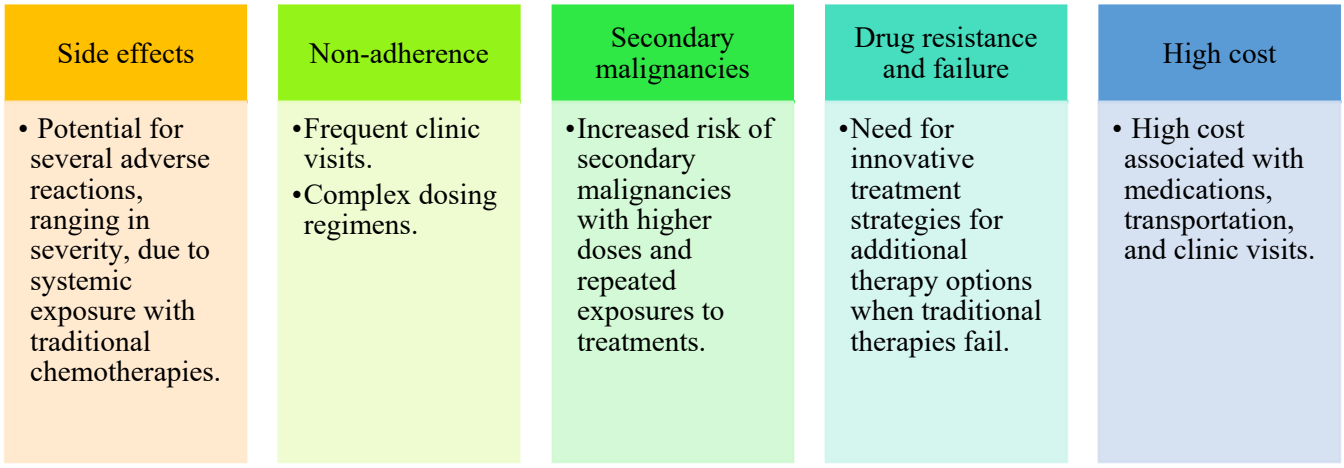

Figure 1. Examples of issues associated with systemic breast cancer treatment options.

2.4. Hormone Therapy

In patients who have hormone-positive breast cancer, hormone therapy, or endocrine therapy, can be used to slow or stop the growth of the breast tumor by stopping the body's ability to produce the hormone or by blocking the receptors [28]. Examples include tamoxifen and aromatase inhibitors like anastrozole, letrozole, or exemestane. Hormone therapy is frequently used in breast cancer management as an adjuvant therapy and is often continued for 5 to 10 years [29]. Endocrine therapy has been used to decrease mortality and prevent reoccurrence of breast cancer. For example, adjuvant tamoxifen decreased mortality at 15 years by a third in women with early-stage estrogen receptor positive breast cancer [30]. The majority of the endocrine therapy used for breast cancer are oral agents, that thus have the advantage of ease of administration. Examples of side effects of endocrine therapy include osteoporosis, menopausal symptoms, blood clots, stroke, nausea, bone pain, depression, and uterine cancer [31]. Additionally, given these agents are prescribed for several years and must be given daily, there is a risk of non-adherence [32]. For instance, in one systematic review that looks at adherence to adjuvant hormonal therapy in breast cancer survivors, adherence ranged from 41 to 72% [32].

2.5. Immunotherapy

Immunotherapy is a growing area for cancer research and generally refers to therapy that is used to enhance a person's own immune system to fight cancer. One type of immunotherapy used in breast cancer is an immune check point inhibitor, which works by

blocking checkpoint proteins, which normally would prevent the immune system, particularly T-cells, from attacking cancer cells [33]. An example of an immune checkpoint inhibitor used in breast cancer is pembrolizumab. Trastuzumab, a monoclonal antibody, is another example of immunotherapy that can be used to treat HER2-positive breast cancer [34]. One concern for immunotherapy is resistance, which can include the patient not responding to the primary dose or some patients relapsing or progressing after a period of treatment, referred to as primary and acquired resistance, respectively [35]. A major limitation of immunotherapy is cost, with most costing more than CAD 100,000 per patient [36]. Additionally, due to the mechanism of action, a possible side effect of immunotherapy is immune related adverse effects (IrAEs), which can occur at any time during and after treatment discontinuation [37]. Possible examples of IrAEs include colitis, hepatitis, pneumonitis, and acute kidney injuries.

3. Changes in Physiological Parameters in Breast Cancer

3.1. General Changes in Cancer That Support Tumor Growth and Progression

It is well recognized that there are "hallmark" characteristics to describe changes that allow cancer to occur, and as more research has been done, this list has evolved [38]. First, modifications occur in cancer cells that allow for chronic proliferation, by evading the normal cell growth and division cycle [38]. For example, cancer cells can acquire the ability to sustain proliferative signals by producing growth factor ligands themselves or by sending signals to surrounding cells to supply growth factors. Epidermal growth factor receptor (EGFR) inhibitors are one class of cancer therapy that target this mechanism of cancer growth [39].

Another change that occurs in cancer cells is the ability to evade growth suppressors. In a normal cell, there is a signal that prevents the cell from dividing, mainly by means of *tumor suppressor* genes. In cancer cells however, this signalling process is disturbed and cell proliferation continues [40]. Examples of these genes are RB (retinoblastoma-associated) and tumor protein 53(TP53). RB normally decides whether a cell should proceed with its normal growth cycle, so a cancer cell with an RB defect is missing this gatekeeper [40].

Cancer cells also can resist cell death. In healthy cells, programed cell death, referred to as apoptosis, is a barrier to cancer development [41]. Extracellular or intercellular signals can trigger apoptosis, if there is a defect with a cell. There are several ways cancer cells are able to escape apoptosis, the most commonly mentioned is the loss of the TP53 tumor suppressor function [41,42].

Like healthy cells, cancer cells must have vascular access to supply nutrients and oxygen and evacuate waste. Thus, another key factor for cancer development is inducing angiogenesis [40]. During tumor progression, there is often continuous sprouting of new vessels to sustain neoplastic growths. Examples of angiogenic regulators are vascular endothelial growth factor-A (VEGF-A) and thrombospondin-1 (TSP-1) [40].

Another characteristic of cancer cells is enabling replicative importability. Normally, cells are limited to a finite number of cell divisions, set by telomerase [43]. Yet, some cancer cells are able to divide without limit. One way is by upregulating expression of telomerase such that they are able to maintain telomeric DNA at lengths sufficient to avoid triggering senescence or apoptosis [43]. Telomerase inhibitors are a class of cancer drugs that target this mechanism [44].

Metastasis is a multistep process that occurs in cancer. Broadly, this involves local invasion, then transfer of cancer cells via nearby blood and lymphatic vessels, and escape of cancer cells into and the parenchyma of tissue [45]. Once cancer cells distribute to distant tissue, they can form small nodules of cancer cells that can grow into larger tumors.

