


Review

Injectable Hydrogels for Cancer Therapy over the Last Decade

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Received: 30 July 2019; Accepted: 17 September 2019; Published: 19 September 2019



Abstract: The interest in injectable hydrogels for cancer treatment has been significantly growing over the last decade, due to the availability of a wide range of starting polymer structures with tailored features and high chemical versatility. Many research groups are working on the development of highly engineered injectable delivery vehicle systems suitable for combined chemo- and radio-therapy, as well as thermal and photo-thermal ablation, with the aim of finding out effective solutions to overcome the current obstacles of conventional therapeutic protocols. Within this work, we have reviewed and discussed the most recent injectable hydrogel systems, focusing on the structure and properties of the starting polymers, which are mainly classified into natural or synthetic sources. Moreover, mapping the research landscape of the fabrication strategies, the main outcome of each system is discussed in light of possible clinical applications.

Keywords: injectable hydrogels; drug delivery; anticancer activity; natural polymers; synthetic polymers; stimuli-responsive materials

1. Introduction

Injectable hydrogels can be defined as three-dimensional hydrophilic polymeric networks with a very high affinity for body fluids that may be delivered into body through a catheter or by direct injection with a syringe [1]. Injectable hydrogels have been proposed in the biomedical field as a platform for tissue engineering, as well as for the delivery of therapeutics (Figure 1) [2–4].

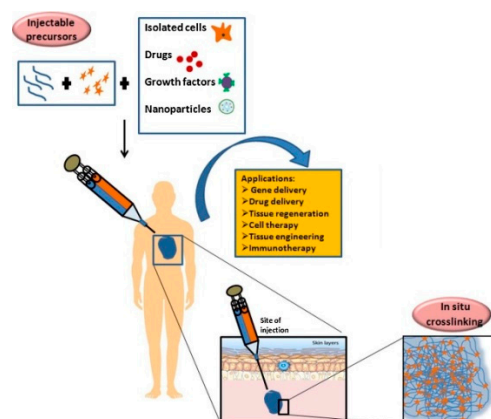


Figure 1. Application of injectable hydrogel systems in biomedical field. Reproduced with permission from [3]. Elsevier, [2018].

A gelling mechanism allows injectable hydrogels to be classified into chemically and physically cross-linked hydrogels [5].

Chemical intermolecular cross-linking can be created by the generation of new covalent bonds between polymer chains via photo- or thermo-irradiation [6], or by specific reaction mechanisms involving Schiff's base formation [7], Diels–Alder cycloaddition [8], Michael-type addition [9], and azide–alkyne (CuAAC) click chemistry [10,11]. The encapsulation of suitable therapeutic agents within the gels during hydrogel formation allows the preparation of three-dimensional structures able to act as a platform for controlled drug delivery or tissue engineering [12]. Chemical hydrogels possess higher mechanical strength (due to high stable crosslink points [13]), longer physical stability, and a prolonged degradation period [14]. Nevertheless, *in vivo* applications appear reduced due to some potential toxic agents, such as cross-linking monomers, photo-initiators, organic solvents, or catalyzers [2]. Non-covalent bonds such as hydrophobic interactions [15], hydrogen bonding [16], ion cross-linking [17], and host-guest interactions [18] can be exploited in the formation of injectable physical hydrogels. Usually, in the synthesis of this kind of structure, the required mild reaction conditions avoid the generation of any toxic by-products. Furthermore, organic solvents, cross-linking catalysts, or photo-initiation processes are not required during the gelation process [2]. On the contrary, physical hydrogels suffer from some drawbacks compared with the chemically cross-linked formulations, particularly related to bond stability and poor mechanical properties [19].

The mechanical properties of injectable hydrogels are a critical parameter for its function and applications, with the nature of gel being evident by a storage modulus G' higher than the corresponding values of the loss modulus G'' [20,21]. The resulting mechanical properties of any injectable hydrogels should be adequate to withstand the deformations occurring in the body [22]. The viscosity of the polymer solution is an important parameter that should also be considered in the case of injectable matrices: Precursor aqueous solutions should possess sufficiently low viscosity, or at least adequate shear-thinning properties, to allow for easy injection [23–25]. This requirement makes molecular weight control, polymer architecture, as well as chemical composition, very important parameters to be controlled in the design of an effective hydrogel system, which should also allow a homogeneous drug dispersion before the gelation of the cross-linked structure [26]. The U.S. Food and Drug Administration (FDA) fixed the upper limit for any injectable solutions to 0.05 Pa s [27]. Upon gelation, a rapid increase in this value was observed, followed by a leveling off over time [28]. The mechanical properties of the whole hydrogel are strictly dependent on another important structural parameter, such as the porosity (e.g., the space between cross-links). An increased concentration or cross-linking density would enhance the mechanical strength, thus promoting the integrity duration of the hydrogels [29]. Nevertheless, this would determine the hydrogel's porosity to be significantly reduced, limiting the movement of nutrients and solutions for either the growth of the cell in tissue engineering applications or the modulation of the release profile in drug delivery [30]. Thus, a valuable balance between these parameters should be achieved.

Clinical applications of injectable hydrogels require some fundamental mandatories, such as biodegradability, biocompatibility, stability, non-toxicity, and suitable mechanical and viscoelastic properties. A biocompatible injectable hydrogel should be non-carcinogenic, non-toxic, and should not induce any chronic or adverse physiological response after its degradation. To develop systems with high biocompatibility towards tissues, cells, and body fluids, natural polymers are more suitable than synthetic cross-linked structures due to their subunits, which are more similar to the natural extracellular matrix [31]. Gradual degradation of the hydrogel into biocompatible by-products should also be considered because of their possible accumulation that could generate adverse effects. Usually, carbohydrates, peptides, and nucleic acids naturally degrade in non-toxic by-products [31]. Among the different applications of injectable hydrogels, cancer therapy is one of the most widely explored [32]. The treatment of cancer by systemic chemotherapeutic procedure, indeed, often determines a high level of cytotoxicity [33] and, to overcome this inconvenience, intratumor delivery of therapeutics employing injectable hydrogels can provide a controlled and targeted release within the tumor site [34].

