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Stimuli-responsive drug delivery system for breast cancer treatment

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Abstract. In the annals of cancer treatment within the domain of nanomedicine, the utilization of stimulus-response drug delivery systems has emerged as a focal point of considerable significance. While a multitude of diverse methodologies are presently employed for the treatment of tumors, the preeminent and most efficacious approach, particularly in the context of intricate scenarios, pertains to the targeted administration of therapeutic and diagnostic nanoparticles into the tumor milieu. These nanoparticles exhibit the inherent potential to acclimatize to the nuanced microenvironment of the tumor, thereby surmounting the challenges posed by tumor heterogeneity. The stimuli-responsive attributes inherent to nanoscale particles can broadly be delineated into two distinct categories: endogenous and exogenous, with a minority manifesting characteristics of both classifications. This scientific review provides an overview of the discourse surrounding exogenous drug delivery systems, which leverage ultrasound and magnetic fields as responsive stimuli, alongside endogenous drug delivery systems employing pH variations and enzymatic cues as triggering mechanisms. The findings of this review emphasize the significance of stimuli-responsive drug delivery systems as a promising strategy to enhance the specificity and efficacy within the sphere of breast cancer treatment. Finally, the review concludes with a discussion on the future directions and potential clinical applications of these systems.

Keywords: Breast Cancer, Stimuli-responsive, Smart Delivery Systems, Drug Delivery.

1. Introduction

Breast cancer is a prevalent and debilitating disease that strikes millions of individuals worldwide. The World Health Organization reported an incidence of more than 2.3 million cases each year [1]. Despite the modern advancements made in medical research and treatments of breast cancer, the overall mortality and morbidity are still high and remain a significant public health concern. Recent treatment

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strategies include several options depending on the severity of the cancer: chemotherapy, radiation therapy and surgical resection. Among all, chemotherapy is the most frequently used systemic treatment due to its capacity to suppress the proliferation of cancer cells [2]. Nevertheless, having the therapeutic agents utilized in chemotherapy to selectively target cancer cells without influencing healthy cells pose a great challenge. This has undesirable consequences such as hair loss, fatigue, appetite loss, nausea and vomiting, and is associated with a high risk of damage to various organs [3].

With the development of nanoscale drug delivery, controllable and specified therapeutic releases based on stimuli-responsive biomaterials have been exploited to surmount the constraints mentioned above. The stimuli-based drug delivery system involves the materials that possess the ability to respond to particular triggers, enabling the controlled release of pharmaceutical substances at precise anatomical sites within the organism. In particular, approaches involving drug release with exogenous stimulation (including magnetic field, ultrasound, and light) and endogenous stimulation (including pH and enzyme) have attracted considerable attention recently. This review discusses the above-mentioned stimuli in responsive drug delivery for breast cancer treatment. Furthermore, this study provides insight into the current challenges and future directions.

2. Exogenous Stimuli-Responsive Drug Delivery System

2.1. Ultrasound-responsive Drug Delivery Systems(URDDS)

2.1.1. Mechanisms of URDDS

Ultrasound-responsive drug delivery systems possess diverse applications in the sector of cancer treatment as a result of their capacity to selectively release medical payloads at tumor sites in response to externally transmitted ultrasounds. The propagation of ultrasound waves in the body triggers physical phenomenon such as pressure variation, acoustic streaming, hyperthermia and cavitation [4]. Hence, these physical alterations could be utilized as stimuli for ultrasound-mediated drug release. The characteristics of URDDS hold great potential for enhancing targeting precision, facilitating deep penetration into tumor tissues, and mitigating adverse effects by modulating the frequency of ultrasound within a defined range [5].

2.1.2. Ultrasound-responsive Nanocarrier

Nanocarriers refer to encapsulating particles characterized by nanoscale dimensions that are specifically engineered to facilitate the transportation and delivery of therapeutic agents to targeted sites within the body. Due to their diminutive dimensions, a solitary cell is capable of up taking one or more nanocarriers for the purpose of transporting the drug payload [4].

