

Thermosensitive hydrogels as drug carriers for breast cancer treatment: a systematic review

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ABSTRACT

Thermo-sensitive hydrogel is a drug delivery system in breast cancer therapy, where the influence of environmental temperature changes will affect the characteristics of the polymer base. This study aimed to determine the effectiveness of polymers in thermo-sensitive hydrogel bases as drug carriers in breast cancer therapy and compared them with traditional intravenous drug release. This study used a systematic literature review (SLR) using selected reporting items for systematic review and meta-analysis guidelines (PRISMA) (P), based on predetermined inclusion criteria, namely English article, thermo-sensitive hydrogel, breast cancer, and original article. An initial database search yielded 618 articles, PubMed (241), Scopus (364), and the Directory of Open Access Journals (DOAJ) (36). To maintain the quality of the data studied in this article, researchers used inclusion and exclusion criteria, where the exclusion criteria used were non-English languages, review articles, proceedings, communications, video articles, and not open access. After the article screening process, 11 articles were obtained which would then be summarized in data extraction. The conclusion of this study shows that the thermo-sensitive hydrogel drug delivery system has advantages in drug release, where the drug will be released continuously, but also has the disadvantage of uncontrolled drug release.

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1. INTRODUCTION

Thermosensitive hydrogels are used for drug delivery systems in breast cancer therapy, where changes in the characteristics of the polymer base are affected by changes in temperature. This study aimed to evaluate the polymers in thermo-sensitive hydrogels as drug carriers in breast cancer therapy and determine their therapeutic effectiveness compared with traditional intravenous drug release. We used a systematic literature review (SLR) to describe the use of polymers as thermal bases in local drug delivery systems in breast tumors. The review was conducted following preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines, using predetermined inclusion criteria to find original English articles that are related to thermosensitive hydrogels and breast cancer. An initial database search yielded 618 articles from PubMed (241), Scopus (364), and the directory of open access journals (DOAJ) (36), and 513 duplicates were removed. To maintain the quality of the data studied in this article, we used inclusion and exclusion criteria to limit the analysis. The exclusion criteria were non-English speaking, review articles, proceedings, communications, video articles, and open-access articles. Ultimately, 11 articles were obtained and summarized in the data

extraction. This study shows that thermosensitive hydrogels are useful for drug delivery systems where the drug will be released continuously, but the drug release is uncontrolled.

Notably, breast cancer has become the deadliest disease in the world, with high incidence and mortality rates. Furthermore, conventional therapy tends to produce harmful side effects, which scientists consider and attempt to mitigate in the development of specific anticancer drug delivery systems [1], [2]. Systemic chemotherapy has the disadvantage of exposing normal tissues to drug-induced toxicity. Cytostatic drugs have non-selective and specific activity. In addition, the release of cytostatic medicines can lead to a rapid increase in concentration, thereby creating a risk of side effects and a decrease in their therapeutic effect [3]. Therefore, to reduce the toxicity and side effects of conventional chemotherapy and increase therapeutic efficacy, targeted drug delivery systems are being developed [2]. One such system is based on hydrogels. A hydrogel is a polymer material with a three-dimensional network that usually exhibits a soft and elastic consistency [4]. In hydrogels, solvent molecules will penetrate the hydrocolloid network formed by the gelator, resulting in elasticity and physical or covalent cross-links [4]. These materials can absorb large amounts of water, small hydrophilic molecules, and nutrients or metabolites, which makes them valuable carriers in tissue engineering and drug delivery systems [5], [6].

Thermosensitive hydrogels are hydrogels whose volume changes with changes in environmental temperature, and they have been widely applied in cancer therapy, especially breast cancer. Thermosensitive hydrogels have the characteristics of a liquid or semi-liquid at room temperature and undergo a sol-gel transition at body temperature. This allows the hydrogel to be loaded with drug compounds in a liquid state, as well as administered by injection. Additionally, hydrogels have stimulus-responsive features, namely the ability to respond to environmental changes, such as temperature, pH, light, ionic strength, and magnetic fields [6], [7]. The hydrogel systems are generally administered locally because the hydrogels tend to be unstable in the gastrointestinal system, inhibiting the drugs from reaching the site of action.

