USE OF HYDROGELS AS CONTROLLED DRUG RELEASE SYSTEMS IN BREAST CANCER

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1. ABSTRACT

The leading cause of death in women worldwide is breast cancer, considered the first most common type of cancer and the fifth most deadly. Current treatments include surgery, chemotherapy, radiotherapy, brachytherapy and hormone therapy, however, these therapies cause side effects in patients such as pain, nausea, vomiting, cytotoxic effects on normal cells and damage to different organs and tissues, and in many cases there is tumor recurrence due to residual malignant cells. Therefore, it is necessary to look for a type of therapy that acts specifically on the tumor area, is effective and does not cause the side effects mentioned above. Hydrogels have emerged as an alternative for the treatment of cancer, due to their properties and the localized action that can be achieved with them. The aim of this review is to determine the response of hydrogels to different external factors and the effect on drug release on cell lines. For this we have searched and collected articles using the keywords: hydrogels and breast cancer, through: ScienceDirect, Google Academic, Springer, Scholarpedia, PubMed and Taylor and Francis. The information discussed will be very useful to guide improvements in future research on hydrogels for the treatment of breast cancer.

Keywords: Hydrogel; Controlled release; Oncology drug; Breast cancer

2. INTRODUCTION

Breast cancer is the most common (11.7% of all new cases) and the fifth deadliest (685,000 deaths in 2020). This is the main cause of death in women worldwide [1]. There are some methods to combat the disease and avoid a radical mastectomy. The most common treatments are: surgery, systemic or regional chemotherapy, radiotherapy, brachytherapy and hormone therapy [2], nausea, vomiting, acute cholinergic gastrointestinal effects, cytotoxic effects on cells, and possible damage to different organs and tissues [3], and possible damage to different organs and tissues [4], tumor recurrence occurs in many cases, which remains a clinical problem [2].

In the case of surgery, disseminated breast cancer cells may remain in a dormant state at the metastatic site for long periods of time until eventually progressing to form metastases in secondary organs such as bone, lung, liver, and brain, even several years after surgical resection of the primary tumor [5]. This makes it necessary to search for new treatment alternatives that cause fewer adverse effects and are more effective in treating the cancer as well as inhibiting recurrence and metastasis.

For several years, important advances have been made in the field of biomedicine in order to avoid the adverse effects of chemotherapy and radiotherapy, the use of hydrogels has emerged as an alternative to improve treatments. Hydrogels are materials whose structure is a three-dimensional network which allows them to absorb large amounts of water because they are made up of polymeric structures and therefore increase considerably in size [6]–[8]. This property allows them to act as sustained and controlled release systems for therapeutic agents, so they have been used for controlled release and targeted delivery of specific drugs at a specific site [4], and targeted drug delivery in situ [9], but have also been used as sensors for the detection of cancer cells, as targeted nanotheranostics [10], [11], as nanotheranostics focused on simultaneous detection and therapy, as well as to create 3D models of cancer cells [12], for better study and understanding [13], [14].

Several review articles on hydrogels have been published in recent years, as well as hydrogels for the treatment of cancer in general or in different types of cancer, but none focus on hydrogels oriented to the treatment of breast cancer. This article is focused on the use of hydrogels for the controlled release of drugs and other substances in the treatment of breast cancer, trying to answer the questions: What factors influence the release process of therapeutic agents, and What are the effects of this type of materials in the treatment of breast cancer?

3. MATERIALS AND METHODS

The search and compilation of the articles used was carried out with the keywords: hydrogels and breast cancer, through: ScienceDirect, Google Academic, Springer, Scholarpedia, PubMed and Taylor and Francis. As inclusion criteria we have used only articles focused on breast cancer, without considering the year of publication, but we have tried to use articles published in the last five years. Finally, 63 articles have been selected, reviewed, and analyzed for the review presented here.

4. RESULTS AND DISCUSSION

4.1. Breast cancer

The most common cause of death in women globally is the breast cancer, with more than 2.2 million cases in 2020 [15], Figure 1 show most common cancer cases and number of cases.