Here, we have reviewed the synthesis and the application of different injectable hydrogels proposed as drug delivery systems for the local delivery of chemotherapeutics. Additionally, stimuli-responsive release of anticancer agents have been treated by the analysis of thermo-, pH-, photo-, or multi-sensitive drug delivery systems, as well as active targeting hydrogels [35]. Based on the main component of the polymer network, herein we have classified the injectable hydrogels reviewed and discussed as synthetic or natural systems. For each class of materials, a summarizing table containing information about composition, carrier and delivery properties, as well as cancer models employed in either in vivo or in vitro experiments has been introduced. Moreover, when available, data about studies in health models have given information about side toxicity and pharmacokinetic profiles. Finally, injectable hydrogels containing nanoparticle systems as functional additive to control the releasing rate have been defined as composite materials, while N/S hybrid hydrogels refer to the simultaneous presence of natural and synthetic polymers within the same polymer structure.

2. Synthetic Injectable Hydrogels

2.1. Polyphosphazenes

Polyphosphazenes (PPZs) are a class of hybrid organic–inorganic macromolecules consisting in a linear or branched skeletal structure of repeating phosphorus and nitrogen atoms with alternating single and double bonds [36]. Each phosphorus atom is linked to two organic side groups, ranging from alkyl and aryl moieties to amino acids (Figure 2) [37].

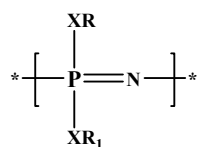


Figure 2. Representation of Polyphosphazenes. X = O, NH; R and R₁ = Alkyl, Aryl, amino acid.

PPZs are obtained via different synthetic routes, with most of the biologically-relevant materials being prepared by a ring-opening polymerization, followed by macromolecular substitution reactions [38]. Either the modification of organic side groups and their ratios, or the attachment of multiple different side groups to the same backbone, allow the preparation of a wide range of PPZs, with finely tuned physical and mechanical properties [39]. The interest in PPZs as materials for the formulation of injectable hydrogels is related to the ability of their aqueous solutions to undergo reversible sol–gel transitions depending on the temperature. In fact, PPZs are in the sol state at room temperature (or below), but they gelate at body temperature. Such transition is tunable by adjusting the balance of hydrophobic to hydrophilic substituents [40]. Furthermore, a growing number of hydrolytically-sensitive PPZ hydrogels have been designed, with negligible toxicity arising from the degradation of by-products generally consisting of H₃PO₄, ammonium, and free organic side groups [41]. On the contrary, the employment of cyclic PPZ architecture should be accurately investigated, because such derivatives are characterized by a relatively long time of degradation which can reduce the biomedical applicability [42]. Although a large number of PPZ polymers have not found commercial success [43], several research groups have developed different types of PPZ injectable hydrogels (Table 1). PPZ-based hydrogels were successfully tested for the delivery of cytotoxic drugs or sRNA to solid tumors, both in vitro and in vivo [40,44–50]. They proved the ability of these systems to extend the release profiles overtime [47] with no-toxicity on healthy mice [46,47] and the possibility to confer targeted behavior [50]. A further upgrade of the use of PPZ was proposed in [51], where the injectable hydrogels consisted of a Camptothecin (CPT) prodrug useful for the treatment of lung and colon cancer cell lines. The insertion of metal ferrite superparamagnetic iron oxide nanoparticles within the hydrogel structure was proved to be a suitable strategy for enabling tumor imaging and magnetic hyperthermia ablation [52,53].

Table 1. Composition and anticancer performance of injectable hydrogels based on polyphosphazenes.

Ref	Composition		Carrier Properties		Delivery Properties		Cancer Model			Health Model	
	Hydrogel (Gelation Process)	Composite Component	Degradation Time (Days)	Smart Responsivity	Bioactive Agent (DL% w/w)	Release Time (Days)	Type	In Vitro	In Vivo	In Vitro	In Vivo
[40]	PPZ (Physical – T)	---	30	---	ME (0.15)	35	Breast	MDA-MB-231	MDA-MB-231	---	---
[44]	PPZ (Physical – T)	---	---	---	DOX (10)	30	Stomach	HSC44Luc	HSC44Luc	---	---
[45]	PPZ (Physical – T)	---	>50	---	DOX (0.3–0.6)	35	Stomach	SNU-601	SNU-601	---	---
[46]	PPZ (Physical – T)	---	---	---	DTX (10)	28#	Stomach	44As3Luc	44As3Luc	---	Mice
[47]	PPZ (Physical – T)	---	10–20	---	DTX (1–3)	10–20	Stomach	SNU-601	SNU-601	---	Mice
							Pancreas	AsPC-1	---		
							Liver	SNU-398	---		
[48]	PPZ (Physical – T)	---	---	---	PTX (0.6–0.9)	60	Colon	DLD-1	---	---	---
							Stomach	SNU-601	SNU-601		
[49]	PPZ (Physical – T)	---	---	---	PTX-DOX (0.6)	60–100#	Stomach	SNU-601	SNU-601	---	---
[50]	PPZ (Physical – T)	---	---	---	sRNA	30#	Prostate	PC3	PC3	---	---
[51]	PPZ (Physical – T)	---	12–25	---	CPT* (10)	60	Lung	A549	---	---	---
							Colon	DLD-1	HT-29		
								HCT-116			
[52]	PPZ (Physical – T)	CoFe ₂ O ₄	30	Magnetic	SN-38 (0.8–0.12)	60	Glioblastoma	U-87	U87	3T3	---
[53]	PPZ (Physical – T)	Zn _{0.47} Mn _{0.53} Fe ₂ O ₄	25	Magnetic	---	---	Glioblastoma	U-87	U87	3T3	Mice

* Conjugated to hydrogel; # from in vivo experiments; DL: Drug loading; T: Temperature; CPT: Camptotecin; DOX: Doxorubicin; DTX: Docetaxel; ME: 2-Methoxyestradiol; PPZ: Poly(organophosphazene); PTX: Paclitaxel; SN-38: 7-ethyl-10-hydroxycamptothecin.

2.2. Poloxamers

Poloxamers (also known as Pluronics) are tri-block amphiphilic polymers consisting of poly(ethylene oxide)-poly(propyleneoxide)-poly(ethylene oxide) (PEO-PPO-PEO) repeating units [54]. They are non-ionic surfactants, with physical and chemical properties depending on the molecular weight and hydrophilic (PEO) to hydrophobic (PPO) balance (Figure 3) [55].

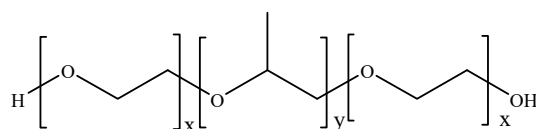


Figure 3. Schematic representation of poloxamers. x : 2–130; y : 15–67.