3.2. Examples of Specific Physiologic Characteristics and Drug Targets in Breast Cancer

Broadly, the tumor microenvironment (TME) refers to the surrounding cells, tissues, and blood vessels that encompass a tumor. In breast cancer, the TME can be categorized as cellular, soluble, and physical components [46,47]. The cellular department can be further divided into local, regional, and metastatic compartments, which refers to the tumor cells, interaction between the tumor cells and an adjacent cell, and interaction with the vascular/lymph cells, respectively. Some examples of the cellular compartment are lymphocytes, plasma cells, dendritic cells, fibroblasts, adipocytes, lymph nodes, and blood [46]. The soluble factors include interleukins, tumor necrosis factor, and vascular endothelial growth factor. Oxygen and pH levels are examples of physical factors. The TME influences the malignant progression and clinical outcome to chemotherapy [48]. For example, in breast cancer, the blood vessels are lined by defective endothelial cells, leading to leaky vessels and reduced blood flow [49]. This decrease in blood flow can lead to impaired chemotherapy delivery.

The TME can also be targeted for drug therapy (Table 1). PD-1/PD-L1 (programmed cell death protein-1/programmed death-ligand 1) inhibitors are one class for drugs that directly act on the TME in breast cancer [46]. PD-1 is expressed on immune cells, like B-cells, T-cells, and macrophages, and when engaged it inhibits T-cell activation and contributes to immune resistance in the TME. Thus, these drugs work by restoring the response of cytotoxic T-cells to cancer cells [50]. Additionally, cancer-associated fibroblasts (CAFs) are an important therapeutic target within the tumor microenvironment. They are key stromal components of the tumor microenvironment and are among the most abundant (about 80%) non-malignant cells in many solid tumors particularly in desmoplastic cancers, such as pancreatic and breast carcinomas, and they significantly influence tissue structure. CAFs actively contribute to tumor progression by driving extracellular matrix remodelling, promoting angiogenesis, and enhancing tumor cell proliferation, invasion, and migration [51]. Beyond these effects, they contribute to the development of an immunosuppressive microenvironment by altering immune cell recruitment and function, enabling tumor immune evasion and therapeutic resistance. Owing to their diverse and critical roles in cancer biology, CAFs have emerged as a promising target for therapeutic intervention, with strategies focused on inhibiting their activation, disrupting their interactions with tumor cells, or reprogramming them toward a tumor-suppressive phenotype [51].

Table 1. Characteristics of the TME in breast cancer and impact on drug delivery strategies.

Characteristic	Impact on Drug Delivery
Leaky vessels and reduced blood flow	Impaired delivery of drugs via blood.
Reduced oxygen	Exploit drug delivery dependent on low oxygen levels.
Decreased pH	pH-dependent site-specific drug release.
High glutathione	Site-specific drug release by breaking of disulfide bonds.
Overexpression of enzymes	Site-specific drug release by utilizing enzymes expressed in TME.

Other properties of the TME that can be used to optimize drug targeting include pH, high glutathione levels, and overexpression of enzymes [52]. In general, the pH of the TME is more acidic, so drug delivery systems can be developed to have drug release at more acidic pHs than the physiological environment. Additionally, high levels of glutathione found in the TME can also be utilized for targeted drug release, by cleaving disulfide bonds on drug carriers.

The immune system also influences breast cancer, with breast cancer generally be classified as moderately immunogenic given its ability to impact and elicit immune responses [53]. In breast cancer, there are diverse populations of immune cells present in the stroma. Immunoediting, the process describing the interaction between the host immune system and tumor cells, involves recognition of cancer cells as foreign and triggering an immune response [53]. However, some of the tumor cell variants can escape the immune response and remain dormant while the immune cells prevent further tumor growth. Eventually, the tumor cells can escape the immune recognition and continue to grow and proliferate through various mechanisms.

Hormone receptor and HER2-positive breast cancer are other unique targets for some breast cancers. The estrogen receptor is involved in proliferation and invasion of cancer in estrogen receptor-positive breast cancer [54]. When estrogen binds to the estrogen receptor it leads to activation of downstream gene expression. Similarly, HER2 plays a role in promoting cell growth and survival in HER2-positive breast cancers [54]. Other examples of targeting pathways in breast cancer are phosphoinositide 3-kinase/mammalian target of rapamycin (PI3K/mTOR), cyclin-dependent kinases (CDK) 4/6, histone deacetylases, and poly (ADP-ribose) polymerases (PARPs) [54].

4. Examples of Innovation in Localized and Targeted Polymeric Drug Delivery for Breast Cancer

Polymeric drug delivery is an evolving field of technology that uses polymeric biomaterials to encapsulate and facilitate effective and safe drug delivery to different body sites for the management of several diseases [55]. Localized drug delivery refers to transfer of a drug to a specific target and is used to optimize drug availability at the site of action while minimalizing side effects due to off-target drug effects. Local drug delivery can be achieved by methods such as implants or injections. Targeted drug delivery is an approach that selectively directs active drug molecules to a specific tissue, organ, cell type, or molecular target (e.g., the tumor site) while minimizing exposure to healthy tissues [56]. The key goal is to increase drug concentration at the desired site of action, improve therapeutic efficacy, and reduce systemic toxicity and adverse effects. A typical localized and targeted drug therapy is achieved by utilizing polymeric drug delivery systems. These systems are constructed using biocompatible polymers, whose properties can be exploited for drug delivery [55]. The rate, time, and place of drug release can all be tailored using this method of drug delivery. Examples of natural polymers used include arginine derivatives, chitosan derivatives, cyclodextrin derivatives, and polysaccharides [9]. Conversely, examples of synthetic polymers used include Poly (N-isopropyl acrylamide)s and Poly (ethylenimine)s [9]. Biodegradable polymers are often used, given that they break down naturally in the intentioned physiological environment and negate the need to remove any devices or material.

In recent years, there has been a surplus of research expanding on the use of locally delivered or targeted polymeric drug delivery systems for breast cancer therapy. Summarized are locally delivered polymeric drug delivery systems for breast cancer treatment. Additionally included are targeted polymeric formulations given systemically but designed such that the drug effects are targeted to breast cancer cells, thus decreasing unwanted side effects (Figure 2).