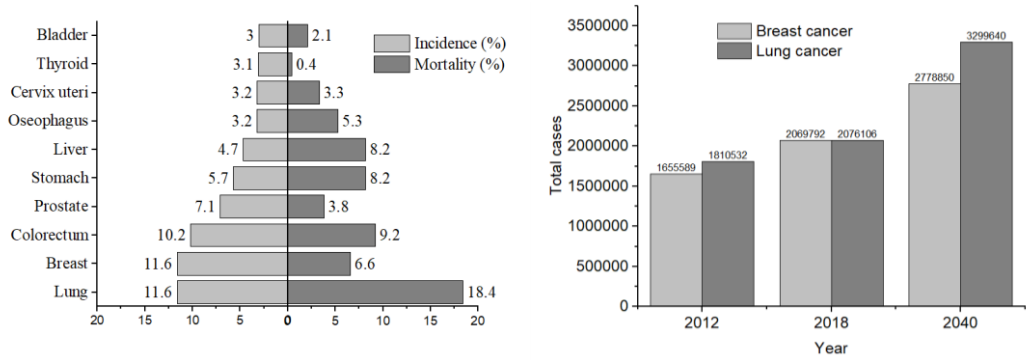

Figure 1. Most common cancer cases (2018) (left), Trends in total cases per year (breast and lung) (right) adapted from [15].

Breast cancer originates in cells that are part of the ducts (85%) or lobules (15%) of the glandular breast tissue. Initially, the tumor is confined where it usually causes not some symptom and there is a low potential for spread. It is curable in patients who have not developed early-stage metastases [16]. As time passes, this cancer may spread into the surrounding breast healthy tissue, generating invasive cancer, and then spread to nearby lymph nodes (regional metastasis) or to other organs in the body (distant metastasis).

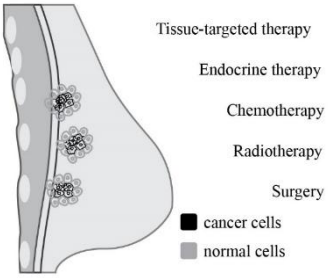

Figure 2. Treatments of breast cancer.

The primary goal of treatment of nonmetastatic breast cancer is to eradicate it from the breast and regional lymph nodes in addition to avoiding metastatic recurrence. For this, the most common procedure is the surgical removal of axillary lymph nodes, followed by radiotherapy postoperative [17], in addition to hormonal therapy, chemotherapy or targeted biologic therapy to treat cancer cells that has spread into the blood. Figure 2, show some common therapies for breast cancer.

The goal of treatment metastatic breast cancer is to prolong life and palliation of symptoms to maintain or improve quality of life. Currently, breast cancer with metastases to distant organs remains incurable with currently available therapies in virtually all affected patients [16], [17].

4.2. Hydrogels

They constitute hydrophilic three-dimensional networks formed by polymeric compounds, which absorb many solvents or physiological fluids, increasing their volume, forming soft and elastic structures that do not dissolve [6-8]. Polymeric compounds are suitable for forming hydrogels due to their long chain structure. The flexibility of these chains allows their deformation for the entry of solvent molecules into the three-dimensional structure and in turn the encapsulation of different substances.

Hydrogels are synthesized by dispersion of prefabricated polymers, polymerization of monomers, and ionic gelation or coacervation of hydrophilic polymers [18]. A large number of polymers have been used, both of natural and synthetic origin, however, due to the needs of biocompatibility, only a few have been used for the structuring of these materials, among the most used synthetic polymers are: polylactic-co-glycolic acid (PLGA) and polyethylene glycol (PEG), as natural polymers have been used: chitosan, polysaccharides, proteins and DNA [19], poly(N-acryloyl glycinamide-co-acrylamide) (PNAm) among other [20]. Synthetic hydrogels have been able to replace natural hydrogels because they have a long shelf life, high water absorption and high gel strength; they also tend to have well-defined structures, are stable under wildly fluctuating conditions, can be modified to produce functionality and have adaptive degradability [21].

The most relevant characteristics of hydrogels are their water content, dimensional stability, wettability, permeability, in addition to biocompatibility and biodegradability. The ability to vary their volume through swelling and contraction (accompanied by the expulsion of the trapped liquid) because of environmental conditions such as pH, ionic strength, temperature, electromagnetic radiation, etc., makes these materials an ideal vehicle for drugs and other species [22].

4.3. Hydrogels for breast cancers

Hydrogels have a wide applicability in the food, agricultural, cosmetic, etc. area, among these the biomedical area for the release of drugs or other species that act for example on cancer cells. When talking about drug mobility and release, the so-called "smart" hydrogels use polymers that respond to pH, temperature, light, an alternating magnetic field (AMF), near-infrared radiation (NIR), etc., [23]. There are also hydrogels that respond to several factors, such as pH and temperature, pH-magnetic field, etc., which combine the action of these factors to achieve a more targeted drug release [19], [24]. The controlled release of drug by the type of hydrogel or external factor used, allows to generate cell apoptosis, metastasis limitation and pre and postoperative tumor inhibition.