In particular, the delivery of therapeutic agents using nanocarriers that respond to ultrasound for cancer treatment is mainly accomplished through the aid of micro/nanobubbles. These bubbles are comprised of a gas core encased by a stabilizing shell of nanocarriers. Additionally, the major constituents consist of the cargo (holds gene, drug etc.) and surface modification ligands, which is visually demonstrated by Figure 1.

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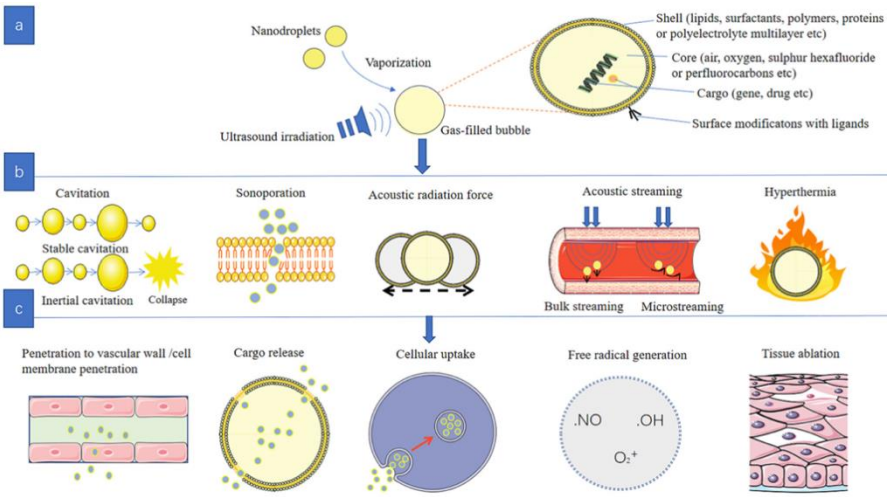

Figure 1. (a): The provided diagram illustrates the structural composition of the bubble. (b): The therapeutic mechanisms underlying the use of bubble-assisted ultrasound. (c): Biological consequences of bubble-assisted ultrasonography [6].

They possess the capability to enhance the targeting of therapeutic medicines due to their distinctive interaction with ultrasound. The utilization of targeted ultrasound stimulation elicits a sequence of dynamic phenomena, including expansion, contraction, oscillation, and forceful collapse of injected micro/nanobubbles, this phenomenon is known as cavitation [7]. The presence of gas within drug delivery vehicles facilitates the generation of acoustic activity, hence reducing the cavitation threshold. This heightened sensitivity to ultrasound enables local activation, release, and distribution of drugs by the carriers [8].

2.1.3. Ultrasound-responsive Nano-particles for Breast Cancer Treatment

This section will analyze the application of ultrasound-responsive micro and nanoparticles of various types in preliminary studies with regard to breast cancer treatments. The preliminary research findings have been succinctly summarized in Table 1.

Table 1. (Preclinical studies of ultrasound-responsive nanoparticles for treatment of breast cancer)

Nanoparticle	**Therapeutic**	**Effect**	**Reference**
Microbubble (RDG-MBs)	PTX	The ultrasonic trigger leads to enhanced drug accumulation in tumors targeted for (TNBC)	[9]
Liposome	Calcein (Model Drug)	Increase albumin uptake in tumor cells	[10]
Polymeric micelle	Paclitaxel	The application of ultrasonic stimuli has been shown to enhance the uptake of drugs and inhibit cellular proliferation in breast cancer tumours.	[11]

[9] devised a novel approach involving the creation of a dual-modal RGD-lipid microbubble (RDG-MBs) that encapsulates the chemotherapeutic agent PTX. This technique is further enhanced by applying the technique of ultrasonic targeted microbubble destruction (UTMD). Additionally, the integration of sulfur hexafluoride is employed to enhance the resolution and sensitivity of ultrasound images. The findings of this study indicate that the RDG-MBs combined with UTMD exhibited enhanced

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internalization by Triple-negative breast cancer (TNBC) cells, leading to a notable enhancement of the inhibitory effect on TNBC cells in an in vitro setting.