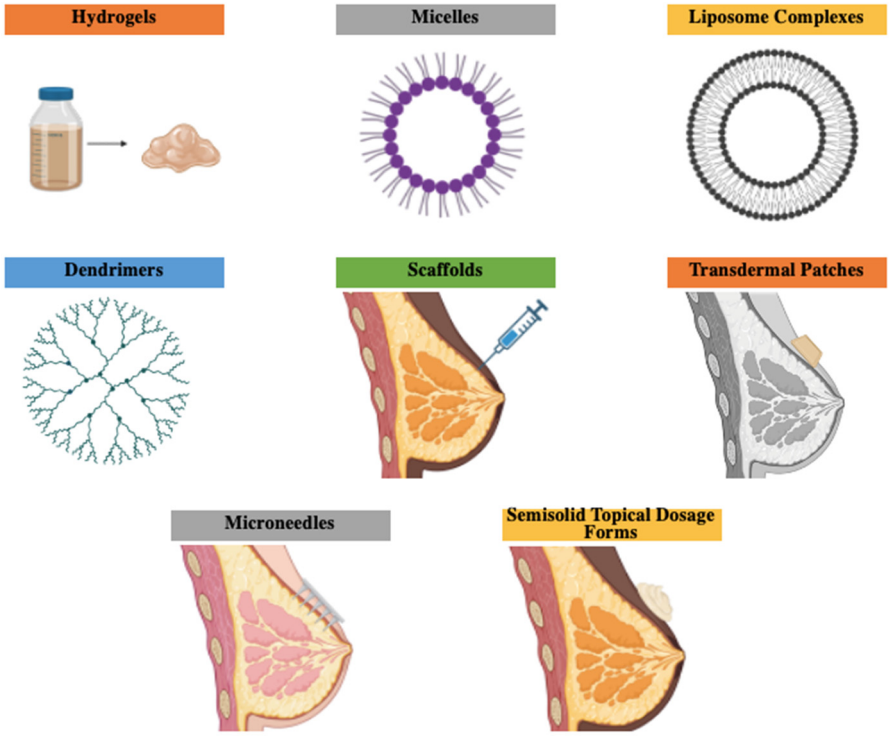

Figure 2. Examples of Localized Polymeric Drug Delivery with Applications for Breast Cancer Treatment.

4.1. Scaffolds

Scaffolds are polymeric injections or implants. Polymer implants are classified as two- or three-dimensional forms made of one or more polymers [57] while polymeric injectables are colloidal solutions that can form a hydrogel, which is typically able to form specific structure after being injected into the respective tissue [58]. Polymer-based hydrogels are made of cross-linked polymeric materials. One of the unique properties associated with hydrogels is their ability to adsorb and retain large amounts of fluids while maintaining their three-dimensional structure [59]. This swelling property can be utilized to control drug release properties. Hydrogels closely mimic biologic tissues and thus have the advantage of minimal side effects from the drug delivery system [60]. The properties of hydrogels can also be modified in such a way that they can respond to external stimuli like pH, temperature, or light. Hydrogels can be classified using various methods which include mesh size, swelling ratio, and microstructure [61]. Hydrogels can be used for local drug delivery by being injected into the tumor site.

Compared to implants, the injectable drug carriers minimize the incision size. Polymer-based implants have been frequently investigated for use in local cancer drug delivery, majorly because of their ability to bypass first pass metabolism. In some instances, the scaffold is injected intra-tumorally to increase concentration of the drug within the target tissue and avoid side effects associated with off-target pharmacological actions [58]. They can also be used for systemic effects to eliminate the needs for repeated doses by providing a sustained release.

In 2020, Yang et al. developed an implantable multi-drug delivery system with time-programmed release based using three-dimensional (3D) printing intended for breast cancer [62,63]. This scaffold was made from poly-lactic-co-glycolic acid (PLGA) and contained the two drugs, 5-fluorouracil and Dactolisib (i.e., NVP-BEZ235). The implantable scaffold was found to release the drug over a long period of time, with a slow-release stage lasting up to two weeks, suggesting the possibility of a one-time implantation. The

formulation also demonstrated prolonged drug levels at the tumor site, with reduced doses needed, and less exposure to healthy tissue. A limitation of the formulation is the need to surgically implant it (Table 2).

In another study, researchers developed biodegradable PLGA implants containing doxorubicin-loaded chitosan nanoparticles [64]. This drug delivery system was subcutaneously implanted into mice with murine breast cancer cell line breast tumors. The implant demonstrated sustained release and tumor-specific drug delivery. When efficacy was measured against multiple injections of doxorubicin at the same amounts/doses, the implants had comparable inhibition of tumor growth.

Scaffolds also have potential use for prevention of tumor recurrence following mastectomy. In one study, researchers prepared 3D-printed scaffold made from caffeic acid grafted to chitosan, sodium alginate, nanoclay, and carbon dots–curcumin nanoparticles [65]. In mice models, the scaffold was found to have good long-term antibacterial effects, wound healing potential, and inhibited postoperative residual cancer cells.

In the setting of triple negative breast cancers, one research group investigated the use of localized drug release from an implantable microporous poly-di-methyl-siloxane (PDMS) for the targeted delivery of Luteinizing Hormone-Releasing Hormone conjugated paclitaxel and Luteinizing Hormone-Releasing Hormone conjugated prodigiosin [66]. Using vitro studies, a significant reduction in the percentage of cell growth in a time-dependent manner was found. In mice models, following partial surgical removal of the tumor and implantation, there was no tumor regrowth six weeks post-treatment implant. At the same time, no adverse effects of the drugs on the liver, kidneys, or lungs were detected.

Similarly, 3D-printed poly (lactic-co-glycolic acid), gelatin, and chitosan scaffold loaded with 5-fluorouracil and doxorubicin hydrochloride have also been prepared [67]. The scaffold had a sponge-like structure and for in situ implantation, drug release was influenced by tumor pH (slightly acidic environment), leading to sustained drug release. This formulation offers another potential option for reducing tumor growth and recurrence, while reducing drug toxicity. The scaffold also had good blood absorption, promoting rapid wound healing.

Electrospun drug delivery systems are another avenue for local drug delivery to the tumor site. Electrospun fibers have several favourable drug delivery characteristics including the ability to manipulate drug release due to their highly porous property, high surface-to-volume ratio, and the ability to encapsulate more than one drug directly into the fibers [68]. Ding and colleagues developed docetaxel-loaded poly-D,L-lactide (PDLLA) fibers for preventing local breast cancer recurrence [68]. In mice models, the locoregional recurrence after primary tumor resection decreased with subcutaneous administration of the formulation docetaxel loaded PDLLA fibers (16.7%) compared with the blank PDLLA nanofibers (88.9%), systemic (75.0%), or locally (77.8%) administered docetaxel and the control group (100%).

Due to the side effects associated with long-term adjuvant chemotherapy postoperatively, one strategy is to release multiple drugs in a time-programmed manner. Researchers utilized this strategy by developing an implantable time-programmed drug release hierarchical-structure ultra-fine fiber device [69]. The electrospun hierarchical-structured fibers had a hydrophilic internal chamber containing polyethylene glycol (PEG) and doxorubicin and the hydrophobic fiber matrix contained poly (d,l-lactic acid) (PLA) and disulfiram. When the drug delivery system was implanted into mice models with resected breast tumors, a rapid release of doxorubicin occurred due to the water absorption of PEG. This allows for rapid residual tumor cell elimination. At the same time, the disulfiram is released in a sustained manner, preventing spread via surrounding tissues and blood vessels and subsequent tumor metastasis.

Hydrogel scaffolds are another option for preventing local breast cancer relapses. Lei and colleagues developed paclitaxel containing hydrogel made of copolymeric poly (ethyleneglycol)-poly (ε-caprolactone)-poly (ethylene glycol) [70]. At room temperature the formulation is free flowing, but once injected it forms a gel within seconds at body temperature and the drug is released in a sustained fashion as it biodegrades. In mice models, the hydrogel containing paclitaxel significantly inhibited tumor recurrence after primary tumor removal compared to systemic and locally administered paclitaxel alone.