Within the structure of hydrogels, a myriad of compounds among these magnetic nanoparticles have been used [25], for their inherent magnetic properties, and usefulness in drug targeting and drug delivery properties. Known as ferrogels or magnetic hydrogels, they feature nanoparticles (NPs) embedded in their structure and due to their characteristics, such as shape, elasticity and movement, they can be controlled by using an AMF [26], [27]. They are ideal candidates for drug mobility because the biological material tolerates magnetic fields [28]. One of the most used materials in ferrogels for drug delivery are iron or iron oxide NPs, which are coated with different biocompatible molecules such as oleic acid or pluronic acid to thus prevent the formation of agglomerates [25], to prevent agglomeration and thus obtain hydrophobic magnetic nanoparticles (MPNs) [29], [31]. In other cases, citric acid has been used to obtain NMPs with unique properties [32], [33]. Some applications have yielded novel results, such as the generation of magnetic supramolecular hydrogels, designed by inclusion of α-cyclodextrins in a copolymer on the surface of the NPMs with PEG, allowing controllable thermoreversible sol-gel transition, it was evidenced that NPM-mediated induction heat caused release of dual-encapsulated drugs and generates a thermal effect that damages cells [34].

Other interesting hydrogels are DNA-based hydrogels, which use DNA because it is biocompatible, has molecular recognition capacity, is programmable and has minimal toxicity. These link chemically or physically DNA molecules to their structure. There are pure DNA hydrogels that are assembled by linking functional nucleic acids into synthetic or natural polymers, and quantum dot DNA hydrogels that are made from DNA molecules [19] to precise control spectral emission [35].

There are also hydrogels containing quantum dots used to detection and/or treatment of cancer, useful for its large surface area, good conductivity, fast charge transfer, presence of surface functional groups, doping ability, low toxicity, water solubility, biocompatibility, cheap, easy to synthetize and photo stable [10].

In this way hydrogels are somehow complex systems, but that same complexity in the case applied to the treatment of breast cancer, allows to achieve specificity and controlled release by manipulating at different levels, both the composition and the action of external factors acting on them.

4.4. Response of hydrogels to external factors

Being made up of polymers, there are several factors that can cause different effects on hydrogels, some of which are reversible [18]. Factors such as pH, temperature and ionic concentration, magnetic fields, etc., (Figure 3), can generate the collapse or phase change of the hydrogel [24], [36]. This response characteristic of hydrogels has allowed the study of a wide variety of conditions for the treatment of breast cancer.

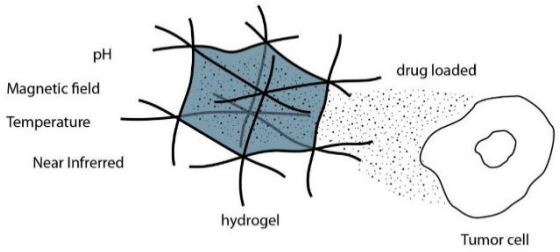

Figure 3. Factors influencing the release of drugs and other species for breast cancer treatment.

4.5. Response to Ph

The response to pH has yielded excellent results, hydrophilic networks are considered to undergo volumetric deformations in response to changes in the surrounding pH, they themselves exhibit ability to associate and dissociate with hydrogen ions depending on the pH of the aqueous medium. They may be appropriate biomaterials for in situ drug release and minimize drug leakage into normal tissue, however, they also present limitations such as release triggered by the acidic tumor microenvironment, person-to-person pH variation, and possible temperature responses [23].

As there is a pH response one can take advantage of this property to achieve drug release at a given pH. It has been observed for example that graphene oxide conjugated with folic acid (GOFA) for doxorubicin (DOX) delivery, releases at pH 5.5, ~5 times more DOX vs at pH 7.4, whereas GOFA-DOX/ hyaluronic acid-chitosan-g-poly(N-isopropylacrylamide (HACPN) only releases a limited amount of DOX at pH 7.4 without causing acute toxicity so, that latter could be an option from a drug delivery system which is safe and effective [37].

On the other hand, the thiolated chitosan hydrogel with thiolated haloisite nanotubes (HNTs) loaded with DOX also pH sensitive, releases DOX slowly at pH 7.4, and rapidly at pH 5.5 (acidic tumor environment) inhibiting the growth of MCF-7, the effect would be due to the cleavage of disulfide bonds by acidic pH, which breaks the three-dimensional network of the gel, releasing DOX. In vivo experiments demonstrated that this kind of gel could inhibit tumoral recurrence, lung metastasis, improve survival levels, and repair surgically damaged tissue [2].