The current study aimed to evaluate the temperature-sensitive polymers used in localized drug delivery systems for breast cancer therapy, based on a systematic review. This review covered a range of natural and synthetic materials used to manufacture hydrogels with different features and behaviors. The changes in the characteristics of hydrogels when they transition from solutions to gels under varying temperatures are essential parameters in drug delivery systems in breast cancer. However, previous reviews have mainly focused on cancer therapy in general. Validation of the transition from solution to gel based on the viscosity profile and effectiveness of the preparation against breast cancer cells was the basis of the present analysis.

2. METHOD

The review was carried out according to the PRISMA guidelines, and it included original peer-reviewed studies based on the following criteria: i) publication in an English-language journal; ii) papers related to thermosensitive hydrogels as drug delivery systems for breast cancer therapy; iii) only original peer-reviewed papers, so editorials, proceedings, communications, letters, and reviews were excluded; and iv) all papers based on formulation, product quality control, and anticancer activity. Three search engines were used to identify studies: Scopus, PubMed, and DOAJ. The following search items were used for the literature search: (*“Thermogels” AND “polymer”*); (*“Nanoparticle” OR “Nanothermogels” AND “Injectable” OR “Localization” OR “In situ” AND “breast cancer” OR “Cancer” AND “Treatment” OR “Therapeutic” OR “Therapy”*); (*“Thermogels” OR “thermosensitive” AND “Hydrogels” AND “polymer” AND “breast cancer” AND “treatment” OR “therapeutics”*) and (*“Nanoparticle” OR “Nanothermogels” OR “Thermosensitive” AND “Hydrogels” AND “Injectable” OR “Localization” OR “In situ” AND “breast cancer” OR “Cancer” AND “Treatment” OR “Therapeutic” OR “Therapy”*). The searches were limited to reports conducted from 2010–2022. No meta-analysis was performed because of the heterogeneity of the studies. The article selection and analysis processes are illustrated in Figure 1. Before reviewing the paper, several categories for data extraction were defined. Forms were created and divided into different types: i) general data were compiled including the author names, paper titles, publication years, and journal names; ii) different materials were categorized based on their function, including polymer types, which were divided into natural and synthetic types; iii) the application of nano thermosensitive hydrogel in biomedicine were identified; iv) thermosensitive nano thermosensitive hydrogels, including cross-linking between the gelling materials, were identified; and v) thermosensitive hydrogel activity against breast cancer was determined, including advantages and disadvantages for in vitro and in vivo therapy. Finally, material sacrifices were determined by material type, polymer type, and activity in breast cancer.