Temperature and pH of the breast cancer tumor environment can also be exploited for drug delivery systems. Fathi et al. (2019) investigated a pH and thermo-responsive hydrogel containing doxorubicin for intratumoral injection [71]. The hydrogel was made up of a blend of poly (N-isopropylacrylamide-co-itaconic acid) (PNIAAm-co-IA) and chitosan (CS). The researchers found that doxorubicin had accelerated release in acidic conditions at 37 °C compared to neutral pH and the temperature of 40 °C.

OncoGel is a paclitaxel containing hydrogel formulation of poly (lactide-co-glycolide) and poly (ethylene glycol) tri-block copolymer (PLGA-PEG-PLGA) [72]. It is a thermosensitive controlled release formulation that is free flowing at temperatures between 2 and 15 °C and water insoluble at body temperature. It is administered via intralesional injection or placement into the tumor cavity. One requirement for use is that the tumor must be accessible for the drug to be injected. The needle used for injection is selected based on the type of lesion it is injected into. In mice with human breast carcinoma xenografts, less than 0.1% of radioactively labelled paclitaxel was measured in the other organs or blood following intertumoral injection of OncoGel [73].

Nanofibers are another method of delivering breast cancer drug therapy. One research group developed pH-responsive polymeric nanofibers encapsulated with an active targeting micellar system that was loaded with paclitaxel [74]. Cholic acid conjugated to poly (bis (carboxyphenoxy) phosphazene) (PCPP) polymeric micelles were used to encapsulate the paclitaxel. The micelles were then encapsulated into the core–shell psyllium husk mucilage nanofibers using electrospinning. The resulting nanofibers were intended for injection subcutaneously near the solid tumor region. In vitro drug release demonstrated sustained drug release over 180 h and were effectively internalized into the skin. Compared to paclitaxel alone, the drug-loaded nanofibers exhibited higher cytotoxicity for 8 days.

Another way researchers were able to formulate 5-Fluorouracil to be delivered locally was by developing a 3D bio-printed two-layer implantable scaffold [75]. The first layer was made of the polymers poly-ε-caprolactone (PCL) and chitosan (CS) and was loaded with 5-Fluorouracil and was designed to release the drug within 4 weeks. The second layer was made from PCL and contained gold nanoparticles; the purpose of the second layer was a radiation enhancer. In vitro testing revealed that 32% of the drug was released after one month with an initial burst release of 17.22%.

Table 2. Emerging innovations in localized polymeric scaffolds targeting breast cancer.

Drug	Formulation	Key Advantages	Reference
5-fluorouracil and NVP-BEZ235	Poly-lactic-co-glycolic acid (PLGA) scaffolds containing 5-fluorouracil and NVP-BEZ235.	Reduced required drug dosage, prolonged time for drug at tumor site, minimized exposure to normal tissue.	[62,63]
Curcumin	3D printed scaffold made from caffeic acid grafted to chitosan, sodium alginate, nanoclay, and carbon dots–curcumin nanoparticles.	Favourable drug release, luminescent properties, and antibacterial properties.	[65]

Table 2. *Cont.*

Drug	Formulation	Key Advantages	Reference
PTX-LHRH and PG-LHRH	PDMS implant loaded with PTX-LHRH or PG-LHRH.	No tumor regrowth after 6 weeks in mice models in triple negative breast cancer following partial surgical removal of the tumor. Decreased off-target side effects.	[66]
Doxorubicin	Biodegradable PLGA implants containing doxorubicin-loaded chitosan nanoparticles.	Sustained drug release and tumor-specific drug delivery. Compared inhibition of tumor growth to multiple injections of the same drug.	[64]
5-fluorouracil and doxorubicin hydrochloride	Poly (lactic-co-glycolic acid), gelatin, and chitosan scaffold loaded with anti-cancer drugs.	Drug release influenced by acidic tumor environment leading to sustained drug release.	[67]
Docetaxel	Docetaxel-loaded poly-D,L -lactide electrospun fibers.	Good biocompatibility improved antitumor efficacy compared to systemically or locally docetaxel alone in mice models.	[68]
Doxorubicin and disulfiram	Structured fibers with a hydrophilic internal chamber containing PEG and doxorubicin and a hydrophobic fiber matrix containing PLA and disulfiram.	Ability of the drug formulation to store and release two drugs with varying release rates at the tumor site.	[69]
Paclitaxel	Poly (ethylene glycol)-poly (ε-caprolactone)-poly (ethylene glycol) hydrogel loaded with paclitaxel.	The hydrogel formulation inhibited locoregional recurrence compared to paclitaxel alone with administered locally or systemically.	[70]
Doxorubicin	Poly (N-isopropylacrylamide-co-itaconic acid) (PNIAAm-co-IA) and chitosan hydrogel loaded with doxorubicin.	Temperature and pH responsiveness of hydrogel can be exploited for sustained drug release at the tumor site.	[71]
Paclitaxel	OncoGel is a paclitaxel containing hydrogel formulation of poly (lactide-co-glycolide) and poly (ethylene glycol) tri-block copolymer (PLGA-PEG-PLGA) (90).	It is a thermosensitive control release formulation administered via intralesional injection or placement into the tumor cavity.	[72]
Paclitaxel	pH-responsive polymeric nanofibers encapsulated with an active targeting micellar system that was loaded with paclitaxel.	In vitro drug release demonstrated sustained drug release over 180 h and were effectively internalized into the skin. Compared to paclitaxel alone, the drug-loaded nanofibers exhibited higher cytotoxicity for 8 days.	[74]
5-Fluorouracil	Two-layer implantable scaffold made of polymers PCL, CS, and was loaded with 5-Fluorouracil.	In vitro testing revealed 32% of the drug was released one month after an initial burst release of 17.22%.	[75]

4.2. Liposomes

Liposomes are closed lipids vesicles comprised of phospholipids bilayers. They are optimal for both drug delivery of hydrophilic and hydrophobic drugs due to their hydrophobic lipid bilayer and internal aqueous core [76]. However, liposomes alone are

easily subject to degradation from acidic pH, enzymes, and the immune system in the biological environment [68]. Drug delivery by liposomes can be improved by modification with polymers, referred to as liposome complexes [77]. Examples of such structural changes include polymer-coated liposomes and polymer-grafted liposomes [76]. One example of liposome complexes that can be used to target drug delivery to tumors is by using a polymer sensitive to the same pH as the tumor matrix (pH 6.5). At this pH, the surface properties of the liposome polymer complex changes, and the drug is released [78].

Doxorubicin is a potent chemotherapy agent used for breast cancer, with high toxicity, including irreversible cardiomyopathy and liver damage. To reduce toxicity of doxorubicin, researchers prepared PEGylated liposomes, labelled with Aptamers (Apt)-A6 that can recognize and bind HER-2 receptors on HER-2-positive breast cancer cells, using thin film hydration methods [79]. The liposomes were found to range in size from 100 to 200 nm. The best formulation had an entrapment efficiency of 93% and had increased uptake into breast cancer cells. Additionally, they were more effective at killing cancer cells than free doxorubicin (Table 3).