Using a different approach, [10] investigated the efficacy of pegylated liposomes conjugated to human serum albumin as an approach of delivering the therapeutic agent calcein to breast cancer cells, employing another novel methodology. Liposomes are lipid-based nanocarriers characterized by a spherical shape and composed of amphipathic layers. They have been extensively investigated due to their advantageous attributes, including low toxicity, high efficacy, and biodegradability [12]. According to the research conducted by [10], it was observed that the uptake of calcein by two breast cancer cell lines, namely MDA-MB-231 and MCF-7, exhibited a statistically significant increase subsequent to exposure to ultrasound. The authors also emphasize the utilization of targeted liposomal formulation in conjunction with ultrasound triggers as a means to achieve a safer, more effective, and site-specific targeting URDDS.

In comparison with liposomes, micelles are characterized by their smaller size as nanocarriers. This characteristic enables micelles to accumulate pharmaceuticals more effectively at the desired location due to the higher permeability and retention effect. To provide further clarification, micelles are composed of surfactants wherein the hydrophilic tails are oriented towards the exterior and the hydrophobic heads are oriented towards the interior. This structural arrangement possesses resemblance to certain characteristics observed in biological transport systems and enables micelles to properly protect insoluble hydrophobic drugs [13]. A preliminary investigation conducted by [11] implements polymeric micelles containing encapsulated paclitaxel for the treatment of a human breast cancer cell line. The experimental findings indicate that their usage of encapsulated paclitaxel in URSDDS resulted in an important improvement of drug uptake, surpassing a 20-fold increase. Furthermore, the stimuli of ultrasonic signals led to a substantial inhibition of cellular proliferation, with a reduction of nearly 90%. The research conducted by [11] provides clarification on the notable cytotoxic effects caused by micellar-encapsulated paclitaxel, specifically when exposed to ultrasound. This finding holds promise for minimizing systemic toxicity while boosting the potential of targeting tumors.

2.2. Magnetic-responsive Drug Delivery Systems

2.2.1. Mechanism of Magnetic-responsive Nano-particles

As a typical external stimulus, magnetic stimulation-responsive nanoparticles are commonly used in magnetic resonance imaging (MRI) and have the ability to penetrate human tissues [14]. The interaction between clusters of magnetic nanoparticles is mainly due to dipole-dipole interaction, which makes magnetic anisotropy, structure, and particle size the main factors affecting their performance. Because of they are extremely small in size (with an average diameter ranging from 1-100nm) and solvent affinity, magnetic nanoparticles can form suspensions in water [15]. However, the properties of high permeability of magnetic-responsive nanoparticles originate from their characteristics of super-paramagnetism.

Unlike bulk magnetic materials, nanoscale particles made from the same material only form a single magnetic domain due to their small size, which means that magnetic ordering does not occur within a certain region [16]. Similarly, in cases where magnetic reversal is required, bulk magnetic materials require a higher Curie temperature (such as iron, which requires a temperature of 770 degrees Celsius), while nanoscale magnetic particles only require room temperature [17]. This also demonstrates the existence of super-paramagnetism, which makes magnetic responsive nanoparticles highly sensitive to external magnetic fields, thus completely different from macroscopic magnets. In an experimental report co-authored by Ji Ma and Kezheng Chen, they discovered a unique phenomenon of super-paramagnetism in submillimeter-sized single crystal magnetite that differs from any known ferromagnetic behavior [18]. Figure 2(a) presents the XRD spectrum of the Fe3O4 porous single crystals (PSCS) before and after calcination, which was obtained using a powder X-ray diffractometer. The figure reveals several sharp and intense peaks that are closely related to the cubic structure of Fe3O4. The slope in Figure 2(b) demonstrates a lattice strain value (Δd/d) of -1.21×10-2 in the Fe3O4 PSCS,

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which is approximately two orders of magnitude larger than other structures of Fe3O4. Due to the effect of super-paramagnetism, the strength of the super-exchange interaction between individual iron ions is significantly influenced.