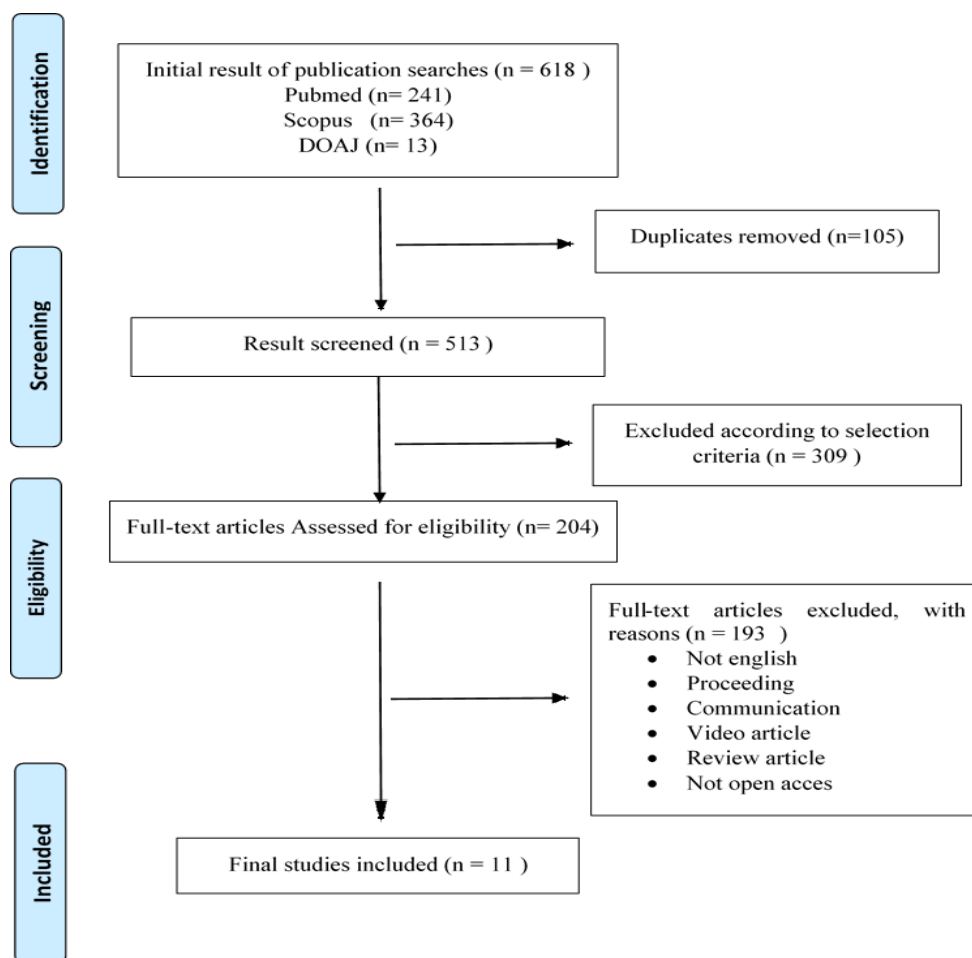


Figure 1. The PRISMA flowchart shows the search for data, the exclusion criteria, the eligibility criteria and the inclusion of articles. The search is limited to the years 2010-2022

3. RESULT AND DISCUSSION

An initial database search yielded 618 articles from PubMed (241), Scopus (364), and DOAJ (36), and 513 duplicate articles were removed. To maintain the quality of the data studied in this article, we used inclusion and exclusion criteria. The exclusion criteria were non-English articles, review articles, proceedings, communications, video articles, and open-access articles. As a result, 11 articles were obtained and summarized, as shown in Table 1 [8]–[18] (see in Appendix).

3.1. Advantages of thermosensitive polymer for drug delivery on breast cancer

The biomaterials used in medical applications often consist of polymers because they have properties that are acceptable to the human body and have the potential to be used in drug delivery systems. Furthermore, polymers can be used in various types of drug delivery systems. The polymers used in drug carrier systems are generally referred to as hydrogels. Hydrogels are a unique class of materials in which a three-dimensional cross-linked polymeric network consisting of physical and chemical bonds can adsorb and retain large quantities of aqueous solvents and biological fluids within the intermolecular spaces. The cross-linked structure of polymers can be promoted by various stimuli, including variations in temperature, pH, or irradiation. In addition, polymers have the advantage of flexible synthesis and simple chemical adjustment to meet specific requirements, such as mechanical strength, biodegradability, and bioactivity [19]–[21].

Biodegradability, biocompatibility, stability, nontoxicity, and appropriate mechanical and viscoelastic properties are all required for the clinical application of injectable hydrogels [22]. After decomposition, a biocompatible injectable hydrogel should be non-carcinogenic, non-toxic, and not cause any persistent or unfavorable physiological responses. Natural polymers are more ideal than synthetic cross-linked structures for developing systems with high biocompatibility toward tissues, cells, and bodily fluids because their subunits are more analogous to the extracellular matrix [23], [24].

Breast cancer therapy is performed repeatedly based on chemotherapy methods, drugs, radiation, or surgery, depending on the location and condition of the tumor. Locally delivered drugs have more advantages as therapeutic options for early-stage cancer than systemic drugs [25]. Natural polymers (dextran, chitosan, hyaluronic acid, gelatin, collagen, and polypeptides) and synthetic polymers are used in cancer tissue as intra-tumor drug delivery hosts for breast cancer therapy [26]. Furthermore, the process of forming hydrogels from polymer nanoparticle systems, or nanofibers with versatile morphology and tensile strength, and intraductal injection using micro-catheters can improve the performance of novel drug delivery therapies [27].

