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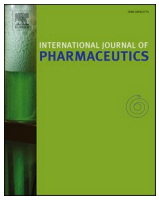

Review

Injectable and implantable hydrogels for localized delivery of drugs and nanomaterials for cancer chemotherapy: A review

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ABSTRACT

Multiple chemotherapeutic strategies have been developed to tackle the complexity of cancer. Still, the outcome of chemotherapeutic regimens remains impaired by the drugs' weak solubility, unspecific biodistribution and poor tumor accumulation after systemic administration. Such constraints triggered the development of nanomaterials to encapsulate and deliver anticancer drugs. In fact, the loading of drugs into nanoparticles can overcome most of the solubility concerns. However, the ability of systemically administered drug-loaded nanomaterials to reach the tumor site has been vastly overestimated, limiting their clinical translation. The drugs' and drug-loaded nanomaterials' systemic administration issues have propelled the development of hydrogels capable of performing their direct/local delivery into the tumor site. The use of these macroscale systems to mediate a tumor-confined delivery of the drugs/drugs-loaded nanomaterials grants an improved therapeutic efficacy and, simultaneously, a reduction of the side effects. The manufacture of these hydrogels requires the careful selection and tailoring of specific polymers/materials as well as the choice of appropriate physical and/or chemical crosslinking interactions. Depending on their administration route and assembling process, these matrices can be classified as injectable *in situ* forming hydrogels, injectable shear-thinning/self-healing hydrogels, and implantable hydrogels, each type bringing a plethora of advantages for the intended biomedical application. This review provides the reader with an insight into the application of injectable and implantable hydrogels for performing the tumor-confined delivery of drugs and drug-loaded nanomaterials.

1. Introduction

The limitations of the chemotherapeutic drugs used to tackle cancer are well known to the medical and non-medical communities (Behranvand et al., 2022). The off-target toxicity (*i.e.*, non-specificity) of these molecules impels a magnitude of side effects that can range from fatigue and hair loss to organ complications (Nurgali et al., 2018; Yan et al., 2020). Besides this critical constraint, cancer cells often develop resistance mechanisms to chemotherapeutics' action (*e.g.*, over-expression of efflux pumps, reprogramming of metabolic pathways) (Musyuni et al., 2022). This behavior has a foreseeable impact on the therapeutic efficacy of the anticancer drugs as well as on patients' survival (Goncalves et al., 2021).

In the last decades, nanotechnology has emerged with the aim to address several limitations of the conventional anticancer drugs (Mitchell et al., 2021). Nanomaterials can be used to encapsulate chemotherapeutic drugs, leading to an improved drug solubility (since the vast majority is hydrophobic) and an enhanced protection from premature degradation during blood circulation (Liu et al., 2023). Nanomaterials are also compatible with the simultaneous encapsulation of different drugs (Mo et al., 2020a; Tonbul et al., 2019; Zhang et al., 2021b), which, in some cases, may result in synergistic anticancer effects. Such is particularly important to overcome the resistance mechanisms exhibited by cancer cells. Notwithstanding these merits, the

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Table 1
Macroscale systems for the tumor-confined delivery of chemotherapeutic agents.

Type of macroscale system	Strengths	Challenges	Ref.
Hydrogels	• Proficient in superficial cancers (*e.g.*, breast cancer, melanoma) • Soft and flexible structure that mimics tissues' extracellular matrix • Potential to be administered through a minimally invasive route (intratumoral injection) • Produced using routine/standard equipment	• Complex to fine-tune the release profile • Some crosslinking methods require time-consuming polymer synthesis/ modification • Prone to swell after injection/ implantation • Mechanical weakness	(Ali et al., 2022; Bettahar et al., 2021; Chee et al., 2024; Kass and Nguyen, 2022; Lv et al., 2018; Mellati et al., 2021; Melo et al., 2022; Patel et al., 2024)
Microneedles	• Proficient in cancers reachable by topical administration (*e.g.,* melanoma) • Excels in minimally invasive and painless transdermal delivery • Allows hierarchically/sequential controlled drug delivery • Prepared using a wide range of materials	• Production requires specific equipment • Mostly limited to topical applications • Variable delivery patterns according to the skin environment • Mechanical weakness	(Faraji Rad et al., 2021; Han et al., 2025; He et al., 2024; Kulkarni et al., 2023; Liu et al., 2022; Lopez-Ramirez et al., 2021; Pereira et al., 2024; Sen et al., 2025; Xiu et al., 2022)
Scaffolds	• Ideal for cancers associated to tissues that provide structural support (*e.g.,* osteosarcoma) • Precisely controllable features in the macro/microscopic range • Allows hierarchically/sequential controlled drug delivery • Enhanced mechanical properties	• Fabrication requires specific equipment • Invasive administration process • Prone to have a long biodegradation • Some production techniques are not compatible with the loading of high drug doses	(Abueva et al., 2017; Hou et al., 2022; Ma et al., 2018; Palo et al., 2017; Sultan and Mathew, 2018; Wang et al., 2024; Wang et al., 2023; Zeng et al., 2016)

main reason underlying the use of nanomaterials in cancer therapy is related to the nanostructures' ability to accumulate in the malignant zone by extravasating through the aberrant fenestrae present in the tumor vasculature (Kalyane et al., 2019; Zi et al., 2022). The defective lymphatic drainage occurring at the tumor site also promotes the retention of the nanostructures in this zone (Kalyane et al., 2019; Zi et al., 2022). In this field, these two events are known as the Enhanced Permeability and Retention (EPR) effect (Kalyane et al., 2019; Zi et al., 2022).

By engineering the physicochemical properties of the nanoparticles (size, surface charge, and corona composition), it is possible to favor the nanostructures' tumor uptake through the EPR effect (Ernsting et al., 2013; Mitchell et al., 2021; Rodrigues et al., 2020; Shinde et al., 2022). Moreover, the nanoparticles' surface can also be decorated with ligands (*e.g.*, folic acid, trastuzumab) that actively target the nanostructures to cancer cells by binding to the respective overexpressed receptors (Choi et al., 2015; Lee et al., 2015). In this way, a wide variety of drug-loaded nanomaterials has been developed due to their potential to improve the efficacy and safety of these drugs (Dang and Guan, 2020; Elumalai et al., 2024; Nikezić et al., 2020). In fact, in multiple pre-clinical *in vivo* cancer models (*e.g.*, tumor-bearing mice), the drug-loaded nanomaterials can outperform the free drug administration (*i.e.*, non-encapsulated drugs) by enabling a more effective and/or safer therapeutic effect (Feng et al., 2019; Lu et al., 2020; Xie et al., 2017; Yu et al., 2015; Zhang et al., 2015). Despite these optimistic results, over the years, only a small number of nanoformulations have been successfully translated into the clinic (Sun et al., 2020a). A key contributor to this scenario is related to the fact that nanomaterials have been engineered to reach the tumor zone through the EPR effect (Sun et al., 2020a). However, the EPR effect was found to be overexaggerated in many pre-clinical *in vivo* cancer models and to not be ubiquitously present on human solid tumors (Danhier, 2016; Dhaliwal and Zheng, 2019). Besides the limitations arising from the EPR effect, the efficacy of active targeted nanoparticles is also limited, being impacted by the nanostructures' ligand density and by the receptor availability in the *in vivo* tumors (Gu et al., 2021). In fact, systemically administered nanomaterials appear to have a lower tumor uptake than expected (Wilhelm et al., 2016). According to Wilhelm *et al.*, the median of the administered nanoparticle dose that reaches the tumor is below 1 % (Wilhelm et al., 2016).

The systemic administration problems that plague the conventional drugs (*i.e.*, poor solubility, unspecific biodistribution, poor tumor accumulation) and the drug-loaded nanoparticles (*i.e.*, unreliable tumor uptake) are factors limiting their full anticancer potential. There are alternative delivery paths that may solve partially some of the systemic administration problems of the conventional drugs/drug-loaded nanoparticles. However, such alternative routes are only applicable to specific types of cancer (*e.g.*, intranasal administration for lung cancer (Monteillier et al., 2018), topical application for skin cancer (Safwat et al., 2018; Zhang et al., 2021a), intravesical administration for bladder cancer (Li et al., 2022), intrathecal administration for leptomeningeal metastases (Khang et al., 2022)). Another promising approach to address the systemic administration bottlenecks lays in the direct delivery of the drugs/drug-loaded nanoparticles into the tumor site by macroscale matrices (Lima-Sousa et al., 2023; Singh and Kesharwani, 2021; Yang et al., 2020). In fact, the incorporation of drugs or drug-loaded nanomaterials into macroscale systems (*e.g.*, hydrogels, microneedles, scaffolds) and their direct injection/implantation into the tumor site has been yielding promising results (Lima-Sousa et al., 2023; Singh and Kesharwani, 2021; Yang et al., 2020) – Table 1. The use of these macroscale systems to mediate a tumor-confined delivery of the drugs or drug-loaded nanomaterials enhances the treatment's efficacy and reduces the side effects (Chen et al., 2020; Fan et al., 2023; Huang et al., 2020; Jiang et al., 2022; Li et al., 2024; Liu et al., 2021c). Moreover, these macroscale systems can be engineered to sustain the release of the drugs or drug-loaded nanomaterials in a controlled-manner (Guedes et al., 2021; Liu et al., 2021a; Matadh et al., 2022; Pandit et al., 2020).

In recent years, the incorporation of chemotherapeutic agents (drugs and drug-loaded nanomaterials) in hydrogels has drawn the attention of multiple researchers. Compared to other macroscale systems (*i.e.*, microneedles, scaffolds), hydrogels aimed at the tumor-confined delivery of chemotherapeutic agents have a relatively simple formulation (Lima-Sousa et al., 2023) – Table 1. The preparation of this type of macroscale system just comprises the careful selection and tailoring of specific polymers/crosslinking agents, followed by their mixture in aqueous media, leading to the assembly of the hydrogel through physical and/or chemical cues (Lima-Sousa et al., 2023). Depending on their administration route and assembling process, these matrices can be

classified as injectable *in situ* forming hydrogels, injectable shear-thinning/self-healing hydrogels, and implantable hydrogels, each type bringing a plethora of advantages for the intended biomedical application (Chen et al., 2020; He et al., 2017; Li et al., 2019; Xie et al., 2017).

In this review, the application of hydrogels for the tumor-confined delivery of chemotherapeutic agents (drugs and drug-loaded nanomaterials) will be explored. In section 2, a general overview of this therapeutic strategy will be given. Then, the potential of injectable *in situ* forming hydrogels (section 3), injectable shear-thinning/self-healing hydrogels (section 4), and implantable hydrogels (section 5) for mediating a tumor-confined delivery of drugs or drug-loaded nanomaterials will be assessed. Lastly, an outlook of the state-of-the-art and future directions about this field will be provided (section 6).

2. Hydrogels for the tumor-confined delivery of chemotherapeutic agents

Hydrogels are hydrophilic polymeric networks that can accommodate within their mesh different types of therapeutics. In this way, hydrogels can readily incorporate in their structure chemotherapeutic drugs with reasonable water solubility (Chen et al., 2023; Ma et al., 2023; Qin et al., 2019). In turn, poorly soluble anticancer molecules are often first loaded into nanoparticles with proper colloidal stability (*i.e.*, nanomaterials with a surface charge and corona composition that allows them to be well dispersed over time into aqueous environments), and subsequently the drug-loaded nanoparticles are incorporated into hydrogels (Jeswani et al., 2023; Mi et al., 2023; Sabino et al., 2021). Considering their administration route, there are two classes of hydrogels that can be used to perform the tumor-confined delivery of drugs/drug-loaded nanoparticles: injectable hydrogels and implantable hydrogels.

As their name states, injectable hydrogels can be extruded through a syringe equipped with a needle, allowing their direct deposition at the tumor site by a minimally invasive manner (Chang et al., 2022; Yang et al., 2018). According to their assembly process, the injectable hydrogels can be sub-classified into *in situ* forming hydrogels or shear-thinning/self-healing hydrogels (discussed in detail in sections 3 and 4) (Chang et al., 2022; Yang et al., 2018). The gelation time of injectable hydrogels plays a decisive role in their performance (Lima-Sousa et al., 2023). After intratumoral injection, these hydrogels must display a fast gelation time to avoid the premature leakage of the chemotherapeutic agents into other tissues (Lima-Sousa et al., 2023). In some cases, the use of implantable (*i.e.*, non-injectable) hydrogels incorporating chemotherapeutic agents is also appealing (Chen et al., 2022; Fan et al., 2022). This approach gains a special relevancy if applied after the surgical resection of the tumor, since in this case, the tumor zone is already exposed by the surgical procedure and thus the hydrogel can be effortlessly implanted (discussed in detail in section 5) (Chen et al., 2022; Fan et al., 2022).

In this way, hydrogels can mediate the delivery and confinement of high doses of chemotherapeutic agents into the tumor site, minimizing systemic exposure and side effects (Fig. 1).

In this regard, Jiang *et al.* performed the intratumoral injection of a shear-thinning/self-healing hydrogel that contained Doxorubicin, verifying its ability to confine the drug within the tumor site for 14 days with minimal distribution to other organs (Fig. 2) (Jiang et al., 2022). In turn, the direct administration of Doxorubicin resulted in poor tumor retention and pronounced leakage into the liver, spleen, lungs, and kidneys, leading to side effects (Jiang et al., 2022).