As mentioned, the tumor microenvironment can be exploited for targeted drug delivery in breast cancer. Specifically, there are notable characteristics of lower extracellular pH and increased angiogenesis capacity of the breast cancer TME. In 2021, Jain et al. utilized these characteristics by developing VEGF antibody functionalized PEGylated sensitive liposomes containing docetaxel [80]. The liposomes were 206 nm in diameter and had an entrapment efficiency of 62%. Compared to free docetaxel, the liposomal formulation had a sustained drug release profile and prolonged blood circulation time. The formulation design promoted increased cellular uptake and targeting into breast cancer cells.

Researchers have also attempted to increase the skin penetration of topically applied tamoxifen by encapsulating it in a liposome-PEG-PEI (poly (ethylene imine)) complex carrier. The formulation was effective as increasing toxicity in breast cancer cells and administration by the transdermal route inhibited 86% of tumor growth in mice models [81].

4.3. Micelles

Micelles can be categorized as self-aggregated colloids derived from amphiphilic molecules [82]. Before a specific concentration is reached, it is referred to as the critical micellar concentration (CMC), and the polymers exist in solution as single molecules. On the other hand, once the CMC is reached, the polymers self-assemble into an external hydrophilic shell and lipophilic core [83]. They are often spherical in shape but can also be rod-like or disk-like [83]. The drug can be released from the micelle either by diffusion or micelle disassembly [84]. Micelles have several unique advantages compared to other conventional drug formulations and these include their small size, easy preparation, and good solubilization properties. Due to their hydrophilic nature, they can also have prolonged blood circulation time [85]. The size of the micelle is an important characteristic for drug delivery, with micelles having sizes less than 30 nm being able to reach poorly permeable tumors [86]. A difficulty associated with micelles is the ability to study their interaction with the biological environment.

One research group prepared micelle drug delivery system for the setting of triple negative breast cancer. The formulation was conjugate methotrexate polyethylene glycol modified chitosan 2,3-dimethylmaleic anhydride (DMMA) polymeric micelles loaded with doxorubicin [87]. Polyethylene glycol (PEG) was used to shield protein adsorption, and the methotrexate can be used to provide targeted drug delivery to local breast cancer tissue by binding to the folic acid receptor overexpressed on the surface of tumor cells. In mice models with breast tumors, the tumor volume was significantly inhibited after 9 days with the micellar treatment compared to the free drug group (Table 3).

Peng et al. formulated Herceptin-conjugated, paclitaxel-loaded, polycaprolactone (PCL)-PEG worm-like nanocrystal micelles [88]. The formulation remained stable in circulation in the TME and rapidly targeted and entered HER2-overexpressing tumor cells while sparing the normal tissue. In mice models, the micelle formulation resulted in an increased tumor size reduction and prolonged survival compared to the free drug alone.

4.4. Dendrimers

Dendrimers consist of hyperbranched, three-dimensional polymers that are made of a central core, branches, and terminal functional groups attached to the branches [89]. Because of their many internal cavities, high customization, and good biocompatibility, they are useful for localized drug delivery [90]. Drugs can either be loaded into dendrimers by non-covalent or covalent interactions [89]. In non-covalent interactions the drug is wrapped inside the dendrimer and shielded from the body's metabolism process while covalent interactions involve the formation of a covalent bond between the drug and dendrimer which must be cleaved before the bound drug is released.

Human epidermal growth factor receptor 2 (HER2)-positive breast cancer cells show a higher expression of the *HER-2* gene, compared to normal adult tissue, making it an ideal target to localize breast cancer therapy. Researchers utilized this fact to deliver targeted therapy of trastuzumab and neratinib loaded in maleimide-Poly (ethylene) glycol-N-hydroxy succinimide-based dendrimers [91]. They found the dendrimers loaded with trastuzumab and neratinib were more selective and had higher antiproliferation activity compared to neratinib alone or neratinib-only loaded dendrimer (Table 3).

4.5. Nanoparticles

Researchers investigated Peptide 1(GEII peptide)-modified polylactic-co-glycolic acid (PLGA)/D-α-Tocopheryl polyethylene glycol 1000 succinate (TPGS) nanoparticles used to deliver salinomycin, a chemotherapy agent with poor aqueous solubility, to breast cancer cells [92]. GEII is a peptide that has high EGFR affinity; EGFR is commonly overexpressed on the surface of breast cancer cells making it a valuable target. PLGA and TPGS modifications allow the NP to be smaller and have improved drug encapsulation efficiency. The NPs were prepared using nanoprecipitation methods and they were found to have improved therapeutic efficacy, including a marked reduction in tumor volume in mice models at 30 days (Table 3).

Another way local delivery to breast cancer cells has been achieved with nanoparticles is targeting CD-44 receptors in cancer cells. Ghosh and coworkers developed mesoporous silica nanoparticles conjugated with hyaluronic acid loaded with the natural antioxidant curcumin [93]. The hyaluronic acid was used to bind with the CD-44 receptors on the breast cancer cells. In mice models, the nanohybrid formulation decreased tumor volume more than free curcumin due to the increased bioavailability and higher uptake into the tumor tissue.

Magnetic nanoparticles present another means of providing targeted drug delivery to local breast cancer tissue in the setting of a magnetic field. Zou and colleagues developed doxorubicin-loaded chitosan-coated mesoporous iron oxide-based magnetic nanoparticles [94]. This formulation demonstrated a concentration-dependent cell proliferation inhibitory action against breast cancer cells. Overall, the formulation had a high potential for breast cancer targeting under an alternating current magnetic field.

Table 3. Emerging innovations in localized polymeric liposomes, micelles, dendrimers, and nanocarriers targeting breast cancer.

Drug	Formulation	Key Advantages	Reference
Methotrexate and Doxorubicin	Conjugate methotrexate polyethylene glycol modified chitosan 2,3-dimethylmaleic anhydride (DMMA) polymeric micelles loaded with doxorubicin.	The micelles promoted accumulation of autophagosomes in tumor cells and also interfered with the degradation process of autophagic flux, ultimately leading to induced autophagic death of tumor cells.	[87]
Paclitaxel and Herceptin	Paclitaxel loaded Herceptin-conjugated nanocrystal micelles with PCL–PEG.	The formulation remained stable in circulation and the TME rapidly targeted and entered HER2-overexpressing tumor cells while sparing the normal tissue.	[88]
Doxorubicin	Liposomal doxorubicin prepared using thin film hydration with saturated and unsaturated lipids. Aptamer-A6 was used to target HER2-positive breast cancer cells.	Doxorubicin-loaded liposomes were more effective at killing cancer cells than free doxorubicin. The aptamer-labelled liposome formulation had increased uptake into cancer cells.	[79]
Docetaxel	VEGF antibody functionalized PEGylated sensitive liposomes containing docetaxel.	Improved cellular uptake and enhanced drug release profile under acidic microenvironments.	[80]
Tamoxifen	Liposome-PEG-PEI complex carrier loaded with tamoxifen.	Increasing toxicity in breast cancer cells compared to tamoxifen alone and administration by the transdermal route inhibited 86% of tumor growth in mice models.	[81]
Trastuzumab and Neratinib	Trastuzumab and neratinib, loaded maleimide-Poly (ethylene) glycol-N-hydroxysuccinimide dendrimers.	Increased breast cancer tissue selectivity, cytotoxicity, and increased cellular uptake.	[91]
Salinomycin	GE11-modified polylactic-*co*-glycolic acid and D-α-tocopheryl polyethylene glycol 1000 succinate salinomycin-containing nanoparticles.	Enhanced therapeutic efficacy, particularly in breast cancer cells that expressed EGFR.	[92]
Curcumin	Mesoporous silica nanoparticle conjugated with hyaluronic acid.	By conjugating hyaluronic acid to the surface of the polymer nanoparticle, they were able to achieve targeted delivery to cancer cells by binding with CD-44 receptors in cancer cells.	[93]
Doxorubicin	Doxorubicin-loaded chitosan-coated mesoporous iron oxide-based magnetic nanoparticles.	High potential for breast cancer targeting under an alternating current magnetic field.	[94]