Among others, PF127 (PEO/PPO balance 70/30) is one of the most widely employed poloxamers for biomedical applications due to the ability to form either micellar nanocarriers for lipophilic drugs (due to PPO content) or hydrogel networks upon reverse thermal gelation. PF127 water solutions (>20% by weight) show a low-viscosity state at 4 °C, while semisolid gels are obtained upon heating to room or body temperature, probably due to micellar packing and entanglement [56,57].

To date, PF127 injectable hydrogels (Table 2) have been proposed as delivery vehicles for drug and drug crystals in the treatment of both blood and solid tumors [58,59]. Interestingly, such systems were found to reverse the multi-drug resistance in MCF-7/ADR cells because of the ability to increase the intracellular drug concentration escaping the efflux pumps on the cell membrane [59]. To extend the drug release profiles overtime, nanoparticle carriers (e.g., micelles or polymeric nanoparticles) loaded with the cytotoxic agent were incorporated into the hydrogels [60–62]. This approach allowed a co-delivery of 5-Fluoruracil (5-FU) and Doxorubicin-loaded Poly(D,L-lactide-co-glycolide) nanoparticles (DOX@PLGA) for the *in vitro* and *in vivo* treatment of melanoma [61]. When metal nanoparticles (e.g., Cu or Au) were used as loaded nanocarriers, photothermal and hyperthermia effects were achieved (Figure 4) [62,63].

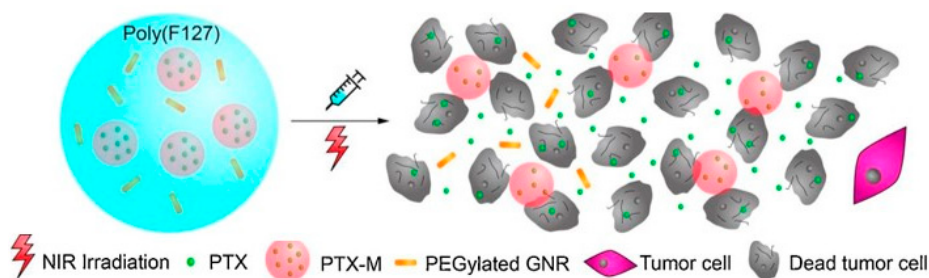


Figure 4. Schematic representation of the PTX-NPs/AuNRs/gel-mediated photothermal-chemotherapy. PTX: Paclitaxel; GNR: Gold NanoRods; NIR: Near InfraRed. Adapted with permission from [62]. Elsevier, [2016].

Despite the advantageous features of poloxamers, these polymers suffer from weak mucoadhesivity, poor mechanical properties, and short residence time due to the easily dissolution at the action site [64]. To overcome these drawbacks, PF127 was mixed with different polymers from synthetic (polyacrylic acid (PAA) or α -Tocopheryl Polyethylene glycol 1000 Succinate (TPGS)) [65,66] or natural (Hyaluronic acid (HA)) [67,68] origin to increase the gel strength [65] and enhance the drug efficiency [66]. Finally, it should be cited the incorporation of cyclodextrins (α -CD) into the hydrogel network for the preparation of effective depot system in cervix and breast cancer treatment [69]. A further improvement consisted in the insertion of graphene oxide (GO) or reduced graphene oxide (rGO) materials, with the formation of hybrid hydrogels with more sustained drug delivery behavior [70].

Table 2. Composition and anticancer performance of injectable hydrogels based on poloxamers.

Ref	Composition		Carrier Properties		Delivery Properties		Cancer Model			Health Model	
	Hydrogel (Gelation Process)	Composite Component	Degradation Time (Days)	Smart Responsivity	Bioactive Agent (DL% w/w)	Release Time (Days)	Type	In Vitro	In Vivo	In Vitro	In Vivo
[58]	PF127 (Physical – T)	---	---	pH	MLX (7.5)	1	Leukemia	K562 HL60	---	---	---
[59]	PF127 (Physical – T)	---	---	---	PTX (2.0) LAP (4.0)	4	Breast	MCF7 MCF7-ADR	---	BT 474	Mice
[60]	PF127 (Physical – T)	MPEG-PCL	---	---	Q* (7.0)	9	Ovary	SK-OV-3	SK-OV-3	---	---
[61]	PF127 (Physical – T)	PLGA	---	---	5-FU (2.0) DOX* (2.0)	35	Melanoma	B16F10	B16F10	---	---
[62]	PF127 (Physical – T)	OCS MPEG-AuNRs	---	---	PTX* (34.8)	18#	Liver	HepG2	HepG2	---	---
[63]	PF127 (Physical – T)	PVP	---	---	Cu ₂ MnS ₂ *	---	Murine breast	4T1	4T1	---	---
[65]	PF127/PAA (Physical – I,T)	---	---	---	OXA (2.3)	1	Colon	SW480	---	IEC-6	---
[66]	PF127/TPGS (Physical – T)	---	---	Temperature	DTX (5.0)	3	Liver	SMMC-7721/RT	SMMC-7721/RT	---	---
[69]	PF127/β-CD (Physical – T)	---	---	Temperature pH	CUR (10)	2	Cervix Breast	HeLa MCF-7	---	L929	---
[70]	PF127/α-CD (Physical – T)	GO	8	---	DOX (6.0) CPT (14)	8 6	---	---	---	---	---
	PF127/α-CD (Physical – T)	rGO									

* Loaded into composite component; # from in vivo experiments; DL: Drug loading; I: Ionic; T: Temperature; 5-FU: 5-Fluorouracil; CD: Cyclodextrin; AuNRs: Gold nanorods; CPT: Camptothecin; CUR: Curcumin; DOX: Doxorubicin; DTX: Docetaxel; GO: Graphene oxide; rGO: Reduced graphene oxide; LAP: Lapatinib; MLX: Meloxicam; MPEG: Monomethoxy poly(ethylene glycol); OCS: N-octyl chitosan; OXA: Oxaliplatin; PAA: Poly(acrylic acid); PCL: Poly(ε-caprolactone); PF: Pluronic F; PLGA: Poly(lactide-co-glycolide); PTX: Paclitaxel; PVP: Polyvinylpyrrolidone; Q: Quercetin; TPGS: α-Tocopheryl polyethylene glycol 1000 succinate.