3.2. Thermosensitive polymers in biomedical applications

Thermosensitive polymers are a type of polymer that change their phase in predictable ways in response to temperature fluctuations. Their capacity to form gels or go through sol-gel transitions at body temperature has gained them significant attention in the field of biomedical applications. This property makes them appealing for a range of applications, including drug delivery, tissue engineering, and biosensing. The use of thermosensitive polymers in several biomedical applications is discussed in the following subsections.

3.2.1. Drug delivery

Thermosensitive polymers can form a gel-like structure at body temperature, which can be leveraged for the release of encapsulated drugs. The release of drugs can be modified by adjusting the gelation temperature or by incorporating stimuli-responsive groups into the polymer structure. Thermosensitive polymers have been used to deliver a wide range of drugs, including proteins, peptides, and small molecules [28], [29].

3.2.2. Tissue engineering

Thermosensitive polymers have been used in tissue engineering applications as injectable scaffolds. These scaffolds can form gels at body temperature, providing a three-dimensional environment for cell growth and tissue regeneration. The injectability of these scaffolds allows for minimally invasive procedures, which can reduce the risk of complications and improve patient outcomes [30]–[32].

3.2.3. Biosensing

Thermosensitive polymers have also been used in biosensing applications because of their ability to undergo reversible phase transitions in response to temperature changes. This property has been exploited in temperature-sensitive biosensors for detecting a wide range of analytes, including glucose, DNA, and enzymes [33]. Copolymers have become increasingly popular in recent years for applications such as medication and gene delivery, tissue adhesion inhibition, and burn sealing. A list of recent breakthroughs in gene delivery can be found elsewhere. Because of the hydrophilicity and mechanical flexibility of the polyethylene oxide (PEO) chain, Pluronic® represents a bio-inert environment [34]. Precise drug targeting systems have been developed to increase therapeutic efficacy and mitigate drug resistance [25]. Considering the importance of medication bioavailability in cancer cells, a nanocarrier system that responds to temperature may help overcome some of the systemic and intracellular delivery hurdles [35], [36]. Thus, several materials have been developed for the construction of thermoresponsive nanocarrier systems. Nanoparticles that respond to hyperthermia have long been considered viable nanocarriers for antitumoral drug delivery systems, and their development has accelerated significantly in recent decades [2], [17].

In the intratumoral drug transport system, where the accumulation of intratumoral nanoparticles is thought to be the result of the enhanced permeability and retention effect, it is possible to increase the accumulation of nanoparticles in tumors by actively targeting them using ligands attached to the outer surface of the nanoparticles [37]. However, there is now consensus that active targeting does not necessarily increase the accumulation of tumor nanoparticles, and a recent review found that it only slightly increased tumor drug absorption on average, revealing 0.9% dose/tumor injected for the active target compared with 0.6% for passively targeting nanoparticles [15], [38].

3.2.4. Thermosensitive polymer drug release mechanisms

Controlled-release drug delivery has fueled the development and marketing of some macro and micro polymeric drug delivery systems, which has sparked the nanoscale development of polymeric nanoparticles for drug delivery. Regulation of polymer biodegradation and drug diffusion out of the polymer matrix is generally used to accomplish controlled drug release from polymeric materials [39]. The condition of the valve (open or closed) determines the release from the thermoresponsive material, which is determined by the temperature of the surrounding environment. The expanded polymer keeps the valve closed below the hydrogel's phase transition temperature, and any drug release that happens in this state is due to drug molecules diffusing through

the hydrogel. Owing of the poor diffusion rates in the hydrogel, little or no drug release is expected for a molecule with a considerable molecular weight [29], [40].