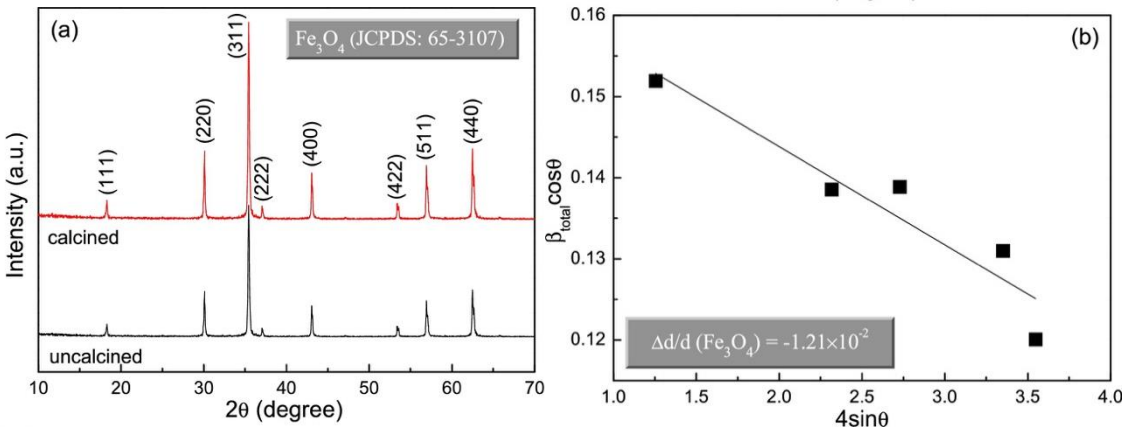

Figure 2. (a) Fe3O4 PSCS before/ after calcination shown by XRD patterns; (b) Linear adaptation of the XRD peak of uncalcinated Fe3O4 PSCS was done using a Williamson-Hall relationship [19].

2.2.2. Application of Magnetic-responsive Nano-particles in Breast Cancer Treatment

As previously mentioned, medicine provides various treatment options for breast cancer. To be more specific, breast cancer is classified into invasive and rare types, with HR+ and HER2- being the most common. Biopsy and imaging examinations are crucial for diagnosis and treatment. Approximately 80% of patients are eligible for surgical treatment, while conservative treatment is available for histologically rare types [20]. The primary goal for drug delivery to breast cancer tissues is to maximize treatment effectiveness while minimizing drug delivery to non-target sites. Magnetic stimulation-responsive nanoparticles can help achieve this objective. Due to the lack of rejection response from biological tissues towards magnetic fields, the magnetic nanoparticles can interact with an external magnetic field to deliver drugs maximally to specific human tissues [21].

The mechanism of superparamagnetism of magnetic-resposive nanoparticles lays the foundation for two of their major clinical uses in breast cancer treatment: #1 the magnetic hyperthermia drug releasing mechanism driven by superparamagnetic nanoparticles (SPMNPS) and #2 drug targeting mechanism guides by magnetic field [22]. Due to the utilization of these biotechnologies, magnetic stimulation-responsive nanoparticles (MNPS) have made significant advances in cancer imaging and treatment.

Magnetic hyperthermia is a widely used clinical approach for treating tumor lesions [23]. It involves using MNPs to generate targeted nanoscale heating effects on tumors by applying an alternating magnetic field (AMF), which results in localized induction heating. This method offers advantages such as strong penetration, minimal human immune response, and precise targeting since they are small in size to reach most of the human body tissues [24]. To achieve the desired effect, it is important for MNPs to have a high specific absorption rate (SAR) while maintaining a small volume to minimize side effects during clinical treatment [25].

$$SAR = \frac{c\Delta T}{\Delta t} \quad (1)$$

The specific absorption rate (SAR) can be calculated in the equation (1) above, where Δt records the change in time while ΔT records the change in temperature and c stands for the specific heat capacity [26].