4.6. Response to an alternating magnetic field

The use of an AMF increases the percentage of in situ drug release [23], [38], can induce a change in the shape of the magnetic gel or its controlled transport [27]. Hydrogels possessing magnetic properties have the ability to provide controlled and specific drug release, in addition to remarkable rheological properties, self-healing, self-forming, and inductive heating capabilities [39]. Inductive heating generates hyperthermia (tissue heating from 41 to 45°C), which improves the efficacy of therapy due to the ablation effect when used along with radiotherapy and/or drug delivery.

Composite nanomaterials based on PEG, methyl ether methacrylate and dimethacrylate and iron oxide NPs encapsulated within hydrogel matrices when heated in the presence of an AMF can control the release of heat as well as the chemotherapeutic agent paclitaxel (PTX) [40]. The ferromagnetic vortex domain functionalized iron oxide hydrogel with DOX simultaneously exhibits remarkable inductive heating and rheological properties, showing decreased tumoral recurrence when compared to the application alone of chemotherapy or hyperthermia applied separately, due to the sustained and selective drug release and the effect of magnetic hyperthermia promoting nuclear internalization of DOX [39]. The chitosan hydrogel with teleketide diffunctional PEG containing docetaxel (DTX) and DOX developed by Xie et al. for synergistic chemotherapy is sensitive to an AMF showing thermal induction, i.e., it produces a considerable amount of heat, which has a more effective antitumor effect than conventional chemotherapy [41].

4.7. Temperature response

Thermosensitive hydrogels have been widely used for their thermo-reversible gelling characteristics that allow them to change from liquid phase (sol) at room temperature or below to solid phase (gel) at body temperature, in this way is trapped in the area where is injected and can locally release drugs by the action of temperature, they are also easy to prepare and apply, biodegradables, retain and release drugs at the tumor specific site [42], [43]. In their structure they contain hydrophobic and hydrophilic components. The thermal effect phenomenon is related to the balance between the hydrophobic and hydrophilic parts of the monomer [44]. However, they present great challenges in anticancer applications, sudden release can cause systemic toxicity due to the high dose of drug [37]. Despite this, research has been developed with in situ thermosensitive chitosan-agarose hydrogels, incorporating e.g., reduced graphene oxide (rGO) and graphene oxide (GO) [45].

The PLGA-PEG-PLGA based thermosensitive hydrogel exhibited the desired thermosensitive characteristics, its sol-gel transition temperature was 30.0±1.0 °C, allowing it to remain in a liquid form to room temperature (25 °C) and change from sol to gel at human body temperature (37 °C), corilagin produced its greatest antitumor impact preventing surgical excision [43].

Another hydrogel based on poly(N-isopropylacrylamide-co-acrylic acid)-g-F68 copolymer, forms micelles which allows to encapsulate triptolide (TPL), it is converted into a hydrogel at 37 °C, exhibiting sustained drug release in vitro in addition to enhanced cytotoxicity compared to free TPL, due to the impact of proapoptosis observed in MDA-MB-231 and MCF-7 cells. After intratumoral injection three times during 14 days at a TPL-equivalent dose of 0.45 mg/kg in line cells 4T1, the nanogel produced lower toxicity and enhanced antitumor efficacy compared to a TPL supply through multiple injections [42].

In the case of poly(organophosphazenes)-based thermosensitive hydrogel which contains l-isoleucine ethyl ester, ethyl-2-(O-glycyl) lactate and α-amino-ω-methoxy-poly(ethylene glycol) 550, adopt a sol state at low temperature and gel state at body temperature. The gel enhanced the solubility of 2-ME 104-fold and this was released from the structure by diffusion, hydrophobic interaction, and superficial wear. The developed formulation showed enhanced antitumor and antiangiogenic activity in an orthotopic mouse tumor model (MDA-MB-231) [46].

4.8. Response to near infrared radiation

Photothermal hydrogels through the material of which they are constituted convert light energy into heat to kill tumor tissue at the tumor site of patients, this is an alternative to avoid the toxicity of radiotherapy and chemotherapy [47]. Is used NIR radiation (750-1000 nm) because it has high tissue penetration depth and hardly interacts with biological components, like: water, melanin, hemoglobin or collagen [48].

Gallic acid and hyaluronic acid-based hydrogel shows sensitivity to near infrared (808 nm), causing tumor removal in KB carcinoma cell xenograft mice, furthermore, suppressing metastasis of orthotopic 4T1-Luc breast tumors [49]. Similarly, there are injectable hydrogels that, when irradiated with NIR radiation, produce an increase in temperature which decreases the viability of cancer cells [45].