The hydrogel shrinks and the valve opens above the phase transition temperature, allowing unfettered diffusion of drug molecules. Furthermore, when the osmotic pressure inside the carrier is higher than the osmotic pressure outside the carrier, the difference in osmotic pressure aids the mass flow of the contents out of the carrier [41], [42]. Although injectable thermosensitive hydrogels exhibit gradual and sustained drug release capabilities, the release from the hydrogel remains unpredictable because drug diffusion and hydrogel degradation are inherently uncontrollable processes that can only be accelerated or inhibited to some extent [39], [43]. Furthermore, release qualities are frequently calculated using average pharmacokinetic parameters of healthy persons, but differences in the microenvironment may significantly influence drug release in diseased patients. Currently, this cannot be accounted for in a general manner [39]. Research on the influence of polymers on drug release time is shown in Table 2.

Table 2. Summary of research articles on the effect of polymers on drug release time

Ref	Drug agent	Release time (day)	Drug release % Cumulative drug release	Thermosensitive evaluation
[17], [44]	TPL	14	Free TPL=90% TPL @Gel Δ25 °C=80% TPL @Gel Δ37 °C=60%	25 to 37 °C
[14], [45]	Dox	15	Dox-liposome=80% Dox-Gel=60%	25 to 47 °C
[12], [46]	Dox on folate conjugated GOFA+HACPN	9	Dox-GOFA pH 5.5=>80% Dox-GOFA pH 7.4=80% Dox-GOFA-HACPN, pH 5.5=20% Dox-GOFA-HACPN, pH 7.4=10%	25 to 37 °C
[11], [46]	TMC	8	(Poloxamer 407: 188 (18%: 0.5%)=>30%) Poloxamer 407: 188 (18%: 1%)=40%	5±0.02 °C; 5±0.02 °C and 37±0.02 °C
[8], [46]	Dox	10 (in pH=5); 17 (in pH=6); 22 (in pH=7)	pH 5=0% pH 6=0.1% pH 7=0.2%	
[15], [47]	Cis	40 minutes	Without NIR light <10% Using NIR light >30%	25-53 °C
[47], [48]	Indocyanine green (ICG)			43-50 °C
[9], [49]	PTX	PTX-PECE: 20 PTX: 3	PTX-PECE: 0.5% PTX: 0.9%	37 °C
[16], [50]	LA	2	3.89 µg	37-43 °C
[18], [46]	Dox	-	-	24; 37 and 44 °C
[10], [46], [51]	Cetuximab-Doxorubicin (CET-Dox)		Free doxorubici=>80% Doxo-TSLs=<40%	37 °C

Regarding polymer carriers of anticancer agents that are administered at disease sites, their efficacy depends on the accessibility of the therapeutic agent delivered to the tumor. The mechanism of drug release from the hydrogel matrix is strongly influenced by drug diffusion ability, matrix swelling, and chemical reactivity of the drug or matrix. Diffusive drug release is the most common drug release mechanism from hydrogels, and this mechanism relies on a matrix or reservoir system. The reservoir system is one of the most common drug delivery systems to date, in which the drug core is surrounded by a polymer film, and the rate of drug release is determined by the composition, molecular weight, layer thickness, and physicochemical properties of the polymer. In addition, drug characteristics, such as solubility, drug particle size, and molecular weight also affect the drug release in the reservoir system. The advantage of reservoir systems is the sustained release of drugs in targeted areas that are difficult to reach through systemic administration and long-term dosing, such as cancer therapy, or where the administration is generally given by injection or intramuscular implantation or subcutaneously [21], [52]. Moreover, the matrix system is similar to the reservoir-based system, in which the drug is evenly distributed as solids in the hydrogel matrix. Factors that affect the kinetics of drug release in the matrix system include wetting of the matrix surface by the media, formation of pores by the medium, pore size, speed of degradation of the drug or polymer, changes in the pH of the matrix environment, and the physical and chemical characteristics of the drug or polymer [21], [52].

4. CONCLUSION

Thermosensitive polymers have had a significant impact on biomedical applications because of their unique properties. They have been used for drug delivery, tissue engineering, and biosensing applications, and their potential for use in other areas, such as wound healing and cancer therapy, is currently being explored. The development of new thermosensitive polymers with improved properties and functionality will continue to drive innovation in biomedical research and ultimately improve patient outcomes. This study indicates that

the thermosensitive gel drug delivery system has advantages in drug release, and the drugs can be released continuously in a local area at the desired temperature. Despite the benefits of thermosensitive gels for less invasive therapy with reduced toxicity, the true drug release from this drug delivery system is unpredictable and uncontrollable because it fundamentally relies on polymer degradation and diffusion.