2.3. Polyesters

During the last decades, thermosensitive in-situ gels of amphiphilic copolymers based on biodegradable polyesters and polyethylene glycol (PEG) have represented a suitable alternative in the intratumoral delivery of hydrophobic therapeutics [71], allowing to recover high drug concentration at the tumor site while overcoming, at same time, the limitations usually associated with the systemic administration of these drugs [72]. The advantages of this class of polymers arise from the possibility to ensure both a physical targeting to the cancer site and a controlled/sustained delivery of hydrophobic drugs [73], as well as from their high biodegradability which allows the obtainment of stimuli responsive and biocompatible delivery platforms [74]. On the other hand, the main drawback of such materials is that their acidic degradation by-products significantly influence the pH value of the surrounding media, with potential limitations in biomedical applications [75].

Different biodegradable polymers have been proposed for the development of injectable hydrogels, each showing peculiar features and biological performances (Table 3). The structures of the main polyesters employed to this regard are sketched in Figure 5.

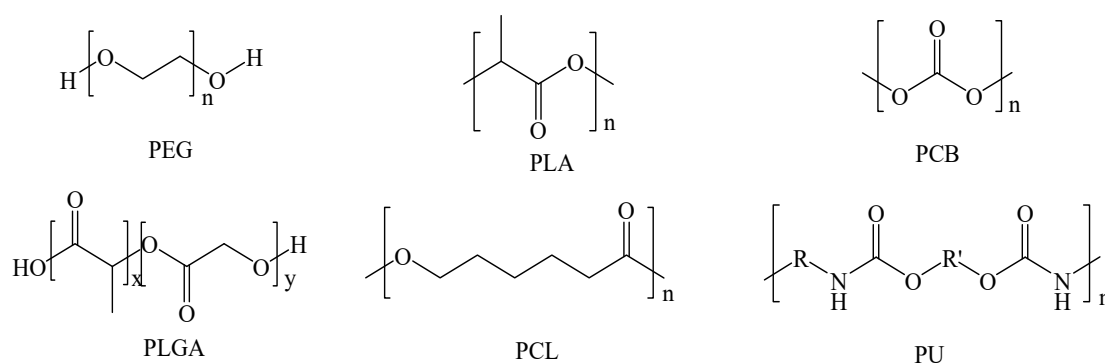


Figure 5. Schematic representation of poly(ethylene glycol) (PEG) and main biodegradable polyesters. PLA: Polylactide; PCB: Polycarbonate; PLGA: Poly(lactide-*co*-glycolide); PCL: Poly(ϵ -caprolactone); PU: Poly(urethane).

Biodegradable poly(*D,L*-lactide)-poly(ethylene glycol)-poly(*D,L*-lactide) (PLA-PEG-PLA) amphiphilic triblock copolymer showed the ability to self-assemble in aqueous medium into core-shell micelles, forming a physical network when exposed to the body temperature [76]. Injectable thermo-sensitive PLA-PEG-PLA for the local delivery of Gemcitabine (GEM) and Cisplatin (CisPt) was employed to promote synergistic combination therapy against pancreatic cancer [77]. Alternatively, poly(*D,L*-lactide) PLA was combined with pluronic L (PL) moieties in the preparation of three-block hydrogels (PLA-PL-PLA) proposed for intraperitoneal therapy of colon cancer [78,79]. This amphiphilic copolymer displayed thermosensitive behavior freely flowing at lower temperatures but turning into gel at body temperature. *D,L*-lactic (LA) acid oligomer combined with methoxy poly(ethylene glycol) and poly(octadecanedioic anhydride) was employed in the preparation of thermosensitive amphiphilic triblock copolymer suitable for local cancer chemotherapy. In particular, paclitaxel (PTX) loaded into LA oligomer nanoparticles could be stored as freeze-dried powders, and easily re-dispersed into aqueous medium at ambient temperature, forming a hydrogel in the injection site [80].

Poly(*D,L*-lactide-*co*-glycolide) (PLGA) and PEG triblock copolymer (PLGA-PEG-PLGA) hydrogels were synthesized via ring-opening polymerization of *D,L*-lactide (LA) and glycolide (GA) in the presence of PEG and Tin (II) 2-ethylhexanoate as macroinitiator and catalyst, respectively. Thermo-induced gelation of amphiphilic PLGA-PEG-PLGA can be related to the micellar aggregation as a consequence of the increase in the hydrophobic interactions between the PLGA moieties and the partial dehydration of the PEG chains [81,82]. Literature data indicates that the transition temperatures of PLGA-PEG-PLGA gels were in the range 10–40 °C for a polymer concentration of 15–20% wt [83]. Copolymer concentration

influenced sol–gel transition temperature, because the formation of the micellar aggregation network was simplified when the concentration of the polymer increased [84]. PLGA–PEG–PLGA gel was proposed as a carrier of topotecan (TPC), DOX, CisPt, and methotrexate (MTX), and employed for the treatment of osteosarcoma in in vivo experiments (Figure 6) [85,86].

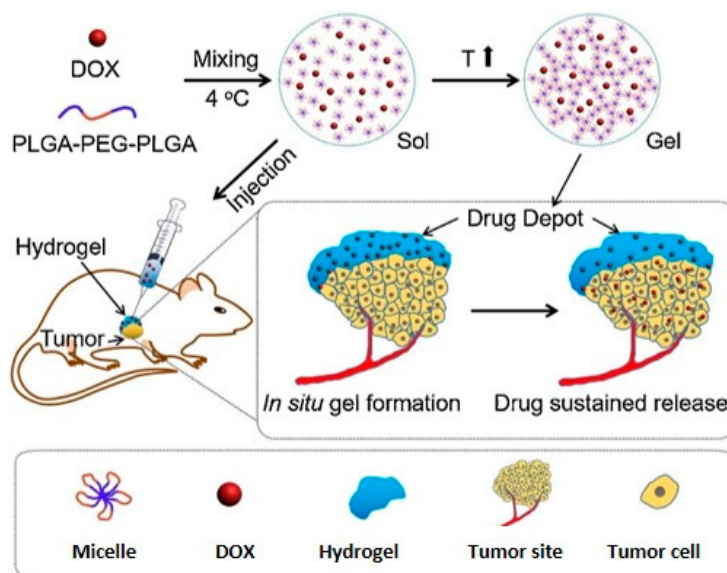


Figure 6. Schematic illustration of localized hydrogel formation and drug release. Adapted with permission from [86]; Elsevier, [2018].