Zhou and co-workers also demonstrated that locally injected *in situ* forming hydrogels can deliver and confine nanoparticles in the tumor site for at least 14 days (Zhou et al., 2020b). In contrast, the direct administration of these nanoparticles resulted in a poor tumor retention (Zhou et al., 2020b). In another work, Kong team showed that injectable hydrogels incorporating drug-loaded nanoparticles could mediate a ≈ 8- and 17-times higher drug retention at the tumor site when compared to the direct administration of the drug-loaded nanoparticles and the free drug, respectively (Huang et al., 2016). As importantly, the local delivery of the drug-loaded nanoparticles mediated by this injectable hydrogel also resulted in minimal off-target leakage (Huang et al., 2016). In another work, Yang's group also reported that the local delivery of artesunate using an injectable hydrogel prompts a high tumor uptake, while the direct administration of this drug resulted in a weaker tumor retention and off-target leakage into the spleen and liver (Ma et al., 2023). Chen and co-workers developed an implantable hydrogel that could locally deliver cisplatin-bonded nanoparticles into the tumor site (Chen et al., 2020). The delivery of the cisplatin-bonded nanoparticles by the implantable hydrogel outperformed the direct administration of these nanostructures (Chen et al., 2020). In fact, the sole use of cisplatin-bonded nanoparticles resulted in a lower tumor uptake as well as greater accumulation in the lungs and kidneys, leading to side effects (Chen et al., 2020).

Besides the hydrogels' capacity to encapsulate chemotherapeutic agents and to confine them into the tumor site, these must also display other important features to ensure their safety. It is crucial that the hydrogels display a good biocompatibility and biodegradability (Kesharwani et al., 2021). In principle, the hydrogel *per se* should not induce any nefarious effects on the different cells found in the tumor microenvironment nor on other organs (Li et al., 2023). In other words, the hydrogel must be highly biocompatible, and the anticancer effect must be derived from the drugs/drug-loaded nanomaterials. In this regard, favoring the use of polymers/(bio)materials approved by the FDA/EMA, or those that are generally recognized as safe by these regulatory agencies, for the hydrogels' assembly can also contribute to their safety (*e.g.*, polysaccharides such as alginate or chitosan, poly(ethylene glycol)-derivatives such as Pluronic F127 (Cattelan et al., 2020; de Freitas et al., 2023; Kantak and Bharate, 2022)). The degradation profile is also a key modulator of the hydrogels' long-term body residence (Shazeeb et al., 2018; Zhu et al., 2015). In this regard, the hydrogels' degradation byproducts should not induce any local or systemic toxicity, being ideality rapidly excreted or integrated in metabolic pathways (Li and Mooney, 2016). Furthermore, the hydrogels' degradation kinetics also regulate the release of the drugs/drug-loaded nanoparticles from the polymeric matrix to the tumor milieu (Li and Mooney, 2016). In this subject, hydrogels assembled with natural polymers often present a faster degradability when compared to their equivalents prepared with synthetic polymers (Kesharwani et al., 2021). Besides the polymer type, the crosslinking chemistry also influences the hydrogels' degradability (Lima-Sousa et al., 2023). As importantly, the swelling profile of the hydrogels should be well controlled since a sharp increase in their volume after inoculation may cause discomfort/pain (Lima-Sousa et al., 2020). If possible, the hydrogels' mechanical properties should be tuned to be comparable to those of the target tissue (Blache et al., 2022; Sun et al., 2020b). Additionally, the hydrogels can also be engineered to release the chemotherapeutic agents in response to stimuli from the tumor microenvironment (*e.g.*, pH, redox) or through external cues (*e.g.*, magnetic fields, NIR light) (Gong et al., 2017; Jiang et al., 2022; Xie et al., 2017; Xu et al., 2017).

The following sections analyze the potential of injectable *in situ* forming hydrogels (section 3), injectable shear-thinning/self-healing hydrogels (section 4) and implantable hydrogels (section 5) for the delivery of chemotherapeutic agents (drugs and drug-loaded nanomaterials).

3. Injectable *in situ* forming hydrogels

Injectable *in situ* forming hydrogels have been extensively explored for mediating a tumor-confined delivery of therapeutic molecules. The preparation and administration of this type of injectable matrix is usually a simple process. Initially, the polymers and the chemotherapeutic agents are loaded into a syringe (gelling agents may also be included), being then injected into the tumor where the gelation will occur (*in situ*

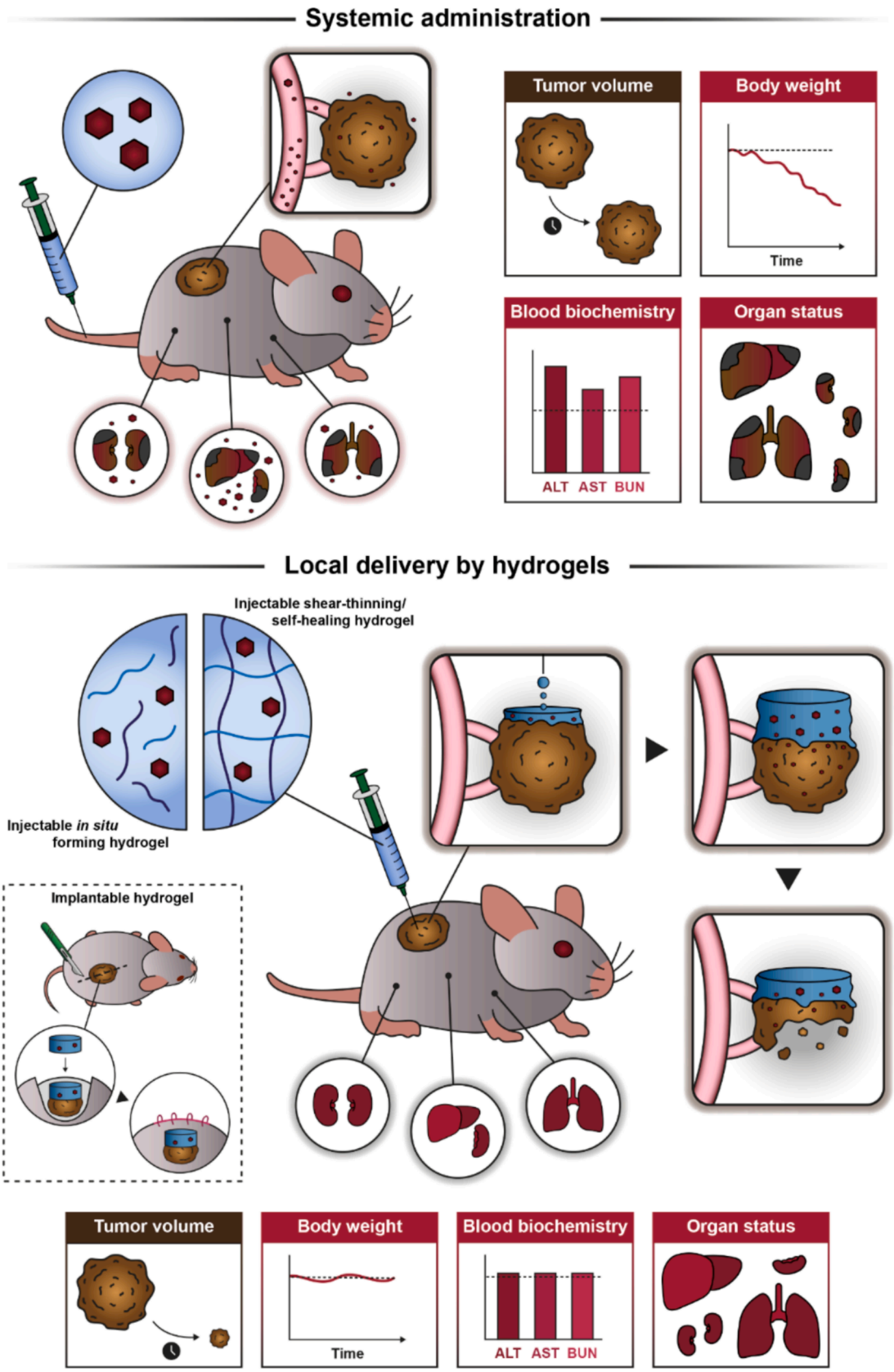

Fig. 1. Schematic illustration demonstrating the limitations associated to the systemic administration of chemotherapeutic agents as well as the hydrogels' capacity to perform a tumor-confined delivery of chemotherapeutic agents with minimal side effects. ALT: Alanine aminotransferase; AST: Aspartate transferase; BUN: Blood urea nitrogen.

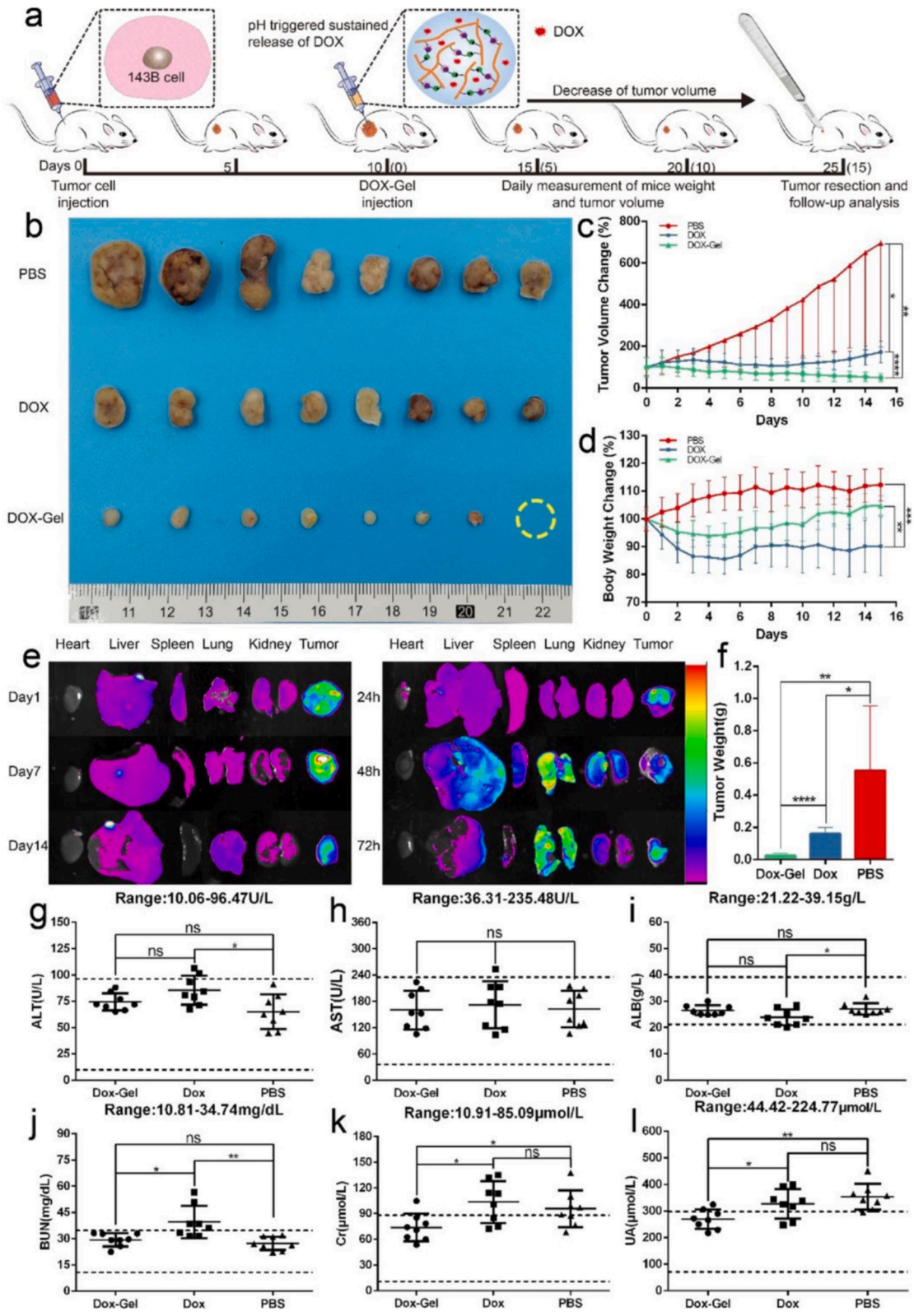

Fig. 2. Therapeutic performance, biodistribution and safety of an injectable shear-thinning/self-healing hydrogel aimed for Doxorubicin delivery. (a) Schematic representation of the *in vivo* protocol. (b) Images of the excised tumors after the different treatments. (c) Tumor volume variation and (d) body weight variation after the different treatments. (e) Biodistribution of Doxorubicin after being delivered by the injectable shear-thinning/self-healing hydrogel (left) or by direct administration (right). (f) Weight of the tumors at the end point of the study. (g-l) Blood biochemical parameters at the end point of the study. PBS: Phosphate buffered saline; DOX: Doxorubicin; DOX-gel: injectable shear-thinning/self-healing hydrogel containing Doxorubicin, prepared using β-cyclodextrin-functionalized carboxyethyl cellulose, ethyl-1-adamantane 4-formylbenzoate and adipic dihydrazide-functionalized carboxyethyl cellulose. Reprinted from (Jiang et al., 2022), with permission from Elsevier. © 2022 Acta Materialia Inc. Published by Elsevier Ltd.

formation) through physical and/or chemical cues (He et al., 2017; Phan et al., 2022). In this regard, it is crucial that this sol–gel transition occurs under biologically compatible conditions.