4.6. Transdermal Patch

Transdermal drug delivery systems include microneedles, adhesive patches, creams, and gels [95]. They offer a steady and controlled rate of absorption into local tissue and the blood stream. Adhesive transdermal patches are generally either reservoir- or matrix-based in design. For reservoir-type patches the rate of drug release is controlled by the rate-limiting membrane where in matrix-based patches, the rate of drug release is dependent on the polymer matrix the drug is dispersed in [96].

Microneedles are a minimally invasive topical drug delivery system that relies on microsized needles penetrating the skin to deliver drug molecules through the dermal layers into systemic circulation. The needles are generally of a height less than 1000 µm [76] and because of the small size, the microneedles can rapidly penetrate the epidermis and dermis layers of the skin with negligible pain. There are different kinds of microneedles including biodegradable, hollow, drug-coated, and solid; and the type of microneedle influences the drug release behaviour that occurs [97]. Key advantages of microneedles compared to other drug delivery systems include bypassing first pass metabolism, minimized systemic side effects, and localized drug delivery. Compared to regular needles, they are convenient, cause less fear, and may be easily self-administered [98]. Topical semisolids like creams and gels are another method for delivering drugs locally, they are advantageous due to their ease of use and patient comfortability, however they are limited by dosing inaccuracy, lack of adhesion, and effective skin penetration [99].

Transdermal drug delivery is an innovative way of transporting chemotherapy agents with the benefit of being non-invasive, bypassing first-pass metabolism, reducing gastric discomfort, and minimizing systemic toxicity [100]. However, not all drugs are ideal for this delivery route; for example, doxorubicin is hydrophilic with a high molecular weight making effective skin penetration challenging. Abu-Huwaij et al. addressed this issue by creating a transdermal patch with carbopol 971 (CP) and polyvinyl alcohol (PVA) loaded with starch-coated iron oxide nanoparticles conjugated to doxorubicin [100]. The patch maintained consistent thickness, weight, and 97% doxorubicin loading. Compared to free doxorubicin patches, the NP patch displayed a fivefold increase in drug penetration into systemic circulation (Table 4).

Table 4. Emerging innovations in localized polymeric transdermal patches targeting breast cancer.

Drug	Formulation	Key Advantages	Reference
Doxorubicin	Transdermal patch with carbopol 971 (CP) and polyvinyl alcohol (PVA) loaded with starch-coated iron oxide nanoparticles conjugated to doxorubicin	Consistent thickness, weight, and 97% doxorubicin loading. Compared to free doxorubicin patches, the NP patch displayed a fivefold increase in drug penetration.	[100]
Resveratrol	Transdermal patches comprised of HPMC E15LV, HPMC-K4M, and PVP K30, glycerol, and capryol 90.	Significantly reduced tumor volume with lower systemic concentrations, compared to the oral formulation.	[101]
Tamoxifen	Multilayer polymer films made of alginate and chitosan, loaded with tamoxifen.	Effective at releasing tamoxifen in a sustained release manner and the release rate could be manipulated by the number of deposited bilayers.	[102]
Paclitaxel	Electrospun patch made of PCL and PVA nanofibers, loaded with paclitaxel.	The optimized fiber has an average diameter of 547 bm and 85% entrapment. The paclitaxel was released from the formulation in a sustained manner over 17 days.	[103]

Resveratrol is a phytoestrogen that may have antiproliferative effects in breast cancer, but it is limited by its low bioavailability and short half-life. To overcome these challenges, Gadag et al. created resveratrol transdermal patches using drug release controlling polymers, namely hydroxypropyl methylcellulose (HPMC) E15LV, HPMC-K4M, and polyvinyl pyrrolidone (PVP) K30, along with glycerol and capryol 90 as penetration enhancer and plasticizer [101]. When applied to the breast of female rats with breast cancer, the patch

significantly reduced the tumor volume with lower systemic concentrations, compared to the oral formulation.

Another avenue for preparing transdermal patches for breast cancer drug delivery is multilayer films. One research group developed multilayer polymer films made of alginate and chitosan, loaded with tamoxifen, which could then potentially be employed as a patch or injected [102]. The film was effective at releasing tamoxifen in a sustained release manner and the release rate could be manipulated by the number of deposited bilayers.

Furthermore, Rehman et al., investigated the use of electrospinning to formulate a patch made of PCL and PVA nanofibers, loaded with paclitaxel [103]. The optimized fiber has an average diameter of 547 nm and 85% entrapment. The paclitaxel was released from the formulation in a sustained manner over 17 days.

4.7. Microneedles

Bhatnagar and colleagues developed polyvinyl pyrrolidone (PVP) and a polyvinyl alcohol (PVA) composite of dissolvable microneedles containing two anticancer drugs, namely doxorubicin and docetaxel, using a micromolding technique [104]. The microneedles were successfully loaded with 533 ± 65 µg and 227 ± 23 µg of doxorubicin and docetaxel, respectively. In mouse models, the microneedles dissolved within one hour of insertion. Compared to intertumoral injections, the doxorubicin and docetaxel microneedles demonstrated greater survival after 16 days with reduced toxicity. One challenge of this formulation is the ability to load the required dose of the drug without compromising the microneedle formulation and strength, although the authors hypothesized that a microdosing strategy or increasing patch size could be used to resolve this problem (Table 5).

Table 5. Emerging innovations in localized polymeric microneedles targeting breast cancer.