Injectable thermosensitive hydrogel can be loaded with either drug or drug-loaded nanoparticles [87]. In particular, the interaction of ionic drugs with specific surfactants has been exploited to achieve sustained release of 2-methoxyestradiol (ME) and Cytarabine (CYT) in the therapy against leukemia and breast cancer, respectively [88,89]. Additionally, drug-loaded particles entrapped in a PLGA–PEG–PLGA hydrogel have been proposed as dual-stimuli responsive drug delivery systems combining the pH-responsivity of the nanoparticles with the temperature response of the PEGylated polyester gels [90,91]. In addition, in a modern scheduled treatment, sustained co-delivery of DOX and sRNA@Poly(ethyleneimine)-Lysine (PEI-Lys) complexes displayed significant synergistic effects in promoting the PLK1 silencing, tumor apoptosis, and cell cycle regulation of osteosarcoma cells [92].

In the pharmaceutical and biomedical fields, the sustained release of both hydrophobic and hydrophilic drugs from a single release device represents a newsworthy challenge, exhibiting different clinical survival advantages compared with the single drug treatment. To this regard, a strategy to realize the synchronous, sustained co-delivery of hydrophilic CisPt and hydrophobic PTX in one injectable device was achieved by synthesis of a Pt(IV) prodrug based on MPEG–PLGA, able to self-assemble in a core-corona micelle showing hydrophobic inner cores where PTX can be incorporated [93].

Finally, a promising strategy involved the use of cytokine-carrying thermosensitive MethoxyPEG (MPEG)–PLGA hydrogels followed by injection of vaccine vectors loading antigens [94]. This device provides a sustained release profile of granulocyte-macrophage colony-stimulating factor, able to facilitate proliferation, recruitment, and maturation of dendritic cells and macrophages at the site of inoculation, providing an efficient tool proposed in the melanoma therapy.

ϵ -Caprolactone was employed in the synthesis of amphiphilic block copolymers bearing PEG pendants. Different injectable Poly(ϵ -caprolactone) (PCL)-based nanocomposite hydrogels with multicomponent compatibility were proposed for the sustainable release of therapeutics, such as PTX, Camptothecin (CPT), 5-FU, and DOX. Three-block copolymers (PEG–PCL–PEG) were prepared by ring-opening polymerization in presence of Tin(II) 2-ethylhexanoate as macroinitiator [73,95–97]. Alternatively, PCL–PEG diblock [98] and PCL–PEG–PCL copolymers [99–102] were synthesized

in the presence of 1,4,8-trioxa[4.6]spiro-9-undecanone to obtain a modified PCL able to undergo PEGylation reaction.

A MPEG-*b*-PCL copolymer diblock was proposed in the synthesis of supramolecular hydrogels by combination with α -CD to achieve an injectable delivery system for the release of PTX, DOX, and CisPt in lung and bladder tumors [32,103]. In these systems, α -CD were selectively inserted onto the linear polymer chains, and the resulted supramolecular complex aggregated in packed columns, mainly formed by host-guest interactions or π - π stacking between polymeric chains [104]. These systems have attracted special interest because of their favorable properties, such as thixotropy and reversibility, with their in situ encapsulation characteristics able to prolong the retention time in cancers, reducing side effects [105]. In another system, the coordination between platinum(II) atoms and carboxylic groups of poly-(acrylic acid) (PAA) blocks induced poly(ethylene glycol)-*b*-poly-(acrylic acid) (PEG-*b*-PAA) self-assembly into micelles, with the supramolecular hydrogels eventually formed by the addition of α -CD [106]. Different supramolecular hydrogels based on PEG block polymers (e.g., nucleobase (adenine/thymine)-terminated PEG) were tested for the buccal delivery of DOX in in vivo mouse models [107]. Folic acid (FA)-modified cationic and amphiphilic MPEG-PCL-PEI-FA was proposed as supramolecular system able to form polyplexes with anionic plasmid for sustained gene delivery effectively inhibiting in vivo tumor growth [108].

Drug delivery systems based on PEG-PCL-PEG were loaded with 5-FU and PXT and tested in in vivo experiments for the treatment of colon and breast tumors, respectively [73,95]. Another promising injectable hydrogel for in situ gel-forming controlled drug delivery systems is based on PCL-PEG-PCL, due to several benefits, such as prolonged drug release, sol-gel transition around the body temperature, and ease of handling, being in a solid state at room temperature [109]. In situ gelling materials based on PCL-PEG-PCL loaded with PTX and CPT were proposed as drug delivery systems against breast and gastro-intestinal cancers, with excellent results in both in vivo and in vitro experiments [96,97]. However, the preparation of the anticancer-gel formulations require high temperatures or extended times, which are unsuitable for formulations containing unstable drugs [110]. Moreover, strong hydrophobicity and high crystallinity of PCL units confer to PCL-PEG-PCL a slow degradation rate, which is not always desirable.

To address this concern, chemical modification of PCL allowed the synthesis of new polymeric systems with improved properties. In particular, PCL modified with cyclic ether pendant groups, i.e., poly(ϵ -caprolactone-*co*-1,4,8-trioxa[4.6]spiro-9-undecanone)-poly(ethyleneglycol)-poly(ϵ -caprolactone-*co*-1,4,8-trioxa[4.6]spiro-9-undecanone), were prepared [111]. The insertion of cyclic ether pendant groups into PCL units was performed by copolymerization of 1,4,8-trioxa[4.6]spiro-9-undecanone with PCL, and the resulting macromer showed modified gelation performances as a consequence of the changing of PCL crystallization properties. By this approach, injectable carriers for DOX and PXT were obtained and proposed for the treatment of breast and liver cancers [99–101,112].

Methoxy poly(ethylene glycol)-*b*-poly(ϵ -caprolactone-*co*-1,4,8-trioxa[4.6]spiro-9-undecanone) (PEG-PCL) diblock copolymer was employed to prepare host-guest inclusion injectable nanocomposite devices based on surface-modified gold nanorods, PTX/PEG-PCL nanoparticles, and α -cyclodextrin [98]. A single local injection of this hydrogel allowed to deliver abundant PTX/PEG-PCL nanoparticles and gold nanorods at the target site, developing remarkable anticancer activity and photothermal effect. Alternatively, the coupling of PTX/PEG-PCL with α -CD allowed the synthesis of supramolecular hydrogels based on the hydrophobic aggregation of pseudorotaxane between cyclodextrins and block copolymers [113].