Physical interactions have been widely applied for driving the hydrogels' *in situ* gelation. In this regard, the ionic crosslinking established between a charged polymer (polyion) and an oppositely charged ion/molecule can be explored for prompting the *in situ* assembly of injectable hydrogels. For instance, Melo and co-workers combined chitosan (positively charged polysaccharide) and $NaHCO_3$ (provides HCO_3^-) in order to prepare injectable *in situ* forming hydrogels for Resveratrol delivery (Melo et al., 2022). In another work, Liu team prepared alginate-based solutions (negatively charged polysaccharide) containing anti-cancer agents that could achieve *in situ* gelation after interacting with the Ca^{2+} ions found in the tumor microenvironment (Chao et al., 2018). Furthermore, hydrophobic interactions can also be explored for preparing injectable *in situ* forming hydrogels by taking advantage from the aggregation of the hydrophobic domains of specific thermoresponsive amphiphilic polymers. Such injectable *in situ* forming hydrogels are often prepared using Poly(*N*-isopropylacrylamide)-derivatives, and Pluronics®/Poloxamers (*i.e.*, poly(ethylene glycol)-poly(propylene oxide)-poly(ethylene glycol)) (Fathi et al., 2019; Norouzi et al., 2021). For instance, Norouzi *et al.* prepared Pluronic F127 formulations containing salinomycin (anticancer agent) that were in a solution state at 4 °C, enabling their injection (Norouzi et al., 2021). Upon heating to body temperature, the formulations achieved gelation due to the aggregation of the poly(propylene oxide)-segments that compose the Pluronic F127 (the thermoresponsive sol–gel transition occurred at around 10 °C). Other polymers (*e.g.,* Agarose) displaying thermoresponsive sol–gel transitions through different mechanisms (*e.g.*, hydrogen bonding) have also been employed in the preparation of injectable *in situ* forming hydrogels (Hou et al., 2018; Lima-Sousa et al., 2020). In this regard, Lima-Sousa *et al.* prepared a formulation based on Agarose and Chitosan that presented a thermo-responsive *in situ* gelation, being this system subsequently explored for the delivery of nanomaterials and a dual-drug combination (Doxorubicin and Ibuprofen) (Lima-Sousa et al., 2020). Other physically-crosslinked injectable *in situ* forming hydrogels aimed for the tumor-confined delivery of chemotherapeutic agents are summarized in Table 2.

On the other hand, covalent bonds can also drive the *in situ* assembly of injectable hydrogels (Ali et al., 2022; Lo et al., 2019). Chemically-crosslinked injectable *in situ* forming hydrogels often display an improved stability and enhanced control over the gelation and degradation profiles (Lima-Sousa et al., 2023). Despite these advantages, their preparation often requires the synthesis or pre-modification of polymers with moieties compatible with the selected covalent crosslinking chemistry (Ali et al., 2022; Lo et al., 2019; Yang et al., 2018). Alternatively, small molecules (*e.g.*, thiolated peptides) and nanoparticles (*e.g.*, poly(dopamine) nanostructures) with reactive groups can also be included in the formulations to ensure the covalent linkage of the polymeric networks, leading to the hydrogels' *in situ* formation (Wan et al., 2021; Zhuang et al., 2022). If catalysts or other aiding molecules are required for the rapid establishment of the covalent bonds, it is also important to ensure their biological compatibility (Lima-Sousa et al., 2023).

Chemical-crosslinking strategies based on Thiol-Maleimide Michael-type additions have been employed to drive the *in situ* gelation of hydrogels. Thiol-Maleimide injectable *in situ* forming hydrogels can be assembled through the simple reaction of polymers (or small bridging molecules) endowed with these chemical moieties (Lo et al., 2019). This reaction can be catalyzed by weak bases avoiding the usage of other potentially harmful molecules (Jansen et al., 2018). Nevertheless, a precise control over the Thiol:Maleimide stoichiometric ratios must be employed to avoid any reaction of the maleimide-grafted polymers with endogenous molecules containing readily available thiol groups (*e.g.*, glutathione) (Gober et al., 2023). For instance, Lo *et al.* verified that the combination of maleimide-grafted poly(glutamic acid) and branched (4-arm) thiolated poly(ethylene glycol) allowed the preparation of injectable *in situ* forming hydrogels (Lo et al., 2019), which were explored for trastuzumab delivery. More recently, the Tetrazine-Norbornene chemistry started to be explored for mediating the *in situ* assembly of injectable hydrogels due to its chemical selectivity and fast reaction without the need of catalysts (Desai et al., 2015). The preparation of tetrazine-norbornene injectable *in situ* forming hydrogels also requires the pre-modification of the polymers with these functional groups (Ali et al., 2022; Desai et al., 2015). In this regard, Ali *et al.* grafted the norbornene functional group into the backbone of carboxymethyl cellulose and conjugated tetrazine to the terminals of a poly(ethylene glycol) derivative (Ali et al., 2022). By mixing these functionalized polymers, an injectable hydrogel assembled *in situ* through the tetrazine-norbornene crosslinking chemistry could be attained, which was then explored for Doxorubicin delivery (Ali et al., 2022). Other injectable hydrogels assembled *in situ* through chemical crosslinking are listed in Table 2.

In this way, the use of injectable *in situ* forming hydrogels can potentiate an improved anticancer effect (Table 2). He et al. formulated an injectable hydrogel using thiolated Hyaluronic acid (crosslinked through disulfide bonds) that was loaded with a multidrug combination of Doxorubicin, Sorafenib, and Metformin (He et al., 2017). *In vivo*, the delivery of the triple-drug cocktail by the injectable hydrogel led to the strongest tumor growth reduction, outperforming the effect mediated by the free triple-drug administration (He et al., 2017). In another work, Xu and collaborators prepared injectable *in situ* forming hydrogels composed of Pluronic F127 that incorporated Quercetin-loaded poly (ethylene glycol)-poly(ε-caprolactone) micelles (Xu et al., 2018). In *in vivo* studies, the delivery of Quercetin-loaded micelles by the injectable Pluronic F127 hydrogel prompted a stronger antitumoral effect when compared to the action of Quercetin-loaded micelles and free Quercetin (Xu et al., 2018). Ho team prepared Thiol-Maleimide and Ionic crosslinked injectable *in situ* forming hydrogels using maleimide-grafted poly (glutamic acid), branched (4-arm) thiolated poly(ethylene glycol), and $ZnCl_2$ (provides Zn^{2+}) (Lo et al., 2019). This dual-crosslinked hydrogel efficiently encapsulated Trastuzumab and coordinated its *in vivo* delivery, resulting in the reduction of the tumor's growth (Fig. 3) (Lo et al., 2019). The therapeutic capacity of other injectable *in situ* forming hydrogels loaded with chemotherapeutic agents is summarized in Table 2.

4. Injectable shear-thinning/self-healing hydrogels

Injectable shear-thinning/self-healing hydrogels have also been applied for the tumor-confined delivery of drugs/drug-loaded nanomaterials (Jiang et al., 2022; Poudel et al., 2018; Xie et al., 2017). The reversible nature of the sol–gel transitions displayed by this class of hydrogels makes their preparation and administration unique (Lima-Sousa et al., 2023). Initially, the hydrogels containing the chemotherapeutic agents are fully assembled directly inside the injection apparatus (Jiang et al., 2022; Xie et al., 2017). Then, the force generated during the extrusion causes a loss in the formulations' viscosity (shear-thinning), enabling their intratumoral injection (Jiang et al., 2022; Xie et al., 2017). When the injection force ceases, the formulations return to their gel state (self-healing), becoming assembled at the tumor site (Jiang et al., 2022; Xie et al., 2017). The preparation of shear-thinning/self-healing hydrogels has been mainly accomplished by exploiting host–guest interactions and the Schiff base reaction due to their reversible nature (Jiang et al., 2022; Poudel et al., 2018; Xie et al., 2017).

Host-guest interactions based on the inclusion complexes formed between polymers functionalized with β-cyclodextrin (host) and adamantane (guest) have been explored to prepare injectable shear-thinning/self-healing hydrogels (Jain et al., 2022). In this way, this approach requires the previous functionalization of the selected polymers with β-cyclodextrin and adamantane (Jiang et al., 2022; Tong et al., 2022). For instance, Tong *et al.* performed the modification of oxidized gellan gum with β-cyclodextrin and adamantane (Tong et al.,

Table 2
Injectable hydrogels for the delivery of chemotherapeutic agents.

Type of administration	Main crosslinking chemistry	Composition	Chemotherapeutic agent	Main outcome[#]	Ref.
Injectable	Ionic crosslinking	Chitosan and HCO_3^-	Doxorubicin loaded TPGS[(1)] nanoparticles	The hydrogels mediated a sustained drug release (≈ 15 % at 24 h pH 7.4)	(Sabino et al., 2021)
Injectable	Ionic crosslinking	Chitosan and β-glycerophosphate	Methotrexate	The hydrogels mediated a sustained drug release (≈ 25 % at 4 h)	(Saeednia et al., 2019)
Injectable	Ionic crosslinking	Chitosan and β-glycerophosphate	Cisplatin	The hydrogels mediated a sustained drug release, diminishing the cancer cells' viability (up to ≈ 17 % at 48 h)	(Peng et al., 2019b)
Injectable	Hydrophobic interactions	Silk fibroin	Salinomycin loaded silk fibroin nanoparticles and Paclitaxel loaded silk fibroin nanoparticles	The simultaneous delivery of the Salinomycin-nanoparticles and Paclitaxel-nanoparticles by the hydrogel led to a stronger tumor growth reduction (RTV[(a)] ≈ 2.3) when compared to the free dual drug administration (RTV ≈ 5.0)	(Wu et al., 2018)
Injectable	Hydrophobic interactions	Pluronic F127	Quercetin loaded methoxy poly (ethylene glycol)-poly (caprolactone) nanoparticles	The delivery of the drug-loaded nanoparticles by the hydrogel led to a stronger *in vivo* antitumoral effect (TW[(b)] = 0.198 g) when compared to the drug-loaded nanoparticles (TW = 0.470 g) and free drug (TW = 0.700 g) administrations	(Xu et al., 2018)
Injectable	Hydrophobic interactions	Poly(γ-ethyl-L-glutamate)-poly (ethylene glycol)-poly(γ-ethyl-L-glutamate)	Doxorubicin	The hydrogels mediated a sustained drug release, leading to cancer cells' apoptosis/necrosis (≈ 49 %)	(Lv et al., 2018)
Injectable	Hydrophobic interactions	Bi(methoxyl poly(ethylene glycol)-poly(lactic-*co*-glycolic acid))-Pt(IV)	Paclitaxel loaded bi(methoxyl poly(ethylene glycol)-poly (lactic-*co*-glycolic acid))-Pt(IV) micelles	The dual-drug delivery mediated by the hydrogel led to tumor regression (TV[(c)] difference ≈ −27 mm^3)	(Shen et al., 2017)
Injectable	Hydrophobic interactions	Alginate-*g*-poly(*N*-isopropylacrylamide)	Doxorubicin loaded alginate-*g*-poly(*N*-isopropylacrylamide) micelles	The hydrogels mediated a sustained drug release, diminishing the cancer cells' viability (up to ≈ 43 % at 24 h)	(Liu et al., 2017)
Injectable	Hydrophobic interactions	Pluronic F127	Gemcitabine	The hydrogels mediated a sustained gemcitabine release (≈ 87 % at 12 h pH 7.4)	(Qin et al., 2019)
Injectable	Hydrophobic interactions	Poly(ε-caprolactone-*co*-lactide)-*b*-poly(ethylene glycol)-*b*-poly (ε-caprolactone-*co*-lactide)	Doxorubicin	The drug delivery mediated by the hydrogel led to a stronger tumor growth reduction (TV ≈ 282 mm^3) when compared to the free drug administration (TV ≈ 600 mm^3)	(Jung et al., 2021)
Injectable	Hydrophobic interactions	Silk fibroin from *Bombyx mori and Antheraea assamensis*	Doxorubicin	The hydrogels mediated a sustained drug release, leading to a decrease in the cancer cells viability (up to ≈ 19 % at 72 h)	(Jaiswal et al., 2023)
Injectable	Hydrophobic interactions	Poly(D,L-lactide)-poly(ethylene glycol)-poly(D,L-lactide)	5-fluorouracil and cisplatin	The delivery of the dual drugs by the hydrogel led to a stronger *in vivo* antitumoral effect (TW ≈ 0.024 g) when compared to the free dual drug administration (TW ≈ 0.109 g)	(Chen et al., 2023)
Injectable	Hydrophobic interactions	Poly(ethylene glycol) grafted with poly(caprolactone) and poly(lactic acid)	Biotin-grafted poly (amidoamine) dendrimer incorporating doxorubicin	The delivery of the drug-loaded nanoformulation by the hydrogel led to a tumor	(Hanurry et al., 2022)

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Table 2 (*continued*)