Chemophototherapy is an alternative that makes use of heat generation and drug delivery for cancer treatment. Injectable ionotropically cross-linked chitosan-based hydrogel incorporating IR780; a molecule with a strong optical absorption and emission in the NIR and doxorubicin, when exposed to NIR light increased the DOX release from the hydrogel by 1.7-fold while cancer cell viability was reduced to 9 %, demonstrating its potential for chemophototherapy against breast cancer [48]. Supramolecular polymer nanocomposite hydrogels exhibit photothermal effect due to the polydopamine and coated gold NPs that are attached to the matrix, the sol-gel transition is activated by NIR radiation, this in turn influences the controlled release of DOX, preventing the recurrence of cancer [20].

4.9. Response to several factors

There are hydrogels of response to various factors, such as pH-temperature, pH-magnetic field, pH-temperature-magnetic field which in many of the cases can enhance the action of the hydrogel by a more controlled release of the drug or substance of action on cancer cells, also improving the results according to individual differences [19], [24]. Hydrogels with pH-temperature response may be beneficial considering that cancer cells have a lower extracellular pH (5-7) than normal cells, as well as a higher temperature [24].

Example of dual pH-temperature response is the doxorubicin-loaded poly(nisopropylacrylamide-co-Itaconic acid) based hydrogel developed by Fathi et al. and evaluated at pH: 7.4 and 5.5 and temperatures of 37 °C and 40 °C. DOX was released more rapidly at pH 5.5 compared to pH = 7.4 due to faster swelling in acidic solution. At pH 5.5, was released more DOX at 37°C than at 40°C. The drug concentration has had an additional effect as an accelerated release of DOX is observed when is used a low concentration under acid pH at 37°C compared to neutral pH at 40°C [24].

The pH, temperature and magnetic field sensitive hydrogel based on N-isopropylacrylamide (NIPAM) and 2-(N,N-diethylaminoethyl) methacrylate with Fe3O4 nanoparticles loaded with methotrexate (MTX) was studied in vitro at three pH levels: 7.4, 6.8 and 5.5, three temperatures levels: 25, 37 and 42 °C in presence of a magnetic field. An 87% release rate of drug was achieved at pH 5.5 and 42 °C, the hyperthermia and MTX release in the presence of an AMF showed an enhanced release at relatively low concentrations [9].

The DOX-loaded hydroxypropylmethylcellulose-iron oxide hydrogel combines e.g. pH-sensitive activation and magnetic drug release. In in vivo assays, it releases less DOX at pH 7.4 than at pH 5.5 without exposure to an AMF, while the DOX released was 57.6% and 78.8% under AMF exposure versus 32.3% and 41.7% without field. In vivo assays using 4T1 mouse breast cancer xenograft observed a temperature increase in the tumor due to magnetic hyperthermia generating cell necrosis [23].

4.10. Drug release and effects on cell lines

The development of hydrogels as drug delivery systems has shown promising results compared to conventional methods. Drug mobility can be given locally or directed to the tumor (Figure 4), this allow direct contact of the medicament with the tissue for a longer time and in high concentrations, avoiding the side effects caused by continuous release [50]. The effects of these systems are varied, both in their action and in the cell lines to which they have preference.

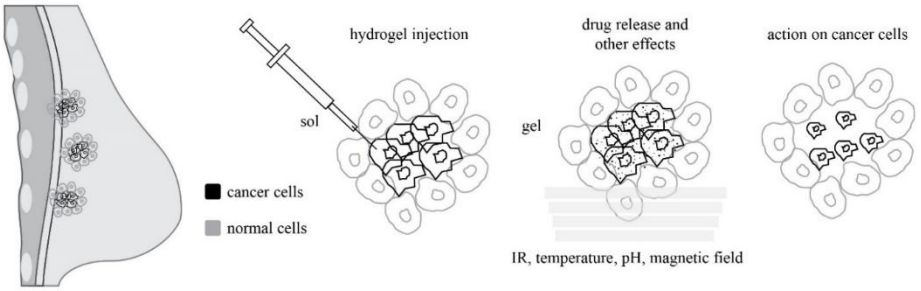

Figure 4. Schematic of desired model of action of hydrogels on breast cancer cells.