Drug	Formulation	Key Advantages	Reference
Doxorubicin and docetaxel	PVP- and PVA-dissolvable microneedles loaded with doxorubicin and docetaxel.	Effective drug permeation through skin in mice models. Compared with intratumoral injection, the microneedle formulation has greater reductions in tumor volume and weight.	[104]
Gemcitabine	3D-printed PEGDA microneedles loaded with gemcitabine.	After insertion into porcine skin, 100% of gemcitabine was released after one hour.	[105]
Ribociclib	HA, PVA, PVP microneedles containing ultradeformable transfersomes loaded with ribociclib.	The drug concentration remained within the therapeutic window for up to 48 h and produced an 8.3-fold reduction of ribociclib concentration in vital organs, decreasing unwanted toxicities.	[106]
ERD308 and Palbociclib	Microneedles loaded with pH-sensitive micelles made up of monoarylated poly (ethylene glycol) (MPEG)-poly (β-amino ester).	Rapid demicellization and restricted drug delivery, with 87% of the drug located in the tumor site.	[107]
CRISPR/Cas9 gene editing plasmids	Soluble microneedle formulation made of oligo-hyaluronic acid.	The microneedles had the ability to be trimmed and bent without damaging the tips, thus better fitting various tumor shape for improved penetration.	[108]

In another study, researchers investigated gemcitabine-loaded polyethylene glycol diacrylate (PEGDA) microneedles for localized drug delivery in inflammatory breast cancer [105]. Given the toxicities associated with gemcitabine given parenteral, along with its short half-life of 15 to 20 min, microneedle formulation offers a unique way to improve gemcitabine drug delivery. The microneedles were made using 3D printing and had 100% drug release after the first hour post insertion in porcine skin.

To minimize side effects associated with ribociclib, investigators created a solvent-free hyaluronic acid (HA), polyvinyl alcohol (PVA), and polyvinyl pyrrolidone (PVP) microneedles containing ultra-deformable transfersomes loaded with ribociclib for hormone receptor-positive and HER2-negative breast cancer [106]. In vitro and in vivo studies showed the drug delivery system provided drug concentration within the therapeutic window for up to 48 h, which could lead to reduced dosing frequency and lower doses. The formulation also produced an 8.3-fold reduction of ribociclib concentration in vital organs, decreasing unwanted toxicities.

Proteolysis-targeting chimeras (PROTACs) is an upcoming technique to degrade disease-related proteins, like the estrogen receptor in breast cancer. To deliver PROTACs locally to diseased tissue, Cheng and co-investigators, developed PROTAC, specifically ERα-degrading PROTAC ERD308, and Palbociclib-loaded microneedle patches for estrogen receptor breast cancer [107]. The PROTAC was encapsulated in pH-sensitive micelles made up of monoarylated poly (ethylene glycol) (MPEG)-poly (β-amino ester), which allowed for sustained drug release. In the ER-positive breast cancer model, the micelle displayed rapid demicellization in the mildly acidic tumor environment. The formulation led to 4 days of sustained drug release with deep tumor penetration and more restricted drug distribution than intravenous drug delivery, with 87% of the drug to the tumor. In mice tumor models, the formulation led to 80% of tumor reduction. Another advantage of the quick demicellization of this formulation is that it reduces the risk of nanomaterial-induced endothelial leakiness (NanoEL), a consequence associated with the microneedles reaching and disrupting the blood vessels in the dermis.

Gene therapy is an upcoming breast cancer treatment approach that involves the introduction of genetic material into cancer cells to alter gene expression and cause cell death and slowed cell growth. Zhang and researchers created a soluble microneedle formulation made of oligo-hyaluronic acid [108]. The microneedles contained nanoparticles with *CRISPR/Cas9* gene editing plasmids to block F-Box protein 44 (FBXO44), delivered alongside hydrophobic photosensitizers. Inhibition of FBXO44 leads to double stranded DNA breakage in cancer cells and thus may be a useful target for triple negative breast cancer. The addition of the photodynamic therapy was used to promote lysosomal escape of the nanocarriers from the delivery system. The researchers found that compared to conventional pure hyaluronic acid-based microneedles, the microneedles had the ability to be trimmed and bent without damaging the tips, thus better fitting various tumor shapes for better penetration.

4.8. Topical Liquid and Semi Solid Drug Products

Due to tamoxifen's poor bioavailability and poor aqueous solubility, it is favourable to find alternative routes of delivery outside of the oral route. To deliver tamoxifen topically, researchers formulated phospholipid-based mixed micelles loaded with tamoxifen delivered in a semisolid formulation made of various amounts of soya lecithin, polysorbate 90, Tween 80, sodium/chloride/dextrose, and water [109]. In in vitro studies, the topical formulation offered controlled release of the drug and had increased cytotoxicity compared to the naïve drug alone. The formulation also enhanced bioavailability in epidermis and dermis skin layers by fivefold and threefold, respectively. For histological studies, the

formulation maintained the integrity of the skin. Specifically, compared to normal saline, conventional formulation, and the mixed micelles, there were no marked changes in the animal skin (Table 6).

Table 6. Emerging innovations in localized polymeric topical liquid and semi solid drug products targeting breast cancer.

Drug	Formulation	Key Advantages	Reference
Tamoxifen	Phospholipid-based mixed micelles loaded with tamoxifen delivered in a semisolid formulation made of various amounts of soya lecithin, polysorbate 90, Tween 80, sodium/chloride/dextrose, and water.	Compared to the naïve drug, the formulation resulted in controlled drug release, amplified skin penetration, and increased cytotoxicity.	[109]
Tetrahydrocurcumin	Nanostructure lipid carriers loaded with tetrahydrocurcumin coated in chitosan.	Compared to the unencapsulated tetrahydrocurcumin, the chitosan-coated tetrahydrocurcumin nanostructure lipid carriers had enhanced in vitro skin permeation, cell uptake, and cytotoxicity in breast cancer cells.	[110]
Raloxifene	Reservoir-based polymeric gel loaded with raloxifene using the two polymers, Eudragit®S100, and colloidal silicon dioxide.	In vitro results demonstrated adequate drug release to allow for once weekly dosing.	[111]
Exemestane	Liquid crystalline gel formulations exemestane, using glyceryl monooleate, Tween 80, and Pluronic® F127.	The formulation had a high encapsulation efficiency, sustained drug release and no notable topical adverse drug reactions.	[112]

To deliver tetrahydrocurcumin transdermally, the active metabolite of curcumin, which is an antioxidant with anticancer properties, one research group prepared nanostructured lipid carriers coated in chitosan [110]. The chitosan was used to improve skin deposition and permeability. Compared to the unencapsulated tetrahydrocurcumin, the chitosan-coated tetrahydrocurcumin nanostructured lipid carriers had enhanced in vitro skin permeation, cell uptake, and cytotoxicity in breast cancer cells.

To overcome the challenges of daily dosing and side effects of the orally delivered raloxifene, Vora et al. investigated a weekly administered transdermal delivery system [111]. Specifically, they developed a reservoir-based polymeric gel loaded with raloxifene. Two polymers were used to prepare the gels: Eudragit®S100 and colloidal silicon dioxide. Both polymers were able to deliver target concentrations of the drug over 7 days during in vitro tests.

Musa et al., developed a liquid crystalline gel formulation loaded with the breast cancer agent exemestane, by the phase separation coacervation method, using glyceryl monooleate, Tween 80, and Pluronic® F127 [112]. The formulation had an encapsulation efficiency of 85–92% and vesicle size of 119.9–466.2 nm. Even with low exemestane concentrations (12.5 and 25 μg/mL), the formulation was able to induce cancer cell death in in vitro effectiveness studies. The formulation led to sustained drug release and did not result in any visible adverse reactions in rat models.