Type of administration	Main crosslinking chemistry	Composition	Chemotherapeutic agent	Main outcome[#]	Ref.
				growth reduction (TGI[(d)] ≈ 58 %)	
Injectable	Hydrophobic interactions	Poly(L-lactide-*co*-glycolide)-poly (ethylene glycol)-poly(L-lactide-*co*-glycolide)	Honokiol loaded Poloxamer 407 nanosuspensions	The delivery of the drug-loaded nanoformulation by the hydrogel led to a tumor growth reduction (TGI ≈ 35 %)	(Lu et al., 2022)
Injectable	Hydrophobic interactions	Poly(D,L-lactide) – poly(ethylene glycol) – poly(D,L-lactide)	Gemcitabine loaded poly (ethylene glycol)-coated liposomes[(2)]	The delivery of the drug-loaded liposomes by the hydrogel led to tumor growth reduction (TW ≈ 1.2 g *vs.* TW of control ≈ 1.7 g)	(Kong et al., 2021)
Injectable	Hydrophobic interactions	Pluronic F127	Salinomycin	The drug delivery mediated by the hydrogel led to a stronger tumor growth reduction (TV ≈ 237 mm^3) when compared to the free drug administration (TV ≈ 953 mm^3)	(Norouzi et al., 2021)
Injectable	Hydrophobic interactions	Poly(lactide-*co*-glycolide)-*b*-poly (ethylene glycol)-*b*-poly(lactide-*co*-glycolide)	TPGS stabilized paclitaxel-nanocrystals and Poloxamer 188 stabilized niclosamide-nanocrystals	The co-delivery of the paclitaxel-nanocrystals and niclosamide-nanocrystals by the hydrogel (TV ≈ 300 mm^3) led to a stronger tumor growth reduction when compared to the hydrogels formulated with a single drug-nanocrystal (TV ≈ 580 or ≈ 755 mm^3)	(Zhao et al., 2021)
Injectable	Hydrophobic interactions	Poly(lactic acid)-poly(ethylene glycol)-poly(*N*-isopropylacrylamide)	Paclitaxel loaded poly(lactic acid)-poly(ethylene glycol)-poly (*N*-isopropylacrylamide) micelles	The hydrogels mediated a sustained drug release (≈ 50 % at 5d)	(Vohidov et al., 2020)
Injectable	Hydrophobic interactions	Poly(D,L-lactide)-poly(ethylene glycol)-poly(D,L-lactide)	Erlotinib-loaded hollow mesopourous silica nanoparticles	The delivery of the drug-loaded nanoparticles by the hydrogel led to a stronger tumor growth reduction (TV ≈ 250 mm^3) when compared to the drug-loaded nanoparticles (TV ≈ 607 mm^3)	(Zhou et al., 2020b)
Injectable	Hydrophobic interactions	Poloxamer 407	Doxorubicin	The hydrogels mediated a sustained drug release, diminishing the cancer cells' viability (up to ≈ 5 % at 72 h)	(Chung et al., 2020)
Injectable	Hydrophobic interactions	Poly(D,L-Lactide)-poly(ethylene glycol)-poly(D,L-Lactide)	Doxorubicin loaded poly (D,L-Lactide)-poly(ethylene glycol)-poly(D,L-Lactide) micelles and bevacizumab	The delivery of the doxorubicin-loaded micelles and bevacizumab by the hydrogel led to a stronger *in vivo* antitumoral effect (TGI ≈ 80 %) when compared to the free doxorubicin and bevacizumab administrations (TGI ≈ 58 %)	(Darge et al., 2019)
Injectable	Hydrophobic interactions	Poly(D,L-lactide-*co*-glycolide)-*b*-poly (ethylene glycol)-*b*-poly (D,L-lactide-*co*-glycolide)	Doxorubicin loaded lipossomes[(3)]	The delivery of the drug-loaded liposomes by the hydrogel led to a stronger *in vivo* antitumoral effect (RTV ≈ 2.7) when compared to the drug-loaded liposomes (RTV ≈ 4.0) and free drug (RTV ≈ 4.9) administrations	(Cao et al., 2019a)
Injectable	Hydrophobic interactions	Pluronic F127 and Pluronic F68	TPGS-coated paclitaxel nanocrystals	The delivery of the drug-based nanocrystals by the hydrogel led to an *in vivo* antitumoral effect (TW ≈ 3.4 g *vs.* TW of control ≈ 8.0 g)	(Wang et al., 2018)
Injectable	Hydrophobic interactions	Poly(ε-caprolactone)-Pluronic 10R5-poly(ε-caprolactone)	Oxaliplatin and tannic acid nanoparticles[(4)]	The delivery of the dual drug-loaded nanoparticles	(Ren et al., 2019)

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Table 2 (*continued*)

Type of administration	Main crosslinking chemistry	Composition	Chemotherapeutic agent	Main outcome[#]	Ref.
				by the hydrogel led to an *in vivo* antitumoral effect (median survival of 38d *vs.* control median survival of 20d)	
Injectable	Hydrophobic interactions	Methylcellulose	Doxorubicin-loaded silica based nanoparticles	The delivery of the drug-loaded nanoparticles by the hydrogel led to tumor regression (RTV ≈ 0.7) while the free drug administration only induced tumor growth reduction (RTV ≈ 2.1)	(Wu et al., 2021)
Injectable	Hydrophobic interactions	Poly(ε-caprolactone-*co*-1,4,8-trioxa [4.6]spiro-9-undecanone)-poly (ethylene glycol)-poly (ε-caprolactone-*co*-1,4,8-trioxa [4.6]spiro-9-undecanone)	Doxorubicin loaded poly (ε-caprolactone-*co*-1,4,8-trioxa [4.6]spiro-9-undecanone)-poly (ethylene glycol)-poly (ε-caprolactone-co-1,4,8-trioxa [4.6]spiro-9-undecanone) nanoparticles	The delivery of the drug-loaded nanoparticles by the hydrogel led to a stronger *in vivo* antitumoral effect (TGI ≈ 75 %) when compared to the drug-loaded nanoparticles (TGI ≈ 43 %)	(Huang et al., 2016)
Injectable	Hydrogen bonding	Agarose and amylose nanoparticles	5-fluorouracil	The hydrogels mediated a sustained 5-fluorouracil release (≈ 187 μg after 12 min)	(Ma et al., 2022)
Injectable	Hydrogen bonding	Chitosan and agarose	Doxorubicin and Ibuprofen	The hydrogels mediated a sustained release of Doxorubicin (≈ 14 % at 48 h pH 7.4) and Ibuprofen (≈ 67 % at 48 h pH 7.4)	(Lima-Sousa et al., 2020)
Injectable	Hydrogen bonding	Chitosan	Disulfiram	The drug delivery mediated by the hydrogel led to a reduction of the cancer cells' viability (up to ≈ 7 % at 48 h)	(Ahsan et al., 2020)
Injectable	Hydrogen bonding	Poly(vinyl alcohol), dextrose, glycerol, sodium tetraborate and C16EMorphBr[(5)]	Doxorubicin	The delivery of the drug by the hydrogel decreases cancer cells' viability (up to ≈ 5 % at 48 h)	(Kuddushi et al., 2020)
Injectable	Hydrogen bonding	β-cyclodextrin functionalized agarose	Doxorubicin (inclusion complexation with ß-cyclodextrin)	The hydrogels mediated a sustained drug release, diminishing the cancer cells' viability (up to ≈ 17 % at 24 h)	(Kim et al., 2019)
Injectable	Hydrogen bonding	Agarose	Doxorubicin	The hydrogels mediated a sustained drug release (≈ 6 % at 12 h pH 7.4)	(Hou et al., 2018)
Injectable	Ionic crosslinking, hydrogen bonding and hydrophobic interactions	Chitosan, hyaluronic acid and β-glycerophosphate	Doxorubicin	The hydrogels were capable of sustaining drug release (≈ 22 % at 60 h at pH 6.86)	(Zhang et al., 2018)
Injectable	Hydrogen bonding, ionic crosslinking and hydrophobic interactions	Chitosan and β-glycerophosphate	5-fluorouracil loaded poly (ε-caprolactone)-poly(ethylene glycol)-poly(ε-caprolactone) micelles and cisplatin	The delivery of the dual drugs by the hydrogel led to a stronger *in vivo* antitumoral effect (median survival of 43d) when compared to the free dual drug administration (median survival of 35d)	(Yun et al., 2017)
Injectable	Ionic crosslinking and hydrophobic interactions	Poly(*N*-isopropylacrylamide-co-itaconic acid), chitosan and β-glycerophosphate	Doxorubicin	The hydrogels mediated a pH sensitive drug release (≈ 37 % at pH 7.4 *vs.* ≈ 99 % at pH 5.5 after 72 h)	(Fathi et al., 2019)
Injectable	Hydrogen bonding and hydrophobic interactions	Poloxamer 407, Poloxomer 188 and xanthan gum	Paclitaxel loaded poly(lactic-*co*-glycolic acid)-based nanoparticles	The delivery of the drug-loaded nanoparticles by the hydrogel led to a stronger *in vivo* antitumoral effect (RTV ≈ 1.5) when compared to the drug-loaded hydrogel (RTV ≈ 2.5), drug-loaded nanoparticles (RTV ≈ 3.0) and free drug (RTV ≈ 3.2) administrations	(Jeswani et al., 2023)
Injectable	Ionic crosslinking and π–π stacking	9-fluorenylmethoxycarbonyl-modified diphenylalanine and glycol chitosan	Doxorubicin	The hydrogels mediated a sustained drug release, diminishing the cancer	(Shim et al., 2021)

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Table 2 (*continued*)

Type of administration	Main crosslinking chemistry	Composition	Chemotherapeutic agent	Main outcome[#]	Ref.
				cells' viability (up to ≈ 15 % at 48 h)	
Injectable	Hydrophobic interactions and hydrogen bonding	Methacrylated hyaluronic acid grafted with poly(2-(3-(6-methyl-4-oxo-1,4-dihydropyrimidin-2-yl) ureido)ethyl methacrylate) and poly(diethylene glycol methacrylate)	Doxorubicin	The drug delivery mediated by the hydrogel led to tumor growth reduction (TV ≈ 878 mm^3 *vs.* TV of the control ≈ 1836 mm^3)	(Liu et al., 2021b)
Injectable	Ionic crosslinking and hydrophobic interactions	Chitosan, β-glycerophosphate and Pluronic F127	5-fluorouracil and methotrexate	The hydrogel was capable of sustaining the release of 5-fluorouracil (≈ 31 % at 12d) and methotrexate (≈ 100 % at 12d)	(Mohammed et al., 2020)
Injectable	Hydrogen bonding, ionic crosslinking and hydrophobic interactions	Chitosan and β-glycerophosphate	Doxorubicin	The hydrogels mediated a sustained drug release, diminishing the cancer cells' viability (≈ 57 % at 24 h)	(Zheng et al., 2019)
Injectable	Hydrophobic interactions and hydrogen bonding	Regenerated silk fibroin and hydroxypropylcellulose	Doxorubicin and Curcumin	The dual-drug delivery mediated by the hydrogel led to a stronger tumor growth reduction (RTV ≈ 1.5) when compared to the hydrogels formulated with a single drug (RTV ≈ 3.8)	(Cao et al., 2019b)
Injectable	Thiol-catechol Michael addition	4-arm thiolated poly(ethylene glycol) and oxidized Poly(*N*-(3,4-dihydroxyphenethyl) methacrylamide-*co*-poly(ethylene glycol) methyl ether methacrylate)[(6)]	Doxorubicin loaded poly(acrylic acid-*co*-4-vinylphenylboronic acid) nanoparticles and Combretastatin-A4 phosphate	The dual-drug delivery mediated by the hydrogel led to a stronger tumor growth reduction (TV ≈ 355 mm^3) when compared to the hydrogels formulated with a single drug (TV ≈ 486 mm^3 or TV ≈ 537 mm^3)	(Yang et al., 2018)
Injectable	Thiol-catechol Michael addition	Poly(dopamine) nanoparticles and thiolated hyaluronic acid	Doxorubicin loaded poly (dopamine) nanoparticles	The hydrogels mediated a sustained drug release (≈ 270 μg at 15d pH 7.4)	(Zhuang et al., 2022)
Injectable	Tetrazine-norbornene click chemistry	Norbornene-functionalized carboxymethyl cellulose and di-tetrazine-functionalized poly (ethylene glycol)	Doxorubicin	The hydrogels mediated a sustained drug release, prompting the death of cancer cells (up to ≈ 62 % at 24 h)	(Ali et al., 2022)
Injectable	Disulfide bonds	Thiol-modified hyaluronic acid	Sorafenib, Doxorubicin and Metformin	The triple-drug delivery mediated by the hydrogel led to a stronger tumor growth reduction (RTV ≈ 2.2) when compared to the triple-drug administration (RTV ≈ 5.9)	(He et al., 2017)
Injectable	Disulfide bonds (aided by DMSO)	Thiolated hyaluronic acid	Doxorubicin	The drug delivery mediated by the hydrogel led to tumor regression (TV difference ≈ −219 mm^3) while the free drug administration led to systemic toxicity	(Xu et al., 2021)
Injectable	Photocrosslinking (mediated by Lucirin-TPO® and 400 nm light)	Poly(ethylene glycol)-dimethacrylate	Paclitaxel-loaded poly(ethylene glycol) coated nanoparticles[(7)]	After tumor resection, the delivery of the drug-loaded nanoparticles by the hydrogel enhanced the mice survival (≈ 55 % at 100d) when compared to the direct administration of the drug-loaded nanoparticles (survival of ≈ 13 % at 100d)	(Zhao et al., 2018)
Injectable	Polymerization (mediated by ammonium persulfate and ascorbic acid)	Methacrylated poly-β-cyclodextrin and *N*-isopropylacrylamide	Adamantane-modified doxorubicin	The drug delivery mediated by the hydrogel led to a stronger tumor growth reduction (RTV ≈ 6.3) when compared to the free drug administration (RTV ≈ 9.4)	(Xu et al., 2017)

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Table 2 (*continued*)