Co-delivery of anticancer agents and radiosensitizer isotopes was exploited in the design of innovative drug delivery systems able to combine the effects of chemo- and radio-therapy with reduction of the damage to normal tissue and improved therapeutic efficiency [114]. Specifically, PEG-PCL-based hydrogels were employed in the preparation of multifunctional devices for the delivery of DOX and β -emitter species, such as iodine-131 and rhenium-188, for the treatment of the

hepatocellular carcinoma [102,115]. Finally, an advanced system involving linear copolymer formed by poly(ϵ -caprolactone) was proposed for transcatheter arterial chemoembolization, a technique based on the combination of chemotherapeutic efficacy from delivered anticancer drugs and a blockage of tumor feeding vessels with an embolic material [116]. Specifically, sulfamethazine-based anionic pH-sensitive block PCL copolymer was fabricated by free radical polymerization [117]. Aqueous solutions of the synthesized copolymer underwent a sol-to-gel phase transition upon lowering the environmental pH, and created a gel region able to cover the physiological conditions and low pH environments typical of the tumor site.

Polyurethane (PU) derivatives, such as poly(amino ester urethane) (PAEU) block copolymers, were employed as drug delivery systems, thanks to their ability to form electrostatic interactions and hydrogen bonds with bioactive molecules, and to exhibit sol-gel phase transition after injection into the body. PAEU copolymers were proposed for the fabrication of injectable radiopaque embolic materials, based on a mixture of an aqueous copolymer solution and Lipiodol, a commercial long-lasting X-ray contrast agent [118]. In particular, exploiting the influence of pH and temperature on the self-assembly capacity of this polymeric material, a dual drug delivery system was proposed as a carrier for the regional release of DOX in the liver compartment. Additionally, target-specific release of CisPt was proposed by incorporation of CisPt chondroitin sulfate-based nanogels into pH- and temperature-responsive PEG-PAEU hydrogels [119]. In this case, ionic interactions, under physiological conditions, between the tertiary amine and sulfate groups allowed to form hydrogel networks able to selectively bind a receptor specifically expressed on cancer cells [120].

Linear copolymers obtained by suitable mixing of polyester monomers were used to synthesize injectable hydrogels with tailored properties due to their specific hydrophobic/hydrophilic balance. To this regard, PCLA-PEG-PCLA triblock copolymer was synthesized using a ring-opening copolymerization involving ϵ -Caprolactone and LA, in the presence of PEG and Tin(II) 2-ethylhexanoate. In particular, amphiphilic copolymer was conjugated with heparin to construct non-anticoagulant heparin prodrugs loaded in thermosensitive hydrogel for anti-metastasis treatment [121] and as a GEM carrier for the treatment of pancreatic cancer [122]. Moreover, PCLA-PEG-PCLA copolymer was modified via polyaddition polymerization with sulfamethazine, acting as anionic pH-sensitive moiety, to synthesize a dual stimuli responsive polymeric system, proposed for the DOX release in liver cancer [123]. Finally, injectable pentablock copolymer hydrogels PEG-PCL-PLA-PCL-PEG, with different ratios of PCL and PLA, were proposed as single-shot sustained release of vaccines. Specifically, vaccine was encapsulated into PLGA nanoparticles and incorporated in the thermoresponsive hydrogels in order to modulate gelation temperature and minimize burst release of antigen and adjuvants in the treatment of melanoma [124]. Nevertheless, the synthetic strategies involving lactide, glycolide, or ϵ -caprolactone derivatives to generate a temperature-sensitive and biodegradable polymeric backbone suffered from the lack of chemical functionality in the parent aliphatic polyesters that makes it difficult to modify the polymeric chains.

A valuable alternative way exploited the employment of methyltrimethylcarbonate (PCB), cyclic carbonates derived from 2,2-bis(methylol) propionic acid (bis-MPA), as synthon for functional biodegradable monomers [16]. Ring-opening polymerization, followed by *N,N'*-dicyclohexylcarbodiimide-mediated condensation, was the synthetic strategy proposed to prepare hydrophilic/hydrophobic PEG-functionalized cyclic carbonate based on 2,2-bis(methylol)propionic Acid (bis-MPA) [125]. Micellization provided a physical cross-linked system, displaying a lower critical solution temperature at values near the body temperature that can be suitable for PXT release against hepatic cancer cells. A different protocol involved the formation of a biodegradable polymeric biomaterial consisting of PEG and a polycarbonate of dihydroxyacetone (pDHA), proposed for the prevention of the seroma post-operative complications following ablative breast cancer surgery [126]. Vitamins E and D-functionalized polycarbonates were proposed as a hydrophobic block in the synthesis of three-block copolymers able to form physically cross-linked injectable hydrogels for local and sustained delivery of herceptin in breast cancer treatment [127,128].

Table 3. Composition and anticancer performance of injectable hydrogels based on polyesters.

Ref	Composition		Carrier Properties		Delivery Properties		Cancer Model			Health Model	
	Hydrogel (Gelation Process)	Composite Component	Degradation Time (Days)	Smart Responsivity	Bioactive Agent (DL% w/w)	Release Time (Days)	Type	In Vitro	In Vitro	In Vitro	In Vitro
[77]	PLA-PEG-PLA (Physical – T)	PLA-PEG-PLA	---	---	GEM* (10) CisPt* (0.2)	10	Pancreas	Bxpc-3	Bxpc-3	---	Mice
[78]	PLA-PL64-PLA (Physical – T)	PLA-PL35-PLA	---	---	DTX (4.5) LL37* (7.5)	24	Colon	HCT 116	---	HEK293	Mice
[79]	PLA-PL35-PLA (Physical – T)	PLA-PL35-PLA	---	---	OXA DTX* (4.4)	14	Murine colon	CT26	CT26	3T3 HEK293	---
[80]	MPEG-POA-LAO (Physical – T)	MPEG-POA-LAO	---	---	PTX* (0.9)	17#	Breast Cervix	MCF7 HeLa	MCF7 ---	---	---
[83]	PLGA-PEG-PLGA (Physical – T)	---	---	---	DOX (1.0) CisPt (1.0) MTX (1.0)	12	Osteosarcoma	Saos-2 MG-63	Saos-2 ---	L929	---
[85]	PLGA-PEG-PLGA (Physical – T)	---	---	---	TPT (1.0)	5	Sarcoma	---	S180	---	---
[86]	PLGA-PEG-PLGA (Physical – T)	---	44	---	DOX (1.0)	15	Osteosarcoma Murine osteosarcoma	Saos-2 K7	---	---	---
[88]	PLGA-PEG-PLGA (Physical – T)	Vesicles	---	---	CYT* (25.4)	12	Leukemia	K562 HL-60	---	---	Rabbit
[89]	PLGA-PEG-PLGA (Physical – T)	Liposome	---	---	ME* (5.6)	70	Murine breast	---	4T1 mice	---	---
[90]	PLGA-PEG-PLGA (Physical – T)	Arg Dendrimers Lys Dendrimers	---	pH	DOX* (13.6) DOX* (14.3)	20	Murine breast	4T1	4T1 mice	3T3 RAW267	---
[91]	PLGA-PEG-PLGA (Physical – T)	SLN	---	pH	ME* (2.05–2.23)	45	---	---	---	---	---
[92]	PLGA-PEG-PLGA (Physical – T)	PEI-Lys	40	---	DOX (1.0) sRNA*	16#	Osteosarcoma	Saos2 MG-63	Saos2 ---	---	---
[93]	MPEG-PLGA (Physical – T)	MPEG-PLGA	---	---	PTX (4.0) Pt* (0.8)	80	Ovarian	SKOV-3	SKOV-3	---	---