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APPENDIX

Table 1. Summary of research articles using thermosensitive polymer carriers for drug delivery

Ref	Years	Purpose of study	Main polymer	Anticancer drug	Result
[8]	2010	This study aimed to determine the effect of hyaluronan as a thermosensitive hydrogel polymer and carrier for doxorubicin (DOX) in local breast tissue chemotherapy.	Hyaluronan	DOX	The results of conjugation between HA-DOX by subcutaneous injection showed a reduction in Cmax of about 19-fold, without reducing the AUC of the plasma drug, and the actual total concentration of DOX in plasma may be higher compared with standard DOX treatment. This may result in a lower required DOX dose to achieve the same plasma and tissue drug levels.
[9]	2012	The hydrogel shown is based on poly (ethylene glycol)-poly(ε-caprolactone)-poly (ethylene glycol) (PEG-PCL-PEG, PECE), which is free-flowing at room temperature and forms a gel within seconds of body temperature, which eventually biodegrades slowly, leaving the drug in a steady and sustained release.	PECE Hydrogel	Paclitaxel (PTX)	Local recurrence after primary tumor resection was significantly affected in mice treated subcutaneously (9.1%) with PTX-loaded PECE hydrogels compared to those without (80.0%), systemic (77.8%) and topical. (75.0%) PTX control, control (100%) (p<0.01).

Table 1. Summary of research articles using thermosensitive polymer carriers for drug delivery
(continued)

Ref	Years	Purpose of study	Main polymer	Anticancer drug	Result
[10]	2016	This study developed an intelligent delivery system of Tamoxifen citrate (TMC)-loaded niosomes by embedding TMC-loaded niosomes in temperature-sensitive hydrogels using different poloxamers to control the localization and activity of TMCs around tumors, causing reduce of side effects and hypertoxicity to other organs.	Poloxamer 407-Poloxamer 188	TMC	The study of TMC-polymer conjugation (conjugated poloxamer 407-188) by hydrogel injection showed that the evolution of poloxamer is linked to the temperature of the gel system. Therefore, it can be adjusted to have the best gelation at body temperature. Rheological research data has shown that there are no viscosity and elasticity values at high temperature, while these values increase significantly at high temperature. This affects the long-term release of TMC from the broadcast technology. In vivo data showed increased immunosuppression with significant drug retention at the tumor site.
[11]	2017	This study aimed to overcome the initial burst release problem that occurs with some in situ drug delivery systems. Isopropyl acrylamide/hyaluronic acid (GO) with folic acid (FA) was the drug delivery carrier for DOX (GOFA-DOX). Then, GOFA-DOX was encapsulated into a thermosensitive and biodegradable hyaluronic acid-chitosan-g-poly (N-isopropyl acrylamide) (HACPN) polymer hydrogel for local drug delivery, thereby providing an improved drug delivery platform for intratumoral anticancer drug delivery.	HACPN	Dox	The results showed that HACPN as an in-situ hydrogel provides fast sol-gel phase transition kinetics around physiological temperatures so that it can function as a depot for the continuous release of GOFA-DOX. GOFA-DOX/HACPN also showed an effective drug dosage and had higher anticancer efficiency than GOFA-DOX/HACPN. Moreover, no side effects were detected, making it practical for local solid tumor treatment.
[12]	2018	Synthesis and characterization studies of thermogelation between poly (carbonate urethane) systems such as PEG, PPG, and PTHF carbonate.	Poly (carbonate urethane system comprising PEG, PPG, and PTHF carbonate).	DOX	A study using a mouse model of hepatocellular carcinoma showed that Dox-loaded poly (PEG/PPG/PTHF carbonate urethane) thermals had excellent antitumor efficacy in vivo and inhibited tumor growth in test samples.
[13]	2019	This study investigates the use of liposomal doxorubicin (DOX-Lip) loaded line (DOX-Lip-Gel) to achieve sustained delivery of DOX, a small hydrophilic drug for the treatment of breast cancer.	A triblock copolymer of poly (D, L-lactide-co-glycolide)-b-poly (ethylene glycol)-b-poly (D, L-lactide-co-glycolide) (PLGA-PEG-PLGA)	DOX	The release of DOX in DOX-Lip-Gel occurs steadily and stably for up to 11 days without burst release, better than that of DOX-Gel. The in vivo antitumor effect was evaluated using an orthotopic breast cancer model, and DOX-Lip-Gel was found to have better antitumor effect and reduced side effects.
[14]	2019	In this study thermosensitive-infrared (NIR)-II light modulated injection hydrogels were produced by supramolecular interactions of conjugated polymers and α -cyclodextrins.	Conjugated polymer (poly(N-phenylglycine)) with α -cyclodextrin	Cisplatin (Cis)	The hydrogel under NIR-II laser irradiation will exert a local photothermal effect that can scavenge highly metastatic triple-negative breast cancer and trigger the on-demand release of Cis via a thermoresponsive gel-sol transition. This system exhibits enhanced antitumor activity and reduced toxicity effects.