Type of administration	Main crosslinking chemistry	Composition	Chemotherapeutic agent	Main outcome[#]	Ref.
Injectable	Polymerization (mediated by tetramethylethylenediamine and ammonium persulfate)	Methacrylated hyaluronic acid and methacrylated dextran sulfate	Doxorubicin	The drug delivery mediated by the hydrogel led to tumor growth reduction (TV ≈ 667 mm^3 *vs.* TV of control ≈ 1713 mm^3)	(Deng et al., 2018)
Injectable	Covalent bond (mediated by epichlorohydrin)	Cellulose	Doxorubicin	The chemotherapy mediated by the hydrogel led to a tumor growth reduction (TV ≈ 238 mm^3 *vs.* TV of control ≈ 1049 mm^3)	(Xing et al., 2018)
Injectable	Catechol-Fe(III) coordinative interactions	Catechol-modified chitosan and Fe $(NO_3)_3$	Doxorubicin and Docetaxel	The dual-drug delivery mediated by the hydrogel led to a stronger tumor growth reduction (TV ≈ 78 mm^3) when compared to the dual-drug administration (TV ≈ 404 mm^3)	(Yavvari et al., 2017)
Injectable	Oxidative coupling (catalyzed by horseradish peroxidase and H_2O_2)	Tyramide-grafted hyaluronic acid	Anlotinib	The drug delivery mediated by the hydrogel led to a tumor growth reduction (TV ≈ 791 mm^3 *vs.* TV of control ≈ 6718 mm^3)	(Gao et al., 2020)
Injectable	Oxidative coupling (catalyzed by horseradish peroxidase and H_2O_2)	Tyramine-modified hyaluronic acid	Doxorubicin loaded triphenylphosphine-funcionalized core shell gold mesoporous silica nanoparticles	The delivery of the drug-loaded nanoparticle by the hydrogel led to tumor regression (RTV ≈ 0.4 *vs.* RTV of control ≈ 5.0)	(Zhou et al., 2020a)
Injectable	Catechol-Fe(III) coordinative interactions	L-3,4-dihydroxyphenylalanine-poly (ethyleno glycol)-gelatin, H_2O_2 and $FeCl_3$	Doxorubicin	The hydrogels mediated a pH sensitive drug release, diminishing the cancer cells' viability (up to ≈ 10 % at 24 h)	(Pham et al., 2020)
Injectable	Thiol-Maleimide Michael addition and ionic crosslinking	Maleimide grafted γ-poly(glutamic acid), 4-arm thiolated poly (ethylene glycol) and $ZnCl_2$	Trastuzumab	The trastuzumab delivery mediated by the hydrogel led to a tumor growth reduction (TV ≈ 251 mm^3 *vs.* TV of control ≈ 604 mm^3)	(Lo et al., 2019)
Injectable	Ionic crosslinking and disulfide bonds	Thiolated chitosan and β-glycerphosphate	Curcumin loaded liposomes[(8)]	The delivery of the drug-loaded liposomes by the hydrogel led to a reduction of the cancer cells' viability (up to ≈ 4 % at 72 h)	(Li et al., 2021b)
Injectable	Thiol-catechol/pyrogallol Michael addition (catalyzed by tyrosinase), hydrogen bond, and Fe(III) coordinative interactions	Tannic acid, 4-arm thiolated poly (ethylene glycol) and $FeCl_3$	Doxorubicin	The drug delivery mediated by the hydrogel led to a tumor growth reduction (RTV ≈ 5.1 *vs.* RTV of control ≈ 8.7)	(Zhu et al., 2021)
Injectable	Oxidative polymerization (mediated MnO_2 nanosheets), ionic crosslinking, π-π and polar-π interactions	Caffeic acid-modified chitosan and MnO_2 nanosheets	Doxorubicin loaded MnO_2 nanosheets	The delivery of the drug-loaded nanoparticles mediated by the hydrogel led to a stronger tumor growth reduction (TV ≈ 762 mm^3) when compared to the free drug administration (TV ≈ 1314 mm^3)	(Wang et al., 2020)
Injectable	Host-guest interactions	α-cyclodextrin and methoxy-poly (ethylene glycol)-*b* poly (ε-caprolactone)-*b*-poly(ethylene imine)-folic acid	Paclitaxel loaded methoxy-poly (ethylene glycol)-*b*-poly (ε-caprolactone)-*b*-poly (ethylene imine)-folic acid nanoparticles	The delivery of the drug-loaded nanoparticles by the hydrogel led to a reduction of the cancer cells' viability (up to ≈ 56 %)	(Liu et al., 2019d)
Injectable	Host-guest interactions	Methoxy poly(ethylene glycol)-*b*-poly(ε-caprolactone-*co*-1,4,8-trioxa [4.6]spiro-9-undecanone) and α-cyclodextrin	Paclitaxel-loaded methoxy poly (ethylene glycol)-*b*-poly (ε-caprolactone-*co*-1,4,8-trioxa [4.6]spiro-9-undecanone nanoparticles	The drug delivery mediated by the hydrogel led to a tumor growth reduction (RTV ≈ 12.5 *vs.* RTV of control ≈ 22.0)	(Liu et al., 2019b)
Injectable	Host-guest interactions	Methoxy poly(ethylene glycol)-*b*-ketal-protected aliphatic poly (carbonate) and α-cyclodextrin	Doxorubicin loaded methoxy poly(ethylene glycol)-*b*-ketal-protected aliphatic polycarbonate micelles and 6-(4-(8-quinolinyloxymethyl)-1H-	The delivery of the dual drugs by the hydrogel led to a reduction of the cancer cells' viability (up to ≈ 12 % at 48 h)	(Dominski et al., 2022)

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Table 2 (*continued*)

Type of administration	Main crosslinking chemistry	Composition	Chemotherapeutic agent	Main outcome[#]	Ref.
			1,2,3-triazol-1-yl)-6-deoxy-D-glucopyranose		
Injectable	Host-guest interactions	Adamantane modified oxidized gellan gum and β-cyclodextrin-modified oxidized gellan gum	Doxorubicin loaded prussian blue nanoparticles	After tumor resection, the delivery of the drug loaded nanoparticles by the hydrogel led to a growth reduction of the recurring tumors (TV ≈ 120 mm^3 *vs.* TV of control ≈ 610 mm^3) and decreased metastases formation	(Tong et al., 2022)
Injectable	Host-guest interactions	α-cyclodextrin and poly(ethylene glycol)-*b*-poly (lactic acid)	Doxorubicin loaded poly (ethylene glycol)-*b*-poly (lactic acid) micelles	The drug delivery mediated by the hydrogels could induce a stronger decrease in the cancer cells' viability (up to ≈ 17 % at 72 h) when compared to the free drug administration (up to ≈ 30 % at 72 h)	(Poudel et al., 2018)
Injectable	Host-guest interactions	β-cyclodextrin grafted with poly(*N*-isopropylacrylamide), adamantyl-terminated poly(ethylene glycol) and α-cyclodextrin	Doxorubicin loaded micelles	The hydrogels mediated a sustained release of the drug loaded micelles, diminishing the cancer cells' viability (up to ≈ 47 % at 24 h)	(Song et al., 2020)
Injectable	Host-guest interactions	α-cyclodextrin and poly(ethylene glycol)	Doxorubicin	The drug delivery mediated by the hydrogel led to tumor growth reduction (TV ≈ 968 mm^3 *vs.* TV of control ≈ 2500 mm^3)	(Dong et al., 2020)
Injectable	Host-guest interactions	Poly(ethylene glycol) functionalized poly(*N*-phenylglycine) and α-cyclodextrin	Doxorubicin	The drug delivery mediated by the hydrogel led to tumor growth reduction (RTV ≈ 2.8 *vs.* RTV of control ≈ 7.8)	(Liu et al., 2019a)
Injectable	Host-guest interactions	Methoxy poly(ethylene glycol)-*b*-poly(ε-caprolactone-*co*-1,4,8-trioxa [4.6]spiro-9-un-decanone) and α-cyclodextrin	Doxorubicin loaded nanoparticles	The hydrogels were capable of sustaining drug release (≈ 47 % at 18d pH 7.4)	(Peng et al., 2019a)
Injectable	Schiff base	Dihydrocaffeic acid-grafted chitosan and oxidized pullulan	Doxorubicin	The hydrogels mediated a pH-sensitive drug release (≈ 52 % at pH 7.4 *vs.* ≈ 87 % at pH 5.5 after 60 h) and achieved gelation *in vivo* after 10 min	(Liang et al., 2019)
Injectable	Schiff base	Carboxymethyl chitosan-functionalized reduced graphene oxide and dialdehyde-poly(ethylene glycol)	Doxorubicin	The hydrogels mediated a pH-sensitive drug release (≈ 64 % at pH 7.4 after 17 h *vs.* ≈ 99 % at pH 6.5 after 8 h) and achieved gelation in 3 – 7 min	(Liu et al., 2019c)
Injectable	Schiff base	Aldehyde-modified pullulan, poly (L-lysine) and branched poly (ethylenimine)	Cisplatin and Doxorubicin	The delivery of the dual drug by the hydrogel led to a stronger *in vivo* antitumoral effect (TGI ≈ 94 %) when compared to the free dual drug administration (TGI ≈ 83 %)	(Cheng et al., 2017)
Injectable	Schiff base	Glycol chitosan and dibenzaldehyde-modified poly (ethylene glycol)	Docetaxel loaded poly(vinyl alcohol)-coated poly(lactic-*co*-glycolic acid) nanoparticles and doxorubicin	The delivery of the dual drugs by the hydrogel led to tumor regression (RTV ≈ 0.9 *vs.* RTV of control ≈ 4.5)	(Xie et al., 2017)
injectable	Schiff base	*N*-carboxyethyl chitosan and dibenzaldehyde-modified poly (ethylene glycol)	Doxorubicin	The hydrogels mediated a pH-sensitive drug release (≈ 42 % at pH 7.4 *vs.* ≈ 89 % at pH 6.8 after 7d) and could induce a stronger reduction of the cancer cells' viability when compared to the free drug	(Qu et al., 2017)
Injectable	Schiff base	Carboxymethyl chitosan and oxidized hydroxypropyl cellulose	Artesunate	The drug delivery mediated by the hydrogel led to a tumor growth reduction	(Ma et al., 2023)

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Table 2 (*continued*)

Type of administration	Main crosslinking chemistry	Composition	Chemotherapeutic agent	Main outcome[#]	Ref.
				(TV ≈ 418 mm^3 *vs.* TV of control ≈ 1008 mm^3)	
Injectable	Schiff base	Carboxymethyl chitosan and oxidized hyaluronic acid grafted with metformin	Oxidized hyaluronic acid-metformin conjugate	After tumor resection, the delivery of the drug by the hydrogel prevented tumor recurrence in 4 out of 5 mice, while the free drug administration only prevented recurrence in 2 out of 5 mice	(Zheng et al., 2023)
Injectable	Schiff base	Acylhydrazide-functionalized carboxymethyl cellulose and oxidized pectin	Limonin	The drug delivery mediated by the hydrogel led to a tumor growth reduction (TV ≈ 354 mm^3 *vs.* TV of control ≈ 1263 mm^3)	(Chang et al., 2022)
Injectable	Schiff base	Oxidized dextran and oxaliplatin-conjugated poly(amidoamine) dendrimer	Oxaliplatin-conjugated poly (amidoamine) dendrimer	The delivery of the drug-loaded nanoparticles by the hydrogel led to a stronger antitumoral effect (RTV ≈ 10.5) when compared to free drug administration (RTV ≈ 19.9)	(Luo et al., 2022)
Injectable	Schiff base	*N,O*-Carboxymethyl chitosan and aldehyde-hyaluronic acid	Paclitaxel loaded poly(ethylene glycol)-coated micelles[(9)] and Cisplatin	The dual-drug delivery mediated by the hydrogel led to tumor regression (TV ≈ 103 mm^3 *vs.* TV of control ≈ 927 mm^3)	(Yang et al., 2022)
Injectable	Schiff base (aided by borax)	Gelatin and oxidized alginate	Doxorubicin	The delivery of the drug by the hydrogel led to tumor growth reduction (median survival of ≈ 24d *vs.* control median survival of ≈ 16d)	(Tian et al., 2022)
Injectable	Schiff base	Aldehyde-modified guar gum and carboxymethyl chitosan	Doxorubicin	The hydrogels mediated a pH-sensitive drug release, diminishing the cancer cells' viability (up to ≈ 28 % at 48 h)	(Pandit et al., 2021)
Injectable	Schiff base	Aldehyde-modified gum arabic and succinic anhydride-modified chitosan	Tween 20-stabelized curcumin nanoemulsion	The hydrogels mediated a pH sensitive drug release, diminishing the cancer cells' viability (up to ≈ 23 % at 48 h)	(Pandit et al., 2020)
Injectable	Schiff base	4-arm poly(ethylene glycol)-benzaldehyde and *N*-carboxyethyl chitosan	Doxorubicin	The delivery of the drug by the hydrogel led to tumor regression (TV ≈ 28 mm^3) while the free drug administration only induced tumor growth reduction (TV ≈ 74 mm^3)	(Zhan et al., 2020)
Injectable	Schiff base	Aldehyde-modified hyaluronic acid and carboxymethyl chitosan	Aldehyde-modified hyaluronic acid-doxorubicin conjugate and gemcitabine	After tumor resection, the delivery of the dual drugs by the hydrogel prevented tumor recurrence in all mice	(Zhuang et al., 2020)
Injectable	Schiff base	Carboxyethyl chitosan and oxidized alginate	5-fluorouracil loaded microspheres	The hydrogels incorporating the drug-loaded microspheres performed a sustained drug release (≈ 56 % after 36d)	(Chen et al., 2019)
Injectable	Schiff base	Dibenzaldehyde-functionalized poly(ethylene glycol) and poly (aspartylhydrazide)	Doxorubicin	The hydrogels mediated a pH sensitive drug release (≈ 22 % at pH 7.4 *vs.* ≈ 80 % at pH 5.5 after 48 h)	(Wu et al., 2019)
Injectable	Schiff base	Carboxyethyl chitosan and aldehyde-modified hyaluronic acid	Doxorubicin	The hydrogels mediated a pH sensitive drug release, diminishing the cancer cells' viability (up to ≈ 50 % at 24 h)	(Qian et al., 2019)
Injectable	Host-guest interactions and Schiff base	β-cyclodextrin-grafted carboxyethyl cellulose, ethyl-1-adamantane 4-formylbenzoate, and adipic dihydrazide-grafted carboxyethyl cellulose	Doxorubicin	The drug delivery mediated by the hydrogel led to a stronger anti-tumoral effect (TW ≈ 0.029 g) when compared to the free drug administration (TW ≈ 0.160 g)	(Jiang et al., 2022)