Among the most used drugs we can mention doxorubicin, paclitaxel and docetaxel, niclosamide has also been used in some cases as an inhibitor for a specific type of cancer [51], epirubicin [52], trastuzumab [53], among others (Table 1), alone or in combination as in the cases paclitaxel-epirubicin [52], or paclitaxel-niclosamide [51].

Table 1. Drugs and other substances used in hydrogels for the treatment of breast cancer.

Type of hydrogel	Name	Type of substance	Exposure technique	Ref.
Injectable	doxorubicin	anthracycline antibiotic	temperature	[37]
Injectable	paclitaxel	vegetable alkaloid	-	[52]

Injectable	docetaxel	semi-synthetic derivative	Temperature Magnetic field	[41]
Injectable	niclosamide	conventional anthelmintic drug	Temperature	[51]
Injectable	epirubicin	anthracycline analogs	-	[52]
Injectable	trastuzumab	monoclonal antibody	-	[53]
Injectable	triptolide	diterpenoid triepoxide		[42]
Magnetic	methotrexate	antimetabolite of folic acid, stoichiometric inhibitor of the dihydrofolate reductase enzyme	Temperature pH	[9]
Injectable	zoledronate	bisphosphonate	NIR	[54]
Injectable	corilagina	gallotannin		[43]
Injectable	honokiol	biologically active bisphenolic agent isolated from Magnolia officinalis	Temperature	[55]
Injectable	resveratrol	a polyphenol nonflavonoid, antioxidant which is found in fruit such as red grapes	-	[56]
Injectable	gefitinib	a drug used to treatment of certain types of cancer	Temperature	[57]
Injectable	2-methoxyestradiol	is an estradiol metabolite with antiangiogenic and antitumor activity	Temperature	[46]

DOX has had excellent results in vitro, the combined therapy of DOX-loaded alginate-chitosan magnetic microspheres with a AMF releases DOX up to 43.2%, an encouraging result for tests in mice as tumors were eliminated without recurrence in the treatment time, demonstrating to have effective antitumor effect (apoptosis and necrosis) in adjuvant postoperative therapy [38]. Gao et al. developed a ferromagnetic vortex domain iron oxide functionalized hydrogel, which when loaded with DOX inhibited the proliferation of MCF-7 cancer cells in mice by cumulative release (35.37%) without the use of AMF, there was also tumor reduction (90%) minimizing the risk of recurrence [39]. Qi et al. obtained similar results by loading DOX into a peptide hydrogel decreasing lung metastasis and prolonging the life of the carrier mice [58].

Zhang et al. used the self-assembled quantum dot NO hydrogel coated with zinc sulfide and loaded with DOX which denatures the DNA of cancer cells increasing the potency of the drug 9 times. In living organisms during treatment, the tumor was significantly reduced confirming the efficiency of this complex [35].

Another study used a dual injectable chitosan/(poly (N-isopropylacrylamide-co-itaconic acid) sensitive injectable hydrogel at pH 5.5 and 37°C, which was effective, but in vivo studies are needed to confirm the potential of this chemotherapeutic system [24]. Wu et al. applied NIR radiation (808 nm) to have a synergistic photothermal effect along with the release of 82.7% of doxorubicin at pH 5.0 from the supramolecular polymer nanocomposite hydrogel (PNAm-PDAAu), slowing tumor recurrence in vivo [20]. Similarly, Lee et al. experimented with mice based on local tumor oxygenation and mild hyperthermia induced with NIR light (660 nm and 808 nm), by intravenous injection of the hydrogel formed in situ which is made up of albumin and PEG, with chlorella and gold nanowires, it was evidenced that tumor (4 T1) growth decreased significantly [59].

The combination of an oncology drug with an anti-inflammatory doxorubicin:ibuprofen loaded on reduced graphene oxide (rGODI) enhanced the anticancer activity of the hydrogel, due to the photothermal heat generated that sensitizes cancer cells (MCF-7) to the therapeutic action [45]. Likewise Hu et al. loaded losartan to the hydrogel formed by peptide derivatives (C16-N/L), sustainably releasing the encapsulated drug, inhibiting cancer-associated fibroblasts and their survival, as well as collagen synthesis in 4T1 tumors. Together with DOX-loaded liposomes, they slowed tumor growth (64%) and lung metastasis (80%), demonstrating that the C16-N/L hydrogel serves as an adjuvant to potentiate (DOX-L) [60]. In a similar study, DOX-modified dextran was loaded into acrylamide-based microcapsules and stimuli-responsive DNA, making drug release pH- and ATP-dependent, evaluating the complex in MDA-MB-231 cells showed that their viability was reduced by 35% [61].