Although there are many types of magnetic responsive nanoparticles, currently the most suitable MNPs for magnetic hyperthermia are primarily composed of iron oxide nanoparticles. By utilizing ion oxide nanoparticles that accumulate selectively within breast tumor cells, this innovative approach allows for precise targeting. When subjected to an alternating magnetic field, these nanoparticles

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generate localized heat, effectively damaging or eliminating cancer cells while minimizing harm to surrounding healthy tissue [27]. In research leads by [25], he and his team studied both the advantages and disadvantages of spherical and cubic iron oxide particles in terms of heat transfer, and concluded that cubic particles have a higher heating efficiency compared to spherical nanoparticles. Figure (2) shows a comparison of the SAR data for two nanoparticles of the same size (20nm) but different shapes: spherical and cubic. Under the same experimental conditions, the data shows that the SAR value of the cubic nanoparticles is nearly 20% higher than that of the spherical nanoparticles [25].

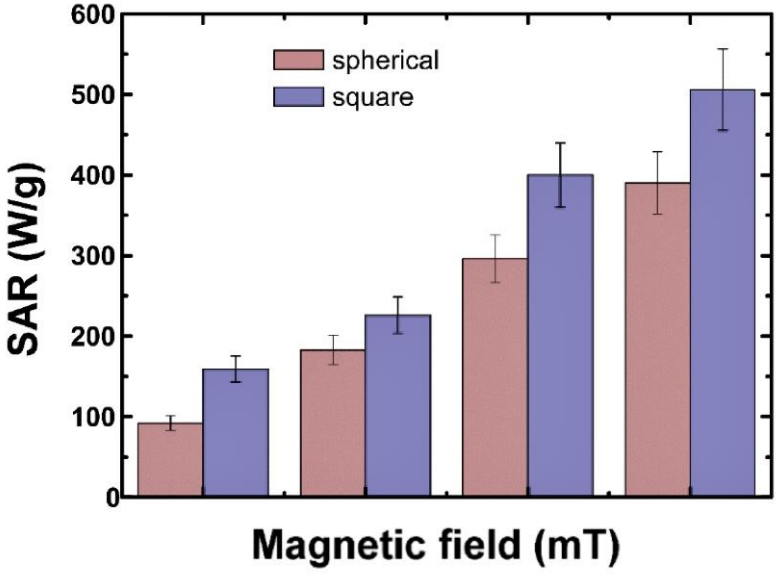

Figure 3. Comparison of SAR data between two types of iron oxide nanoparticles with similar composition but different shapes [25].

According to research, it has been demonstrated that cubic-shaped iron oxide nanoparticles exhibit superior magnetic heating efficiency, making them a significant advancement in the field of magnetic hyperthermia for cancer treatment [28]. These highly targeted and thermally conductive iron oxide nanoparticles can specifically heat tumor tissue through magnetic hyperthermia, effectively killing breast cancer cells and preventing the spread of cancer cells from the source [27].

3. Endogenous Stimuli-Responsive Drug Delivery System

In addition to exogenous stimuli, endogenous stimuli are more often targeted by researchers targeting drug delivery systems. To date, researchers have successfully devised numerous nano drug carriers that facilitate prolonged release of drugs. These nanoparticles release drugs in response to various endogenous stimuli, such as changes in pH, enzymes, PDA, ROS, temperature or two or more combinations of them.

3.1. PH-responsive Drug Delivery System

3.1.1. Mechanism of pH-responsive Drug Delivery System

pH-responsive nanoparticles are currently one of the most popular study domains. This is mainly owing to the fact that the pH of the environment near each tissue in the human body changes, for example, the pH of the stomach is approximately 1, but the pH of surrounding tissues closer to the stomach increases as they proceed away from the stomach [29]. In normal human blood vessels, the pH is usually around 7.2 to 7.4, but around tumor cells, the pH appears weakly acidic (with a pH of around 5.5 to 6.0). Based on the characteristics of this difference between the normal cells and the pathological cells, researchers

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have designed many nano-carriers such as liposomes, high molecular polymers, hydrogels, etc. They can be hydrolyzed or swelled in a slightly acidic environment to achieve the targeted drug release effect.