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Table 2 (*continued*)

Type of administration	Main crosslinking chemistry	Composition	Chemotherapeutic agent	Main outcome[#]	Ref.
Injectable	Schiff base and ionic crosslinking	Poly(*N*-isopropylacrylamide)-functionalized chitosan, dibenzylaldehyde-functionalized poly(ethylene glycol) and {Mo154}	Doxorubicin	The hydrogels mediated a pH sensitive drug release (≈ 39 % at pH 7.4 *vs.* ≈ 97 % at pH 5.5 after 5 h)	(Guedes et al., 2021)
Injectable	Schiff base and ionic crosslinking	Acrylic acid-modified chitosan, oxidized alginate, adipic acid dihydrazide and $FeCl_2$	Doxorubicin	The hydrogels mediated a sustained drug release (≈ 52 % at 48 h pH 7.4)	(Mondal and Chatterjee, 2022)
Injectable	Schiff base, hydrogen bonding and hydrophobic interactions	Aldheyde-modificed tannic acid and (oligo)lysine-modified Pluronic F127	5-fluorouracil	The hydrogels mediated a pH sensitive drug release (≈ 38 % at pH 7.4 *vs.* 58 % at pH 5.0 after 6d)	(Li et al., 2021a)
Injectable	Schiff base and ionic crosslinking	Oxidized pectin and chitosan	5-fluorouracil	The hydrogels mediated a sustained drug release (≈ 83 % at 12 h pH 7.4)	(Li et al., 2020)
Injectable	Host-guest and hydrogen bonding	β-cyclodextrin-grafted heparin, Pluronic F127 and α-cyclodextrin	Doxorubicin	The hydrogels mediated a pH sensitive drug release, diminishing the cancer cells' viability (up to ≈ 36 % at 84 h)	(Zhou et al., 2022)

— The most important data with significance was selected; **(a)** – Relative Tumor Volume; **(b)** – Tumor Weight; **(c)** – Tumor Volume; **(d)** – Tumor Growth Inhibition; **(1)** – D-α-tocopheryl polyethylene glycol 1000 succinate; **(2)** – Formulated with dipalmitoylphosphatidylcholine, 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-N-(maleimide(polyethylene glycol)) and DPP – BTz; **(3)** – Formulated with Soybean phosphatidylcholine and colesterol; **(4)** – Formulated with poly (lactic acid)-Pluronic 10R5-poly(lactic acid); **(5)** – C16EMorphBr: [4-(2-(hexadecyloxy)-2-oxoethyl)-4-methylmorpholin-4-ium bromide; **(6)** – Oxidixed with $NaIO_4$; **(7)** – Formulated using poly(lactide-*co*-glycolide), poly(lactide-*co*-glycolide)-poly(ethylene glycol), poly(caprolactone)-poly(ethylene glycol) and poly(vinyl alcohol); **(8)** – L-α-phosphatidylcholine, cholesterol and Chitooligosaccharides; **(9)** – Formulated with monomethyl poly(ethylene glycol)-poly(ε-caprolactone-*ran*-trimethylene carbonate).

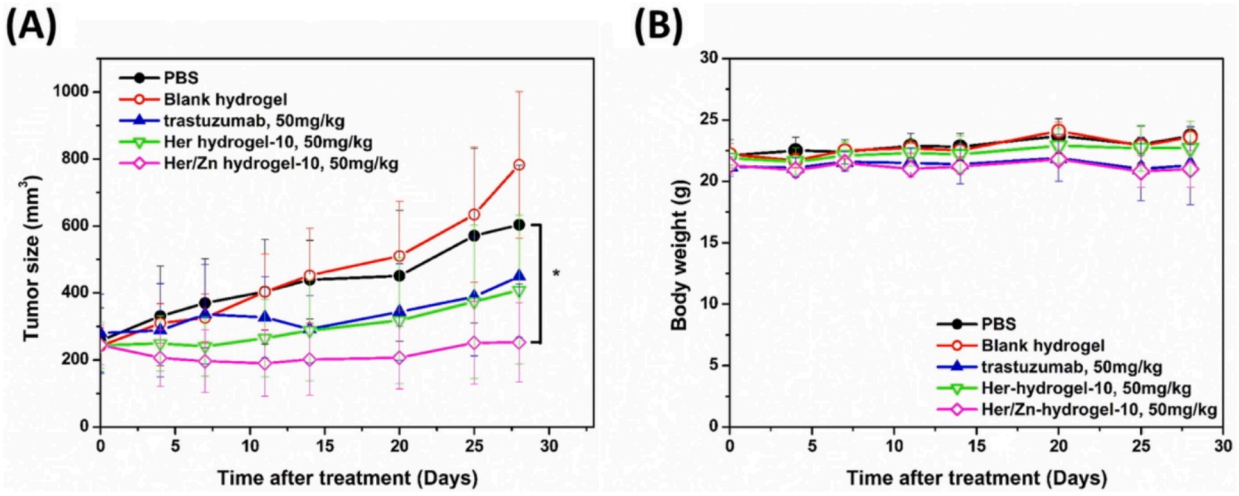

Fig. 3. Therapeutic capacity of injectable *in situ* forming hydrogels incorporating Trastuzumab. (A) Tumor volume variation and (B) body weight variation after the different treatments. PBS: Phosphate buffered saline; Blank hydrogel: injectable *in situ* forming hydrogel crosslinked by Thiol-Maleimide reaction (formulated using maleimide-grafted poly(glutamic acid) and branched (4-arm) thiolated poly(ethylene glycol)). Her hydrogel-10: injectable *in situ* forming hydrogel encapsulating Trastuzumab, crosslinked by Thiol-Maleimide reaction (formulated using maleimide-grafted poly(glutamic acid) and branched (4-arm) thiolated poly(ethylene glycol)). Her/Zn hydrogel-10: injectable *in situ* forming hydrogel encapsulating Trastuzumab, crosslinked by Thiol-Maleimide reaction and ionic crosslinking (formulated using maleimide-grafted poly(glutamic acid), branched (4-arm) thiolated poly(ethylene glycol), and $ZnCl_2$). Reprinted from (Lo et al., 2019), with permission from Elsevier. © 2019 Acta Materialia Inc. Published by Elsevier Ltd.

2022). By mixing β-cyclodextrin-functionalized oxidized gellan gum and adamantane-functionalized oxidized gellan gum, an injectable shear-thinning/self-healing hydrogel was assembled, which was explored for the encapsulation and delivery of Doxorubicin-loaded Prussian blue nanoparticles (Tong et al., 2022). Another popular type of host–guest interaction that has been explored for preparing injectable shear-thinning/self-healing hydrogels explores the penetration of the α-cyclodextrin cavity by the linear hydrophilic chains of specific amphiphilic polymers (Liu et al., 2019a). This type of host–guest interaction (also known as "molecular necklaces") can also be achieved through the penetration of the α-cyclodextrin cavity by linear hydrophilic polymeric segments immobilized on nanostructures' surface (Dominski et al., 2022; Poudel et al., 2018). In this regard, Poudel *et al.* formulated poly(ethylene glycol)-poly(lactic acid) micelles loaded with Doxorubicin, and exploited the interaction between the poly(ethylene glycol)-coated micelles and α-cyclodextrin for preparing shear-thinning/self-healing hydrogels (Poudel et al., 2018). Additional Host-Guest injectable shear-thinning/self-healing hydrogels aimed for the tumor-confined delivery of chemotherapeutic agents are described in Table 2.

Schiff base reactions between primary amines and aldehydes have also been employed in the production of shear-thinning/self-healing hydrogels (Mo et al., 2021). Hence, polymers with abundant primary amine functional units (*e.g.*, chitosan-derivatives, poly(lysine), branched

poly(ethylenimine)) have been a popular choice to produce injectable hydrogels crosslinked through Schiff base reactions (Cheng et al., 2017; Qu et al., 2017). Attaining aldehyde-functionalized polymers can be accomplished by grafting small molecules with this functional group (*e.g.*, 4-formylbenzoic acid) into the polymer's backbone (Liu et al., 2019c; Qu et al., 2017). Alternatively, the oxidation of specific polymers (*e.g.*, dextran, hydroxypropyl cellulose, pectin) using sodium periodate also renders materials with multiple aldehyde groups (Chang et al., 2022; Luo et al., 2022; Ma et al., 2023). In this regard, Qin group explored the Schiff base reaction between multi-aldehyde pectin and acylhydrazide-functionalized carboxymethyl cellulose (provides primary amines) in the assembly of injectable shear-thinning/self-healing hydrogels aimed for Limonin delivery (Chang et al., 2022). Other injectable shear-thinning/self-healing hydrogels assembled by the Schiff base reaction are listed in Table 2.

In this way, the use of injectable shear-thinning/self-healing hydrogels for mediating the delivery of chemotherapeutic agents can potentiate an enhanced therapeutic outcome (Table 2). Qu *et al.* formulated an injectable shear-thinning/self-healing hydrogel based on the Schiff base reaction between *N*-carboxyethyl chitosan and di-benzaldehyde-modified poly(ethylene glycol) (Qu et al., 2017). This injectable shear-thinning/self-healing hydrogel could mediate a stronger release of Doxorubicin when exposed to a slightly acidic medium (mimics the tumor microenvironment), promoting an *in vitro* anticancer effect that could outperform the free drug administration (Fig. 4) (Qu et al., 2017).

In another work, Xie *et al.* prepared an injectable hydrogel composed of glycol chitosan and di-aldehyde-functionalized poly(ethylene glycol) (Xie et al., 2017). The Schiff base crosslinking granted a shear-thinning/self-healing behavior to the hydrogel, which incorporated Docetaxel-loaded poly(lactic-*co*-glycolic acid)-based nanoparticles and Doxorubicin (Xie et al., 2017). *In vivo*, the delivery of the dual chemotherapeutic agents (*i.e.*, Docetaxel-loaded nanoparticles and Doxorubicin) by this hydrogel was capable of inducing tumor regression (Xie et al., 2017). Lu team prepared an injectable shear-thinning/self-healing hydrogel incorporating Doxorubicin by exploiting both host–guest interactions and Schiff base reaction (Jiang et al., 2022). This was accomplished by first complexing β-cyclodextrin-functionalized carboxyethyl cellulose with ethyl-1-adamantane 4-formylbenzoate (a small molecule that contains both the adamantane and aldehyde functional groups) (Jiang et al., 2022). This host–guest complex was then reacted with adipic dihydrazide-functionalized carboxyethyl cellulose by Schiff base reaction, leading to the hydrogels' assembly (Jiang et al., 2022). *In vivo*, the delivery of Doxorubicin mediated by this hydrogel led to tumor regression while the free Doxorubicin administration could only reduce the tumor's growth (Jiang et al., 2022). The therapeutic capacity of other injectable shear-thinning/self-healing hydrogels loaded with chemotherapeutic agents is summarized in Table 2.

5. Implantable hydrogels

Implantable hydrogels have also been explored for mediating the delivery of chemotherapeutic agents into the tumor or into the tumor bed (Chen et al., 2020; Li et al., 2019; Yu et al., 2020). The administration of implantable hydrogels requires a surgical procedure (Chen et al., 2020; Li et al., 2019), thus being a therapeutic strategy with a considerable degree of invasiveness. Nevertheless, the surgical resection of the tumor is a first-line treatment of many early-stage cancers (Debela et al., 2021). In this case, since the tumor site is already exposed by the surgical procedure, pre-assembled hydrogels containing the chemotherapeutics agents can be directly implanted into the tumor bed to assist in the elimination of the remaining/residual cancer cells (Li et al., 2019; Yu et al., 2020).