Some researchers use PTX which unlike others inhibits cell division and combined with hydrogels has given promising results, for example the thermosensitive gel made up of biocompatible poly (ethylene glycol)-poly (3-caprolactone)-poly (ethylene glycol) copolymers (PECE) loaded with PTX, released the drug by suppressing cancer cells through apoptosis in in vitro assays and in in vivo studies only one of 36 mice had late postoperative tumor recurrence, in addition to having the lowest percentage of lung metastasis (54.6%) prolonging the life span [62]. Wang et al. used a double-network hydrogel loaded with paclitaxel NPs (PTX-NPs-DN), releasing the drug locally to MCF-7 and MD-MBA-231 cell lines, reducing tumor size and killing postoperative residual cells in mice [63].

There are other drugs used to a lesser extent for oncological therapy, one of them being trastuzumab, studied by Lo et al. who retained said drug in hydrogels made up of γ-PGA-MA and PEG-SH, releasing it in the body in a sustained manner, having an antiproliferative effect on BT-474 cells. One of the hydrogels showed excellent tumor growth inhibition due to the role of Zn enhancing drug release [53].

Table 2. Main effects of hydrogels in vivo and in vitro treatments.

Hydrogel	**Model (in vitro)**	**Highlights**	**Model (in vivo)**	**Highlights**	**Ref.**
halloysite-g-chitosan	MCF-7	growth inhibition of MCF-7	metastatic breast cancer	inhibition of recurrence, improve survival rate and repair surgical defect tissues.	[2]
maleimide-modified γ-polyglutamic acid (c-PGA-MA) and poly (ethylene glycol)	BT474	the viability of BT474 line cells is of 60% after 90 hours	BT-474 xenograft tumor	slight tumor inhibition	[53]
corilagin and low-molecular-weight chitosan-PLGA-PEG-PLGA	4T1	significant tumor growth inhibition	4T1 breast tumor xenograft	the tumor growth inhibitions in vivo were lower than in vitro	[43]
poly(organophosphazene)	MDA-MB-231	The cell viability decreased as a function of 2-ME concentration	breast cancer orthotopic	showed no tumor inhibition effect during the initial treatment, but after the tumor growth was decreased	[46]
hydroxypropyl methyl cellulose (HPMC)/Fe3O4	-	-	4T1 mouse breast cancer xenograft	recovered without any recurrence or metastasis	[23]
hyaluronic acid-chitosan-g-poly(N-isopropylacrylamide)	MCF-7	Tumor growth decreased after 3 days of treatment	xenograft tumor mouse	enhanced the anti-tumor efficacy	[37]
oleic acid-Fe3O4 nanoparticles PLA-PEG-PLA	MCF12-A and MCF-7	exhibited a potent cytotoxicity against MCF-7 cells	breast cancer	significant decrease of tumor volumes	[31]
DOX-loaded magnetic magnetic alginate-chitosan microspheres	MCF-7	significant cytotoxicity	xenografted mice tumor	all tumors were removed and there was no recurrence	[38]
magnetic hydrogel functionalized by ferromagnetic vortex-domain iron oxide	MCF-7	Inhibition the proliferation of MCF-7 cells.	tumor-bearing mice	almost complete elimination of tumors (more than 90% tumor shrinkage)	[39]
dual-drug-loaded magnetic hydrogel	MDA-MB-231	time-dependent cell proliferation inhibition behaviours	triple negative breast cancer	good antitumor action was achieved after 4-day treatment	[41]
poly (N-isopropylacrylamide- (N-isopropylacrylamide-) co-acrylic acid)-g-F68 copolymer	MDAMB-231 and MCF-7	tumor cell cytotoxicity is a function of dose and time	4T1 tumor-bearing mice	low systemic toxicity and anticancer efficacy	[42]
supramolecular poly(N-acryloyl glycinamide-co-acrylamide)	-	-	breast cancer	no locoregional tumor recurrence was observed	[20]
hyaluronic acid (HA)-based hydrogel	4T1	Show pro-apoptotic effect	mice carrying 4T1 breast tumors	inhibition primary tumor growth and effectively prevented recurrent growth.	[52]
PLGA-PEG-PLGA	MDA-MB-231	sustained drug release for up to 8 days	TNBC xenograft	tumor growth inhibition rate about 68.8%	[51]

hexapeptide-based hydrogel	MDA-MB-231 and 4T1	antitumor effect due to gradual release of drug.	breast cancer	Is showed karyolysis, suggesting cell death.	[58]
poly(ethyleneglycol)-poly(3-caprolactone)-poly(ethylene glycol)	4T1	significant anti-tumor cytotoxicity	4T1 breast cancer	The drug is released in a constant and sustained manner and gradually biodegrades	[62]
Paclitaxel-nanoparticles-loaded double network	MCF-7 and MD-MBA-231	cancer cell killing ability	MDA-MB-231	A significantly decrease in tumor mass and a slowdown in tumor recurrences are observed	[63]
γδ T cell-stimulating hydrogel coated by zoledronate	MDA-MB-231 and T24	significant killing occurring	breast cancer	significantly inhibited tumor growth	[54]