3.1.2. pH-responsive Drug Delivery System for triple- negative breast cancer

As one of the most difficult types of breast cancer to cure, triple negative breast cancer has always been a difficulty that drug developers are trying to overcome. However, researchers have created a novel course of treatment using pH-responsive targeted drug delivery systems. As early as [30] proposed using PCNDXR to treat triple- negative breast cancer, confirming the feasibility of using the PCN platform as a pH- responsive carrier [30]. Since then, the potential of pH-responsive drug delivery systems in the management of triple-negative breast cancer has been extensively studied by researchers. Furthermore, [31] designed an Artemisin (ART) dimer. This dimer can be carried on liposomes and hydrolyze under acidic conditions to release drugs. And the effect of this drug on triple negative breast cancer has been confirmed through experiments [31]. Chaudhari D and colleagues designed a pH sensitive liposome loaded with paclitaxel (PTX) and validated its heterogeneous release in acidic and medium environments, opening up an effective and safe formula [32]. [33] used pH responsive bonds to connect Doxorubicin (Dox) and aminoglutethimide (AGM), creating a family of pH responsive poly-L-glutamic acid (PGA) composite conjugates. The utilization of pH responsive bonds was then used to complete a significant amount of drug production.

In addition, scientists are also attempting to improve drugs that target other cancers to meet the specificity of triple negative breast cancer. In 2016, there was an attempt to apply DNA damaging platinum-based compounds, which had been proven to have specific effects on cancer cells, to the treatment of TNBC [34]. In 2019, [35] used pH responsive degradable Zeolitic iminazole frameworks (ZIFs) loaded with DOX as a nanodrug delivery system and successfully managed to survive 80% of experimental mice after 40 days [33]. What is more, pH responsiveness can easily combine with other stimuli to form multi-responsive molecules. In a 2017 work, [36] and his research team synthesized a poly (AA-b-NIPAAm) copolymer (PAA-b-PNIPAAm). This copolymer is responsive to stimuli including temperature, pH, and enzymes. In 2021, a new type of targeted nanoultrasound contrast-enhanced nanobubbles was prepared, which can not only consciously accumulate in acidic tumor cells, but also be further treated by introducing photodynamic therapy through ultrasound contrast agents [37].

The above methods have been effective in killing cancer cells, but in clinical practice, their safety and efficiency still need to be confirmed.

3.2. Enzyme-responsive Drug Delivery System

3.2.1. Mechanism of Enzyme-responsive

Enzymes are another factor of great concern. Enzymatic-responsive materials are usually very beneficial, mainly because enzymes play a central role in cellular regulation and activity. The secretion of enzymes has precise spatial and temporal control, and the structural characteristics of enzymes make them highly specific to certain substrates. Therefore, in terms of accuracy, enzyme-responsive drug delivery system is more advantageous compared to other endogenous stimuli. Enzymatic reactive nano-carriers can protect drugs from degradation during transportation and selectively release drugs within tumors. Research has identified that compared to normal cells, multiple enzymes secrete more and have higher concentrations in tumor cells and tumor related cells, such as endothelial cells and macrophages.

3.2.2. Enzyme-responsive Drug Delivery System for Triple- negative Breast Cancer (TNBC)

TNBC lack the expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (Her 2) [38]so it is difficult to achieve the same targeted treatment as other breast cancers. But scientists still find some specific enzymes that can serve as target sites. Renoux B and colleagues prepared a method for selectively releasing the potential monomethylauristatin E in the tumor microenvironment of TNBC, targeting the extracellular vesicles of tumors β-Glucuronidase is a drug delivery system that responds to drug release. The therapeutic efficacy of this intervention has been

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demonstrated in experimental studies with mice [37]. [39] synthesized and characterized an enzyme responsive peptide (MSN-AP-FA-PEP-S-Sn) through physical and chemical techniques. In repeated experiments, this silica-based nanoparticle showed targeted diagnostic ability, which can effectively inhibit tumor growth and reduce liver and kidney toxicity. [40] also utilized higher concentrations of β-Glucuronidase prepared tubulin destabilizer prodrug 17a. This prodrug exhibits high selectivity towards cancer cells pretreated with β-glucuronidase and can promote the specific release of highly efficient but systemic toxic tubulin destabilizer. In mouse experiments, it has also been confirmed that this prodrug can maintain high efficacy of tubulin destabilizer without causing significant damage to organs.