The implantable hydrogels can be prepared by a broad array of techniques and crosslinking chemistries since these already are fully assembled prior to their insertion into the surgical site (Chen et al., 2020; Shen et al., 2018; Yu et al., 2021; Yu et al., 2020). In fact, implantable hydrogels can be prepared not only using the crosslinking chemistries described in sections 3 and 4, but also through additional ones (Chen et al., 2020; Shen et al., 2018). For instance, Yu and co-workers developed an implantable methacrylated hyaluronic acid and silk fibroin-based hydrogel for the delivery of Curcumin loaded nanoparticles, that was assembled through photocrosslinking (mediated by

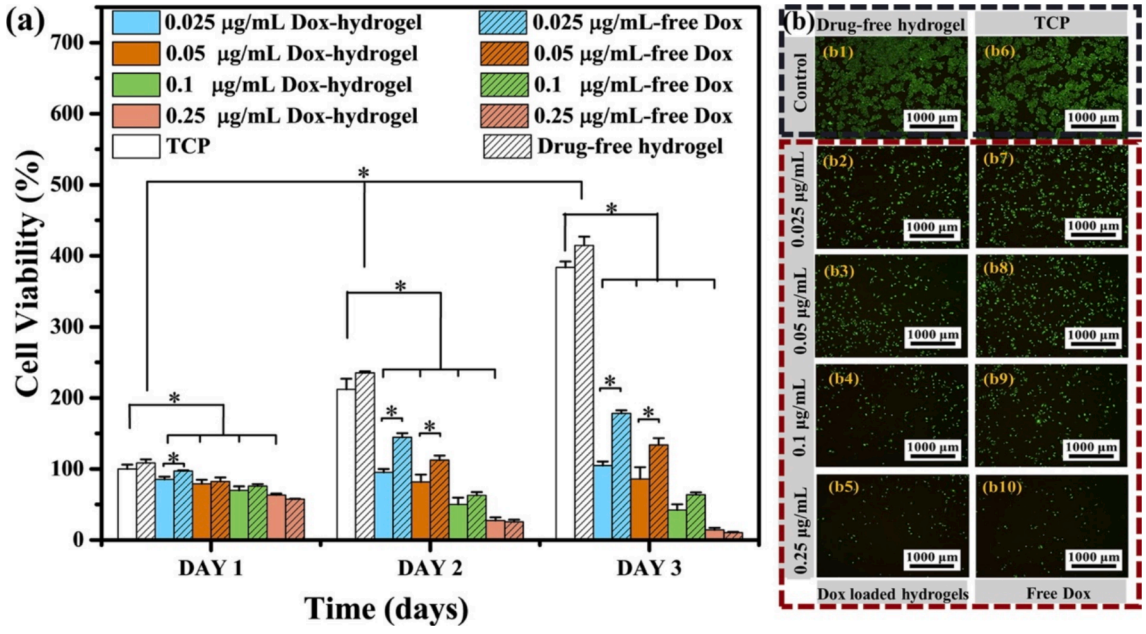

Fig. 4. Therapeutic capacity of injectable shear-thinning/self-healing hydrogels incorporating Doxorubicin. (a) Viability of cancer cells exposed to the different treatments. (b) Live/dead staining of cancer cells exposed to the different treatments. Dox-hydrogel: injectable shear-thinning/self-healing hydrogel containing Doxorubicin, prepared using N-carboxyethyl chitosan and di-benzaldehyde-modified poly(ethylene glycol); Free Dox: Doxorubicin; TCP: Tissue culture plate (non-treated control); Drug-free hydrogel: injectable shear-thinning/self-healing hydrogel, prepared using N-carboxyethyl chitosan and di-benzaldehyde-modified poly (ethylene glycol). Reprinted from (Qu et al., 2017), with permission from Elsevier. © 2017 Acta Materialia Inc. Published by Elsevier Ltd.

Irgacure 2959 and UV light) and hydrophobic interactions (enhanced by alcohol vapor treatment) (Yu et al., 2021). In another work, Tian's team prepared an implantable hydrogel by co-polymerizing [2-(Methacryloyloxy)ethyl]dimethyl-(3-sulfopropyl)ammonium hydroxide and bis(2-methacryloyl)-oxyethyl disulfide (with the assistance of ammonium persulfate and tetramethylethylenediamine), that was explored for Sunitinib delivery (Yu et al., 2020). Additional implantable hydrogels aimed for the tumor-confined delivery of chemotherapeutic agents are summarized in Table 3.

In this way, the use of implantable hydrogels for mediating a localized delivery of chemotherapeutic agents can lead to an improved therapeutic outcome (Table 3). Chen and co-workers prepared an implantable hydrogel composed of poly(*N*-(3-aminopropyl)methacrylamide hydrochloride-*co*-*N*-[tris(hydroxymethyl)methyl]acrylamide) and oxidized dextran (Schiff base crosslinking) that was loaded with cisplatin-conjugated albumin nanoparticles (Chen et al., 2020). The *in vivo* implantation of this hydrogel containing cisplatin-nanoparticles at the tumor's surface prompted a stronger antitumoral effect when compared to the direct administration of cisplatin-nanoparticles and free cisplatin (Fig. 5) (Chen et al., 2020).

Shen and co-workers prepared an implantable hydrogel by combining branched (4-arm) maleimide-grafted poly(ethylene glycol) and GCRDGPQGIWGQDRCG peptide (Thiol-Maleimide crosslinking) (Shen et al., 2018). This hydrogel was loaded with Doxil® (poly (ethylene glycol)-coated liposomal Doxorubicin) and Losartan, and upon implantation at the tumor's vicinity, it could reduce the tumor's growth (Shen et al., 2018). Li and co-workers developed an implantable hydrogel based on chondroitin sulfate multialdehyde, branched polyethylenimine and branched polyethylenimine-functionalized graphene oxide nanoparticles loaded with Doxorubicin (Schiff base crosslinking) (Li et al., 2019). After tumor resection, the implantation of this hydrogel containing Doxorubicin-loaded nanoparticles could delay longer the tumor's recurrence when compared to the direct administration of the free drug (Li et al., 2019). Tian team also implanted a hydrogel containing Sunitinib after the surgical resection of the tumor, verifying its capacity to slow the growth of the recurring tumors (Yu et al., 2020). The therapeutic capacity of other implantable hydrogels loaded with chemotherapeutic agents is summarized in Table 3.

6. Conclusions and future perspectives

In this review, the preclinical application (*in vitro* and *in vivo* studies) of hydrogels for performing the local delivery of drugs and drug-loaded nanoparticles was analyzed, being the focus given to injectable *in situ* forming hydrogels, injectable shear-thinning/self-healing hydrogels, and implantable hydrogels.

Essentially, the three types of hydrogels demonstrated the ability for encapsulating drugs and/or drug loaded nanoparticles. The undeniable benefit of this approach was highlighted by the hydrogels' capacity to confine the chemotherapeutic agents into the tumor site, with minimal leakage to off-target organs such as the liver, spleen, and lungs. This crucial feature could address the main limitations of the direct administration of chemotherapeutic drugs, which was plagued by a poor tumor-homing capacity and distribution to non-diseased organs. Even though the loading of drugs into nanoparticles could ameliorate their biodistribution, the drug-loaded nanoparticles still had a limited tumor retention and expressive off-target distribution. In this regard, hydrogels could also mediate a tumor-confined delivery of drug-loaded nanoparticles with minimal leakage to other organs.

Injectable hydrogels were extensively explored for mediating the local delivery of chemotherapeutic agents into the tumor site, which could be derived from their minimally invasive administration route. In what concerns injectable *in situ* forming hydrogels, those assembled through physical interactions rose among their chemically-crosslinked equivalents. This phenomenon is likely correlated with the fact that physically-crosslinked *in situ* forming hydrogels could be readily prepared using commercially available reagents (*i.e.*, as-received without any purification/modification). In fact, many commercially available polymers can *per se* form hydrogels *in situ* (*e.g.*, Pluronic F127, Agarose) or achieve *in situ* gelation with the aid of common external reagents (*e.g.*, chitosan plus β-glycerophosphate). Despite their ease of preparation, the stability of the physically-crosslinked *in situ* forming hydrogels is more prone to be challenged by the *in vivo* environment. On the other hand, chemically-crosslinked *in situ* forming hydrogels generally displayed a well-controlled gelation and degradation, favoring their *in vivo* integrity. Still, their preparation required the modification of the polymers with functional groups compatible with the envisioned crosslinking chemistry (*e.g.*, Thiol and Maleimide, Tetrazine and Norbornene). However, such chemical modification protocols are not accessible to a broad spectrum of researchers. Although high-priced, some functionalized polymers are starting to become available from chemical suppliers, which may expand the use of chemically-crosslinked *in situ* forming hydrogels. Regarding the injectable shear-thinning/self-healing hydrogels, those assembled by exploring cyclodextrin-based host–guest interactions and Schiff base reactions were widely investigated for the tumor-confined delivery of chemotherapeutic agents. With few exceptions, the preparation of this class of injectable hydrogels also required some type of chemical modification procedure (*e.g.*, adamantane grafting, sodium periodate oxidation). Still, this additional step was outshined by the convenience of the injectable shear-thinning/self-healing hydrogels. Due to their reversible sol–gel transitions, these hydrogels were already assembled in the injection apparatus, and re-assembled when the injection force ceased. This feature is of critical importance since it makes the preparation, storage and administration of this class of hydrogels a straightforward process. Lastly, the implantable hydrogels could be prepared by an extended set of techniques and crosslinking chemistries since these are not dependent on specific sol–gel transitions during their *in vivo* administration. Nevertheless, the administration of implantable hydrogels required a surgical procedure, which imparts a considerable degree of invasiveness to this approach. Fortunately, this inconvenience could be circumvented by using the implantable hydrogels after the surgical resection of the tumor, rendering them with an enormous potential for adjuvant chemotherapy regimens.

Undoubtedly, the local delivery of drugs and/or drug-loaded nanoparticles mediated by hydrogels outperformed the conventional administration routes of these agents. *In vivo*, the hydrogels' capacity to confine the chemotherapeutic agents into the tumor tissue resulted in an improved therapeutic outcome and in a reduction of the side effects. In some cases, the local delivery of the chemotherapeutic agents by the hydrogels could even induce tumor regression. Nevertheless, in *in vivo* studies, the chemotherapeutic regimens mediated by the hydrogels mostly prompted a reduction of the tumor's growth. In this way, the use of hydrogels for performing a tumor-confined delivery of chemotherapeutic agents has not yet reached its maximal therapeutic capacity. However, this cutting-edge technology has room to improve exponentially in the next years (detailed below).

Indeed, the potential of hydrogels for cancer related applications is supported by several clinically used products. In 2004, Vantas® (Endo Pharmaceuticals Inc), an implantable non-biodegradable hydrogel that mediates a subcutaneous release of histrelin acetate, was approved by the FDA for the palliative treatment of advanced prostate cancer. In 2015, SpaceOAR® (Boston Scientific), an injectable *in situ* forming biodegradable hydrogel that acts as a perirectal spacer to protect the rectum from the radiation used on prostate cancer, received FDA clearance. In 2020, JELMYTO® (UroGen Pharma), an injectable thermo-responsive *in situ* forming hydrogel containing Mitomycin-C, also received FDA approval for low-grade upper tract urothelial cancer. Some hydrogels have also been suggested for the management/treatment of the side effects associated to conventional cancer therapies (*e.g.*, MuGard®, Regenecare®). A recently listed clinical trial (clinicaltrials.gov identifier NCT04062721) also intends to study an injectable

Table 3
Implantable hydrogels for the delivery of chemotherapeutic agents.

Type of administration	Main crosslinking chemistry	Composition	Chemotherapeutic agent	Main outcome[#]	Ref.
Implantable	Hydrogen bonding and ionic crosslinking	Cellulose grafted with carboxilic acid groups and cellulose grafted with quaternary ammonium groups	Doxorubicin	The hydrogels mediated a sustained drug release (≈ 35 % at 5d pH 7.4)	(Hujaya et al., 2018)
Implantable	Covalent bond (mediated by 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride)	Poly(L-glutamic acid-*co*-L-lysine)	Doxorubicin	The hydrogels mediated a pH sensitive drug release (≈ 10 % at pH 7.4 *vs.* ≈ 50 % pH 4 after 96 h)	(Ma et al., 2017)
Implantable	Polymerization (mediated by ammonium persulfate and tetramethylethylenediamine)	Salecan-*g*-SS-poly(itaconic acid-*co*-2-hydroxyethyl methacrylate)[(1)]	Doxorubicin	The hydrogels mediated a sustained drug release, diminishing the cancer cells' viability (up to ≈ 30 % at 48 h)	(Hu et al., 2017)
Implantable	Thiol-Maleimide Michael type addition	Maleimide-grafted chitosan and thiolated hyaluronic acid	Doxorubicin loaded graphene-based nanomaterials	The delivery of the drug-loaded nanoparticles by the hydrogel led to a reduction of the cancer cells' viability (up to ≈ 50 % at 24 h)	(Costa et al., 2023)
Implantable	Schiff base and hydrogen bonding	Oxidized dextran, quaternary ammonium carboxymethyl chitosan and tetrasulfide-bridged mesoporous silica nanoparticles	Doxorubicin loaded tetrasulfide-bridged mesoporous silica nanoparticles	The delivery of drug-loaded nanoparticles by the hydrogel led to a reduction of the cancer cells' viability (up to ≈ 66 % at 24 h)	(Hu et al., 2024)
Implantable	Photocrosslinking (mediated by lithium phenyl-2,4,6-trimethylbenzoylphosphinate and 405 nm light)	Poly(ethylene glycol)-dimethacrylate and serin methacryloyl	Gambogic acid loaded poly (lactic-*co*-glycolic acid) nanoparticles and Decitabine	After tumor resection, the delivery of the dual drugs by the hydrogel decreased tumor recurrence (by 40 %) and metastases formation	(Mi et al., 2023)
Implantable	Disulfide bonds	*N*-acetyl-L-cysteine-grafted chitosan and lipoic acid-grafted pullulan	Cyclopamine-loaded CRRRRRR peptide-modified poly(ethylene glycol)-coated liposomes	After tumor resection, the drug delivery mediated by the hydrogel led to a growth reduction of the recurring tumors ($TV^{(a)}$ ≈ 425 mm^3 *vs.* TV of control ≈ 1619 mm^3)	(Chen et al., 2022)
Implantable	Photocrosslinking (mediated by Irgacure2959 and 365 nm light) and hydrophobic interactions (enhanced by alcohol vapor treatment)	Silk fibroin and methacrylated hyaluronic acid	Curcumin loaded chitosan-tripolyphosphate nanoparticles	The hydrogels mediated a pH-sensitive Curcumin release, diminishing the cancer cells' viability (up to ≈ 45 % at 48 h)	(Yu et al., 2021)
Implantable	Schiff base	Poly(*N*-(3-aminopropyl) methacrylamide hydrochloride-*co*-*N*-[tris(hydroxymethyl)methyl] acrylamide) and oxidized dextran	Cisplatin-loaded human serum albumin nanoparticles	The delivery of the drug-loaded nanoparticles by the hydrogel led to a stronger *in vivo* antitumoral effect (median survival of 54d) when compared to the drug-loaded nanoparticles (median survival of 36d) and free drug (median survival of 31d) administrations	(Chen et al., 2020)
Implantable	Polymerization (mediated by ammonium persulfate and tetramethylethylenediamine)	Polymerized [2-(Methacryloyloxy) ethyl]dimethyl-(3-sulfopropyl) ammonium hydroxide and bis(2-methacryloyl)oxyethyl disulfide	Sunitinib	After tumor resection, the delivery of the drug by the hydrogel slowed the growth of the recurring tumor	(Yu et al., 2020)
Implantable	Photopolymerization/ photodimerization (mediated by Eosin-Y, triethanolamine, *N*-vinyl-2-pyrrolidinone and 365 nm light)	Anthracene-conjugated methacrylated-alginate	Doxorubicin	The hydrogels mediated a pH sensitive drug release (≈ 20 % at pH 7.4 *vs.* ≈ 55 % at pH 5.0 after 6d)	(Batool et al., 2020)
Implantable	Polymerization (mediated by potassium persulfate and sodium thiosulfate)	Polymerized poly(ethylene glycol) methyl ether methacrylate and acrylic acid	5-Fluorouracil	The delivery of the drug by the hydrogel decreases cancer cells' viability (up to ≈ 19 % at 72 h)	(Yue et al., 2019)
Implantable	Ionic crosslinking	Alginate and calcium sulfate	5-fluorouracil and irinotecan	The hydrogels mediated the release of the dual drug combination (≈ 100 μg of 5-fluorouracil and ≈ 10 μg of irinotecan after 18 h)	(Emi et al., 2019)
Implantable	Schiff base	Multialdehyde-chondroitin sulfate, branched poly(ethylenimine) and branched poly(ethylenimine)-functionalized graphene oxide nanoparticles	Doxorubicin loaded branched poly (ethylenimine)-functionalized graphene oxide nanoparticles	After tumor resection, the delivery of the drug-loaded nanoparticles by the hydrogel delayed longer tumor's recurrence when compared to the free drug administration	(Li et al., 2019)
Implantable	Thiol-Maleimide Michael type addition	4-arm maleimide-grafted poly (ethylene glycol) and GCRDGPQGIWGQDRCG peptide	Doxil and Losartan	The delivery of the dual agents by the hydrogel led to tumor growth reduction (TV ≈ 1525 mm^3 *vs.* TV of control ≈ 2381 mm^3)	(Shen et al., 2018)