In 2020, Jin et al. used corilagin/LC/PPP (CPH and CCPH) thermosensitive hydrogels exhibiting 61.24% antitumor effects when loading abraxane, with this combination cell proliferation (Ki67) decreased, there was restriction of tumor stromal growth and extended necrosis in cancer cells [43].

Shou et al. studied particles of an N-isopropylacrylamide solution (pNIPAM) doped by black phosphorus quantum dots and loaded with zoledronate, exhibiting results in activation and expansion of T-γδ cells, in addition to having NIR light-controlled release, cancer cell activity showed inhibition by 70% in the MBA-MD-231 cell line, reducing tumor volume considerably [54].

Other researchers used magnetite nanocomposites (MNCPs) loaded with methotrexate at low doses, obtaining 87% AMF-activated controlled release at pH 5.5 and 42°C, showing up to 28% viability for MCF-7 cells, requiring in vivo studies to corroborate the antitumor efficacy [9].

Combining oncology drugs has always been a complex challenge but encapsulating them and having a controlled release facilitates and improves their use. It has been achieved to add DOX and PTX to the PEGylated/Fe3 O4 /α-CD complex to kill recurrent cancer cells, after resection the release was controlled by an AMF, the remaining hydrogel destroys tumor cells constantly, achieving long-term efficacy with no recurrence occurrence in cured mice and significant survival [34]. Xie et al. designed a magnetic hydrogel (DDMH) promoting the release with an AMF, obtained asynchronous controlled release of DTX and DOX, in addition to remarkable synergistic antitumor activity for the MB-231 cell line in mice. DDMH is considered a potential nanosystem to improve synergistic chemotherapy treatment in CM [41]. Table 2 summarizes main effects of hydrogels in vivo and in vitro studies.

5. CONCLUSIONS

Current treatments for breast cancer are invasive for the organism because the drugs administered are not localized in situ, which delays the anticancer effect by killing healthy cells, producing side effects in the patient among other discomforts.

Among the advantages of hydrogels that can be extracted from the review is their capacity to administer high concentrations of therapeutic agents in a localized manner, although supplying high concentrations does not genera greater cytotoxicity, however, a sustained release is achieved avoiding in most cases the affectation of healthy tissues, although in some cases the opposite has been observed, being a parameter that still needs to be improved.

Apart from drugs such as doxorubicin, paclitaxel, methotrexate, zoledronate and triptolide, antibodies such as trastuzumab and herbal medicinal agents such as corilagin with abraxane and 2-methoxyestradiol have also been used in combination to achieve synergistic effects. Due to the response of hydrogels to certain factors: temperature, pH, NIR radiation and magnetic fields, it has been possible to improve the controlled release of drugs towards cancer cells, inducing environmentally specific release kinetics, generating cell apoptosis, limiting metastasis and pre- and postoperative tumor inhibition. Multi-responsive hydrogels allow to improve the specificity

of the release, however, other variables that may affect the behavior, such as drug concentration, must be considered.

The combination of various therapies such as photothermia and chemotherapy, hyperthermia and chemotherapy generate a more potent synergy to kill cancer cells and prevent breast cancer recurrence. The main effects observed in in vitro and in vivo studies are varied, but mainly inhibition of cancer cell proliferation, reduction or retardation of tumor growth and elimination through different mechanisms, such as inhibition of cell division, denaturation of cancer cell DNA or sensitization of cancer cells, in most cases a decrease in tumor recurrence is observed.

Different drug concentrations have been evaluated, as well as different levels of the various factors that affect controlled drug release, the results found can serve as a guide to improve or test other levels that produce even better results in the treatment of breast cancer or make combinations, or programmed increases in temperature, magnetic field, NIR, etc.

Factors to consider in the design of hydrogels for breast cancer treatment are to reduce toxicity, side effects and delay drug release from hydrogels, as well as to consider postoperative recurrence and metastasis.

6. CONFLICTS OF INTEREST

The authors do not have any interest conflict.

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