Table 3. Cont.

Ref	Composition		Carrier Properties		Delivery Properties		Cancer Model			Health Model	
	Hydrogel (Gelation Process)	Composite Component	Degradation Time (Days)	Smart Responsivity	Bioactive Agent (DL% w/w)	Release Time (Days)	Type	In Vitro	In Vitro	In Vitro	In Vitro
[94]	MPEG-PLGA (Physical – T)	---	---	---	GM-CSF (15–25)	14	Murine Melanoma	B16 B16-F10	B16-F10	---	---
[95]	PCL-PEG (Physical – T)	---	---	---	5-FU (1.0)	7	Colon	CT26	CT26	---	---
[73]	PEG-PCL-PEG (Physical – T)	MPEG-PCL	---	---	PTX* (8.3)	20	Breast	4T1	4T1	---	---
[96]	PCL-PEG-PCL (Physical – T)	---	---	pH	PTX** (20)	30	Liver Breast	HepG2 MCF7	---	L929	Mice
[97]	PCL-PEG-PCL (Physical – T)	PCL-PEG-PCL	---	---	CPT* (4.1–13.5)	14	Colon	---	CT26	L929	---
[98]	MPEG-PCL- α -CD (Physical – T)	MPEG-PCL AuNRs	14 3 [§]	---	PTX* (3.0)	14	Murine Breast	4T1	4T1	---	---
[100]	PCL-PEG-PCL (Physical – T)	PCL-PEG-PCL	---	---	PTX* (1.25, 2.5)	45	Erlich ascites Ovarian	EAC ---	EAC OVCAR-3	---	---
[101]	PCL-PEG-PCL (Physical – T)	PCL-PEG-PCL	---	pH	DOX* (1.0)	35	Liver Breast	HepG2 ---	---	Bcap-37	---
[102]	PCL-PEG-PCL (Physical – T)	HA	---	pH	DOX ¹³¹ I* (0.5–2)	35	Liver	HepG2	HepG2	---	---
[32]	MPEG-PCL- α -CD (Physical)	MPEG-PCL	---	---	PTX* (18.8)	3	Lung	A549	---	---	---
[103]	MPEG-PCL- α -CD (Physical)	MPEG-PCL	---	pH	DOX* (15) CisPt* (20)	8	Bladder	EJ	---	HEK293	---
[106]	MPEG-PAA- α -CD (Physical)	MPEG-PAA	---	---	CisPt* (0.5–1.0)	4	Bladder	EJ	---	HEK293	---
[107]	APEGA/TPEGT- α -CD (Physical)	---	---	---	DOX (0.2–0.6)	11	Buccal	---	U14	L929	---
[108]	MPEG-PCL-PEI- α -CD (Physical – SE)	---	---	---	PTX (10) pDNA	7 [#]	Liver Lymphoma	HepG2 Bcl-2	---	HEK293 LO2	---
[112]	PCL-PEG-PCL/ MPEG-PPFEMA (Physical – T)	---	---	---	PTX (4.2) DOX (4.2)	42	Breast	MCF7	Bcap-37	---	---

Table 3. Cont.

Ref	Composition		Carrier Properties		Delivery Properties		Cancer Model			Health Model	
	Hydrogel (Gelation Process)	Composite Component	Degradation Time (Days)	Smart Responsivity	Bioactive Agent (DL% w/w)	Release Time (Days)	Type	In Vitro	In Vitro	In Vitro	In Vitro
[113]	MPEG-PCL- α -CD (Physical)	MPEG-PCL	---	---	PTX* (1–3)	20	Murine breast	---	4T1	---	---
[115]	PCL-PEG-PCL (Physical – T)	Liposome	---	---	¹⁸⁸ Re DOX* (2.0)	10	Murine liver	BNL-Luc	BNL-Luc	---	---
[117]	PCLMA-PEGMA-SMA (Chemical – RP)	---	---	pH	DOX (0.2–0.4)	27	Liver	HepG2	VX2	L929	---
[118]	PAEU (Physical – T, pH)	---	---	---	DOX (10)	14	Liver	HepG2	VX2	L929	---
[119]	PEG–PAEU (Physical – T)	CHS-Nanogel	28	pH	CisPt* (0.2)	14	Lung	A549	---	3T3	Mice
[121]	PCLA-PEG-PCLA (Physical – T)	PCLA-PEG-PCLA	35	---	Hep*	10	Cervix	HeLa	HeLa	HaCaT	---
[122]	PCLA-PEG-PCLA (Physical – T)	MMT	56	---	GEM* (10)	7	Pancreas	---	Panc-1	293T	---
[123]	PCLA-PEG-PUSSM (Physical – T)	---	28	pH	DOX (5.0)	28	Liver	HepG2	VX2	293T	---
[124]	PEG-PCL-PLA-PCL-PEG (Physical – T)	PLGA	30	---	OVA (0.8) MPL (0.6) QA (1.1)	30	Melanoma	---	B16 OT-I B16 OT-II	---	---
[125]	Bis-MPA-PEG (Chemical – ROP)	---	---	Temperature	PTX (3.9)	7	Liver	HepG2	---	---	---
[126]	PEG-pDHA (Physical)	---	1	---	---	---	Breast	---	Rat	---	---
[127]	VitE-PCB-VitE (Physical)	---	42	---	TZB (4.0)	16		MCF-7 BT474	---	HDF	---
[128]	VitD-PCB-VitD VitE-PCB-VitE (Physical)	---	---	---	TZB (4.0)	42	Breast	BT474	BT474	---	Mice