4. Challenges and Future Directions

Overall, despite the substantial preclinical evidence supporting the potential of stimuli-responsive drug delivery systems for targeted modulation of therapeutic effects, there remains a paucity of clinical trials, particularly in the context of triple-negative breast cancer, a therapeutic domain that currently faces limited treatment alternatives. It is imperative to ensure the translation of in-vitro and in-vivo methodologies into clinical research, with a primary focus on the preservation of safety and adherence to ethical considerations.

4.1. Challenges and Future Directions of USRDDS

One of the primary concerns of the USRDDS pertains to the lowered drug encapsulation capacities presented by ultrasonic sensitive nanoparticles. More precisely, it has been observed that materials with higher loading performance tend to possess comparatively lower levels of responsiveness. Therefore, it is necessary to employ higher frequencies of ultrasound for the purpose of releasing drugs from said materials. It is important to note that this process may potentially result in the disturbance of adjacent tissues. The development of nanoparticles with high drug encapsulation capacities and the ability to be triggered by low ultrasonic energies might yield significant advantages. Moreover, it is imperative for ultrasound responsive nanoparticles to focus on the application of degradable materials in order to ensure both efficacy and the mitigation of any detrimental effects.

4.2. Challenges and Future Directions of Magnetic-responsive Nanoparticles

Magnetic hyperthermia could offer a minimally invasive and targeted therapeutic option, complementing traditional treatments like surgery, chemotherapy, and radiation. While further research and clinical trials are necessary to fully establish its efficacy and safety, magnetic hyperthermia represents a compelling avenue for advancing the treatment landscape for breast cancer patients.

4.3. Challenges and Future Directions of Endogenous Stimulus Responsive DDS

The advantage of endogenous stimulation over exogenous stimulation is that its stimulating factors are spontaneously generated by cancer cells and do not require additional human assistance, making it a less energy consuming and more convenient approach. Nevertheless, the intricate and dynamic internal microenvironment of the human body contributes to variations in physiological conditions between individuals, hence posing additional challenges for the targeted therapy of cancer cells by endogenous stimulus response drug delivery systems. The pH-responsive DDS mentioned above requires nano-carriers to be able to unload drugs in slightly acidic environments near cancer tissue, while also protecting drugs in neutral blood and strongly acidic digestive tract environments. This puts forward strict requirements for researchers of biomaterials. To develop enzyme-responsive drug delivery systems (DDS), it is imperative to conduct preliminary investigations on enzymes that exhibit a substantial concentration disparity between normal and cancer cells throughout cellular processes. Subsequently, efforts should be directed towards identifying responsive molecules for these enzymes and establishing their connection to nanocarriers. This is not only a high demand for material researchers, but also a high demand for tumor researchers. What is more, the endogenous stimuli in the body vary depending on the type of cancer and individual, and not all drugs can be used as a single carrier. This is

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the reason why most endogenous stimulation drug delivery systems are currently difficult to use in clinical practice, and it is a problem that scientific researchers need to solve.

5. Conclusion

The above content describes in detail the principle and current situation of two exogenous stimuli (ultrasound, magnetic field) and two endogenous stimuli (acid-base, enzyme) as drug response targets in targeted drug delivery systems for breast cancer treatment. This review provides a brief insight into the contributions made by scientists in these areas over the past decade. Although people have come a long way in developing new responsive nano-drug delivery systems. Yet, the findings in most laboratories are still far from clinical use. It is anticipated that this analysis will facilitate a rapid comprehension of the subject matter for readers, while also encouraging further investment by researchers to support the advancement and practical application of these studies.

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Xien Gu, Zimeng Li, and Aizhu Liu contributed equally to this work and should be considered as co-first author.

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