5. Possible Next Steps and Recommendations

As evident by the numerous examples of innovative localized drug delivery formulations being investigated for breast cancer, breast cancer drug delivery has made a lot of progress. Although several novel localized polymeric drug delivery systems have been developed, none have advanced beyond the research phase or been integrated into breast cancer treatment guidelines. This accentuates the need for continued research and efforts to overcome the existing barriers. One issue with localized breast cancer therapies is the ability to target metastatic sites, along with the ability to accurately target the breast cancer tissue [113]. One solution to this would be administering low-dose systemic chemotherapy in combination with the local therapy or the local therapy may be designed to deliver sufficient concentrations to metastasis, especially if it is sustained release. To help improve precision to tumoral drug delivery, imaging modalities could be an option [113]. Another issue facing localized breast cancer therapies, specifically topical products like patches or creams, is the concern of cytotoxicity. For drug delivery systems that are self-administered, like patches or creams, there is the risk of contamination with non-target tissue, other persons, or improper disposal. A key solution to this would be the need for proper education and counselling on use and disposal of the medication. One area of breast cancer drug delivery that should be further explored is drug therapy release from breast implants. Given that mammaplasty is commonly performed during breast cancer management, breast implants represent a unique opportunity for localized drug delivery. Drug-eluting implants could provide sustained and targeted release of therapeutic agents at the site of disease or reconstruction, potentially reducing the need for additional procedures, hospital visits, and systemic drug exposure. This strategy warrants further investigation as a novel approach for adjuvant breast cancer therapy. Studies have been done to investigate implants that contain drug to prevent post-operative complications, but it could be considered for applications in adjuvant chemotherapy (Figure 3) [114]. Another restriction to the current literature is the utilization of mice models and the differences that exist between mice models and human breast cancer. For example, differences exist between mammary gland development, tumor origin, and hormone receptor status. Utilization of alternative models including larger animal models would be beneficial [115]. More broadly, there are also general barriers to the production of localized polymeric drug delivery systems, including large scale production of them. The lab process of making the technologies is not often easily scaled to larger industrial settings, along with cost of materials and equipment. Additionally, all studies identified during the literature search were pre-clinical, highlighting the barrier of advancing to clinical phases, despite some having impressive findings, due to issues like regulatory approval, funding, and ethical barriers. Specifically, there remain significant barriers to translating pre-clinical studies in animal and in vitro models into patient-centered clinical trial outcomes, such as overall survival [116,117]. Developing more innovative preclinical models that more closely replicate human disease while incorporating clinically relevant endpoints may improve the inclusion of promising developmental therapies into clinical trials. The clinical development and implementation of these agents are further challenged by the complexity and time commitment of clinical trials, and ethical considerations related to their safety and efficacy. A more harmonized approach to research and development of oncology drugs, with pooled resources and global collaboration, may assist in overcoming some of the many barriers to advancements in oncology drug development. Lastly, personalized medicine is an attractive approach for delivery of breast cancer treatment. Specifically utilizing genetic testing and acknowledging the diversity of breast cancer to deliver patient specific treatment regimens that exploit localized therapies to limit side effects [118].

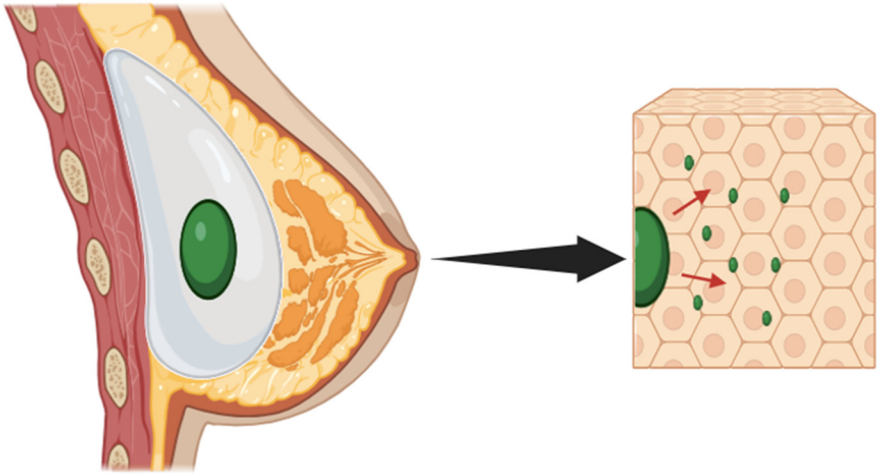

Figure 3. Example of sustained drug release from drug loaded breast implant.

6. Concluding Remarks

Breast cancer is a prevalent illness that many die from each year despite the availability of various drug therapies and surgical regimens. As such, there is a need for continuous innovative treatment strategy development for breast cancer management. Localized drug delivery using polymer formulations is one approach for delivering the drug while minimizing drug exposure and systemic side effects. Utilizing polymers in these formulations offers a unique way to use their attractive and varying properties including biodegradability and sustained release mechanisms. Various formulations, like hydrogels, patches, and injections are being developed and the unique breast cancer tumor microenvironment can be exploited to further increase successful and safe drug therapy. Future research should build on these innovations with the aim of reducing side effects, increasing drug efficacy, and improving health outcomes in this population.

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Abbreviations

3D	Three-dimensional
Aptamers	Apt
BCS	Breast-conserving surgery
BRCA	Breast cancer gene
CAF	Cancer-associated fibroblasts

CDK	Cyclin-dependent kinases
CMC	Critical micellar concentration
CP	Carbopol 971
CS	Chitosan
DMMA	Dimethylmaleic anhydride
DNA	Deoxyribonucleic acid
EBRT	External beam radiotherapy
EGFR	Epidermal growth factor receptor
ER	Estrogen receptors
FBXO44	F-Box protein 44
HA	Hyaluronic acid
HER2	Human epidermal growth factor receptor 2
HPMC	Hydroxypropyl methylcellulose
IrAEs	Immune-related adverse effects
MPEG	Monoarylated poly (ethylene glycol)
mTOR	Mammalian target of rapamycin
NanoEL	Nanomaterial-induced endothelial leakiness
PARPs	Poly (ADP-ribose) polymerases
PCL	Poly-ε-Caprolactone
PCPP	Poly (bis (carboxyphenoxy) phosphazene)
PD-1	Programmed cell death protein-1
PD-L1	Programmed death-ligand 1
PDLLA	Poly-D,L-lactide
PDMS	Poly-di-methyl-siloxane
PEG	Polyethylene glycol
PEGDA	Polyethylene glycol diacrylate
PEI	Poly (ethylene imine)
PI3K	Phosphoinositide 3-kinase
PLA	Poly (d,l-lactic acid)
PLGA	Poly-lactic-co-glycolic acid
PNIAAm-co-IA	Poly (N-isopropylacrylamide-co-itaconic acid)
PR	Progesterone receptors
PROTACs	Proteolysis-targeting chimeras
PVA	Polyvinyl alcohol
PVP	Polyvinyl pyrrolidone
RB	Retinoblastoma-associated
TME	Tumor microenvironment
TP53	Tumor protein 53
TPGS	D- α-Tocopheryl polyethylene glycol 1000 succinate
TSP-1	Thrombospondin-1
VEGF-A	Vascular endothelial growth factor-A

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