Table 1. Summary of research articles using thermosensitive polymer carriers for drug delivery
(continued)

Ref	Years	Purpose of study	Main polymer	Anticancer drug	Result
[15]	2019	The purpose of encapsulation in this study is to protect Lauric acid (LA) from degradation phenomena that occur in living organisms. This nanomaterial is very suitable for triggering interference in the breast cancer cell line (MCF-7) by thermal induction at 43 °C (melting temperature LA).	Combination of silica and lauric acid (SiO ₂ @LA)	LA	The combination of heat treatment at 43°C and LA encapsulation with a biocompatible silica shell will provide a pro-apoptotic/inflammatory effect and increase the effectiveness of therapy in breast cancer cells. This concept underlies the design development of new thermoresponsive nanomaterials as anticancer agents.
[16]	2020	Localized and sustained-release thermosensitive hydrogels were developed in the intra-tumor Triptolide (TPL) isopropyl delivery system. The amphiphilic structure of the copolymer poly (N-isopropyl acrylamide-co-acrylate)-g-F68 will form nanomicelles that efficiently encapsulate TPL, and turn into hydrogels at 37°C.	Poly (N-isopropyl acrylamide-co-acrylic acid)-g-F68 copolymer	TPL	TPL isopropyl nano-gel resulted in lower systemic toxicity and higher antitumor efficacy compared to multiple TPL injections. These findings indicate that TPL thermoresponsive hydrogel injection has the potential for safe and effective cancer therapy.
[17]	2020	Study of acrosome modification to polar lipid fraction E (PLFE) hybrid archeosomes with lipid tetraether composition isolated from thermoacidophilic archaeons. The combination of sulfolobus acidocaldarius and the synthetic lipid diester dipalmitoylphosphatidylcholine (DPPC) serves as a base in the direct delivery of DOX.	Hybrid acrosome	DOX	The data show that the PLFE/DPPC archeosome ratio (3:7) is stable and can be used as a thermosensitive liposome. These liposomes can release drugs affected by changes in temperature, with a temperature of 37°C to 42–44°C and can be used in medical interventions in the treatment of mild hyperthermia in patients with tumors.
[18]	2020	In this research of nanoparticle-liposome drug delivery systems targeted at cancer cells, the chemotherapeutic agent release system is a drug delivery system activated by NIR laser light that allows application in local photothermal therapy. Combined chemotherapeutic agent release systems have shown increased efficiency in cancer therapy.	Thermosensitive liposomes (TSL)	DOX	The study demonstrated the stability of CET-DOX-CMNP-TSL particles at an average diameter of about 120 nm. The absorption ability of TSL into breast cancer cells increases with the addition of the CET layer. The combined use of NIR laser irradiation in cancer therapy using CET-CMNP-TSL and CET-DOX-CMNP-TSL will decrease the survival of breast cancer cells along with increasing tumor surface temperature. In addition, data show that breast cancer cell survival with CMNP-TSL plus NIR will decrease after adding DOX to CMNP-TSL.