(*continued on next page*)

Table 3 (*continued*)

Type of administration	Main crosslinking chemistry	Composition	Chemotherapeutic agent	Main outcome[#]	Ref.
Implantable	Thiol-Acrylate Michael type addition	Acrylated hyaluronic acid and GCRDGPQGIWGQDRCG peptide	Sunitinib loaded poly (ethylene glycol)-coated nanoparticles[(2)]	The hydrogel mediated a MMP-2 responsive Sunitinib-nanoparticle release, being able to reduce cancer cells' viability (up to ≈ 43 % at 48 h)	(Fu et al., 2022)
Implantable	Ionic crosslinking and hydrophobic interactions	Poloxamer 407, hyaluronic acid, κ-carrageenan and calcium chloride	5-fluorouracil	The hydrogels mediated a sustained drug release (up to ≈ 80 % at 72 h)	(Dinh et al., 2022)
Implantable	Hydrophobic interactions and hydrogen bonding	Carbomer 974P, poloxamer 407 and poloxamer 188	Paclitaxel nanocrystals	After tumor resection, the delivery of the drug-loaded nanocrystals by the hydrogel prevented lung metastases and tumor recurrence	(Fan et al., 2022)
Implantable	Hydrophobic interactions	Pluronic F127	Amine-functionalized poly (dopamine)-coated Imatinib-based nanocrystals	The delivery of the drug-based nanocrystals by the hydrogel led to an *in vivo* antitumoral effect ($TW^{(b)}$ ≈ 0.121 g *vs.* TW of control ≈ 0.586 g)	(Ci et al., 2019)

– The most important data with significance was selected; **(a)** – Tumor Volume; **(b)** – Tumor Weight; **(1)** – Salecan grafted with itaconic acid, 2-hydroxyethyl methacrylate and *N,N'*-bis(acryloyl)cystamine; **(2)** – Formulated with Poly(D,L-lactide)-poly(ethylene glycol)-poly(D,L-lactide).

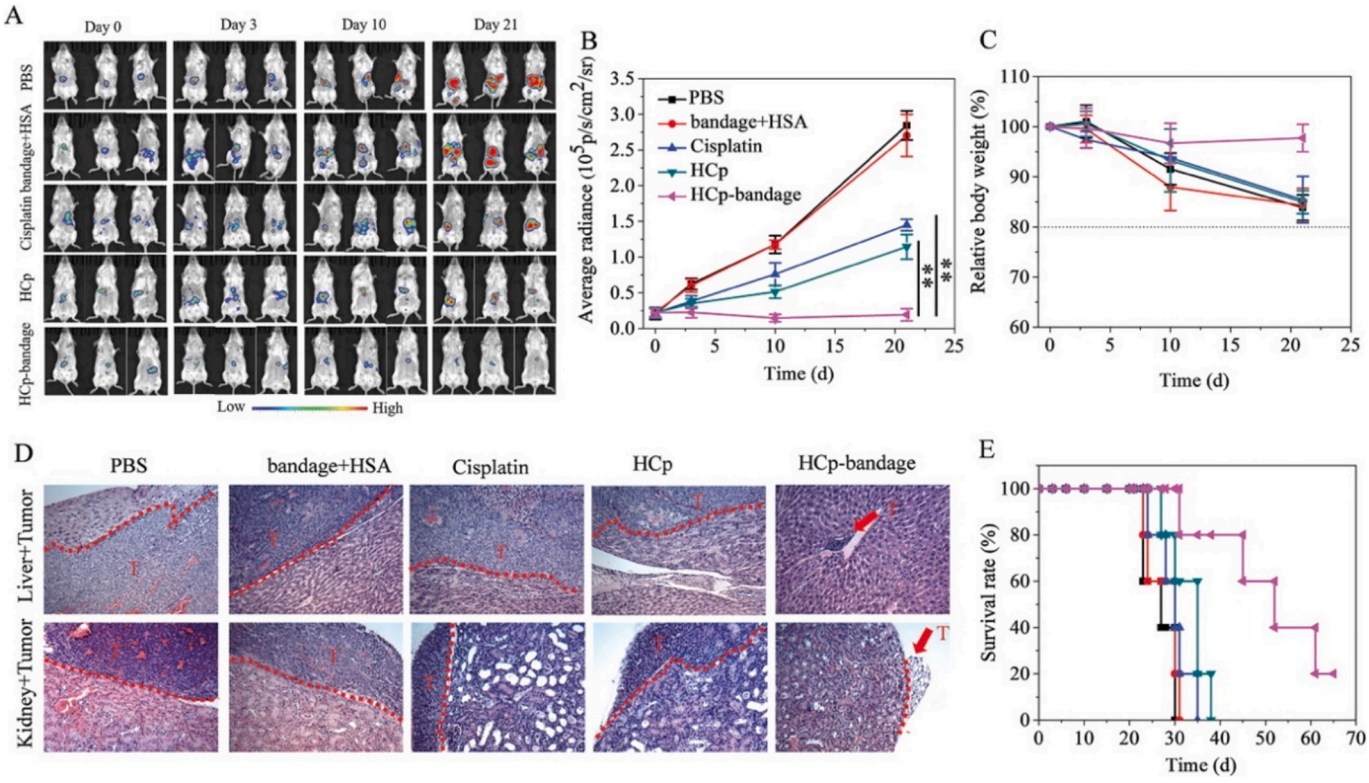

Fig. 5. Therapeutic capacity of an implantable hydrogel incorporating cisplatin-conjugated albumin nanoparticles. (A) Bioluminescence imaging of the tumor and (B) bioluminescence levels after the different treatments. (C) Body weight variation overtime. (D) Hematoxylin & Eosin staining of the liver and kidney sections after the different treatments. (E) Mice survival rates along time. HCp-bandage: implantable hydrogel incorporating cisplatin-conjugated human serum albumin nanoparticles, prepared using poly(N-(3-aminopropyl)methacrylamide hydrochloride-co-N-[tris(hydroxymethyl)methyl]acrylamide) and oxidized dextran; HCp: cisplatin-conjugated human serum albumin nanoparticles; Bandage + HSA: implantable hydrogel incorporating human serum albumin, prepared using poly(N-(3-aminopropyl)methacrylamide hydrochloride-co-N-[tris(hydroxymethyl)methyl]acrylamide) and oxidized dextran; PBS: Phosphate buffered saline. Reprinted from (Chen et al., 2020), with permission from John Wiley & Sons, Inc. © 2020 Wiley-VCH GmbH.

hydrogel incorporating mifamurtide and granulocyte–macrophage colony-stimulating factor for providing local immunomodulation after radiofrequency ablation of unresectable colorectal liver metastases.

Despite this potential, the industrialization and clinical application of hydrogels incorporating chemotherapeutic agents in cancer therapy is still scarce. Accelerating the translation of this macroscale technology may be achieved by tackling a multitude of factors that span from the hydrogels' assembly to their therapeutic validation. For instance, the synthesis and/or functionalization of the polymers used for preparing the hydrogels may be improved by using automatized computer-assisted systems (*e.g.*, Chemputer) or microfluidic/microreactor platforms (Gromski et al., 2020; Su et al., 2018). These state-of-the-art apparatuses may also ease the preparation of the injectable *in situ* forming hydrogels' precursor solutions as well as the production of the injectable shear-

thinning/self-healing and implantable hydrogels (Wei et al., 2022). Such equipments may also contribute for scaling-up these processes with a high batch-to-batch fidelity in compliance to Good Manufacturing Practices. Favoring green chemistry approaches in all the polymer- and hydrogel-related processes may be an important landmark for the environmental sustainability of this therapeutic approach (Haque et al., 2022; Kobayashi, 2016; Trombino et al., 2023). On the other hand, it is also crucial to improve the anticancer capacity of the chemotherapeutic agent-loaded hydrogels. In this regard, the incorporation of additional therapeutic entities (*e.g.*, immunomodulators (Liang et al., 2024), radiosensitizers (An et al., 2024), or photothermal/photodynamic agents (Gao et al., 2024; Xu et al., 2020)) in the hydrogels may be a steppingstone for the achievement of a multimodal effect concomitant with total tumor eradication. In this way, it is also fundamental to fine-tune the hydrogels' degradation kinetics for allowing a controlled delivery of all encapsulated agents in a sequential and rational manner. Likewise, integrating structures with biosensing capabilities in the hydrogels could also offer a route to monitor the treatment's response or tumor's recurrence (Sun and Chen, 2024). Furthermore, the administration of hydrogels, especially those that are implanted, can carry some risk of infection. Such threat may be addressed by encapsulating antibacterial agents (*e.g.*, silver nanoparticles (Hu et al., 2023)) in the hydrogels or by using polymers with intrinsic antibacterial activity (*e.g.*, poly(lysine) (Cui et al., 2024) or chitosan (Pouso et al., 2024)) in the hydrogels' composition. It is also important to standardize the experimental conditions employed on the different physicochemical tests (*e.g.*, hydrogel volume to release medium volume ratio, medium' type and composition) as well as on the *in vitro* (*e.g.*, cell density, medium volume, incubation time, evaluation timepoint) and *in vivo* (*e.g.*, tumor-bearing model type, initial tumor volume, hydrogel volume) anticancer assays. Establishing such guidelines will allow a greater correlation between the different available studies, thus being a step-forward towards the translation of these hydrogels. The adoption of state-of-the-art *in vitro* models (*e.g.*, spheroids (Mo et al., 2020b), organ-on-a-chip (Qu et al., 2023)) for investigating the efficacy and safety of the injectable and implantable hydrogels is also crucial. These advanced *in vitro* models can contribute for a more accurate selection of the lead formulations for the subsequent *in vivo* assays, thus accelerating the discovery pipeline. Similarly, the widespread use of advanced *in vitro* (*e.g.*, luminescent-based ATP quantification) and *in vivo* (*e.g.*, bioluminescence-based tumor monitoring) screening protocols will be important to complement the data of the standard/routine assays (*e.g.*, tetrazolium-based assays for *in vitro* anticancer effect, tumor volume measurement for *in vivo* anticancer activity). Also, even though the three types of hydrogels demonstrated excellent safety in preclinical studies, it is of utmost importance to execute long-term *in vivo* studies in order to fully depict the hydrogels' long-term biocompatibility. Likewise, the execution of long-term *in vivo* studies is also fundamental to fully understand the hydrogels' capacity to prevent tumor's recurrence.

Overall, injectable *in situ* forming hydrogels, injectable shear-thinning/self-healing hydrogels, and implantable hydrogels are cutting-edge macroscale systems capable of performing a tumor-confined delivery of chemotherapeutic agents, opening a venue for more effective and safe anticancer treatments.

CRediT authorship contribution statement

Manuel R. Pouso: Writing – original draft, Investigation. **Bruna L. Melo:** Writing – original draft, Investigation. **Joaquim J. Gonçalves:** Writing – review & editing. **Ricardo O. Louro:** Writing – review & editing. **António G. Mendonça:** Writing – review & editing, Supervision, Funding acquisition. **Ilídio J. Correia:** Writing – review & editing, Supervision, Project administration, Funding acquisition. **Duarte de Melo-Diogo:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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