* Loaded into composite component; # from in vivo experiments; DL: Drug loading; I: Ionic; T: Temperature; RP: Radical polymerization; ROP: Ring-opening polymerization; SE: Solvent evaporation; Arg: Arginine; 5-FU: 5-Fluorouracil; CD: Cyclodextrin; APEGA: Adenine-terminated poly(ethylene glycol); AuNRs: Gold nanorods; CHS: Chondroitin sulfate; CisPt: Cisplatin; CPT: Camptothecin; CYT: Cytarabine; pDHA: Polycarbonate of dihydroxyacetone; pDNA: Plasmid DNA; DOX: Doxorubicin; DTX: Docetaxel; GEM: Gemcitabine; GM-CSF: Granulocyte-macrophage colony-stimulating factor; HA: Hyaluronic acid; Hep: Heparin; LAO: Lactic acid oligomers; Lys: Lysine; ME: 2-Methoxyestradiol; MMT: Montmorillonite; bis-MPA: 2,2-bis(methylol)propionic acid; MPEG: Monomethoxy poly(ethylene glycol); MPL: Monophosphoryl lipid A; MTX: Methotrexate; OVA: Ovalbumin; OXA: Oxaliplatin; PAA: Poly(acrylic acid); PAEU: Poly(β -aminoester urethane); PCB: Polycarbonate; PCL: Poly(ϵ -caprolactone); PCLA: Poly(ϵ -caprolactone-*co*-lactide); PCLMA: Poly(ϵ -caprolactone) monomethacrylate; PEG: Polyethylene glycol; PEGMA: Methoxypoly(ethylene glycol) monomethacrylate; PEI: Poly(ethylene imine); PL: Pluronic L; PLA: Polylactide; PLGA: Poly(lactide-*co*-glycolide); POA: Poly(octadecanedioic anhydride); PPFEMA: Poly(2-(perfluorobutyl)ethyl methacrylate); PTX: Paclitaxel; PUSSM: Poly(urethane sulfide-sulfamethazine); QA: Quil A; SLN: Solid lipid nanoparticles; SMA: Sulfamethazine-acrylamide; TPEGT: Thymine-terminated poly(ethylene glycol); TPT: Topotecan; TZB: Trastuzumab; Vit: Vitamin.

2.4. Polyacrylates

Photo-induced radical polymerization involving acrylate monomers and/or functionalized macromers represents an alternative to thermal gelation in the preparation of injectable hydrogels able to be self-assemble after injection following a UV-irradiation (Figure 7) [129,130].

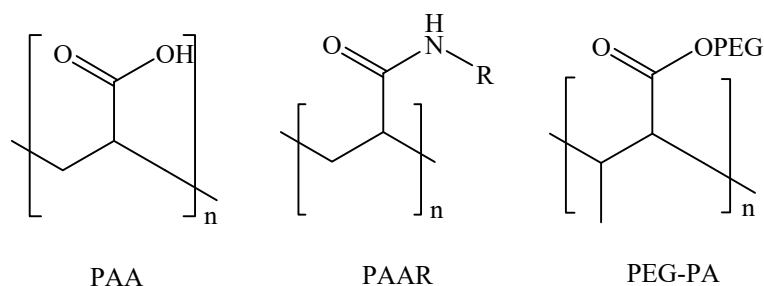


Figure 7. Schematic representation of the main acrylate polymers. PAA: Poly(acrylic acid); PAAR: *N*-alkyl poly(acrylic amide); PEG-PA: PEGylated poly(methacrylic acid).

The main component of this class of materials enclosed PEG acrylate polymers (PEG-PA), which was designed to allow the insertion of PEG properties (e.g., non-cytotoxicity, non-immunogenicity, and ability to reduce opsonization) within a hydrogel network, showing increased drug loading capability and retention time and improved mechanical properties (Table 4) [23,131].

This approach was investigated in the treatment of glioblastoma, employing a system based on polyethylene glycol dimethacrylate (PEGDMA). The photopolymerizable monomer was UV-irradiated in the brain tumor resection bed and employed for the delivery of Temozolomide (TMZ) and Paclitaxel (PTX) [132,133]. This approach could present several advantages, including the killing of the tumor cells that, after the resection of the main primary tumor, could infiltrate the brain tissue and the parenchyma.

Hybrid materials were also prepared by incorporating carbon nanotubes [134] or Zn ferrite nanoparticles [135] for breast cancer treatment by combined DOX/photothermal and thermal ablation therapy, respectively. Injectable hydrogels, proposed for the thermo-responsive delivery of different drug molecules to prostate cancer *in vivo*, were prepared by radical polymerization of oligo(ethylene glycol) methacrylate (OEGMA) monomers [136]. In another study, PAA was combined with a poly[4-(2,2,6,6-tetramethyl piperidine-*N*-oxyl)aminomethylstyrene]-*b*-poly(ethylene glycol)-*b*-poly[4-(2,2,6,6-tetramethyl piperidine-*N*-oxyl)aminomethylstyrene] (PMNT-PEG-PMNT) triblock copolymer to obtain a redox-active polyion complex for the local protein therapy of murine colon cancer [137].

A different approach involved the synthesis of specific gold nanorods incorporated into the three-dimensional network achieved by radical polymerization of methacrylated poly- β -cyclodextrin (MPCD)-based macromer and *N*-isopropylacrylamide (NIPAAm) as a poly(*N*-Alkylacrylamide) (PAAR) derivative [138]. The hydrogel, exhibiting near-infrared and pH responsivity, was efficiently loaded by host-guest interactions with adamantane-modified DOX prodrug, and its efficiency was tested in *in vitro* tests against MCF7 (breast) and HeLa (cervix) cancer cells, and in *in vivo* experiments carried out in the treatment of murine sarcoma.

Alternatively, thermoresponsive supramolecular poly(*N*-acryloyl glycylamide-*co*-acrylamide) (PNAm) hydrogels, bearing polydopamine-coated gold nanoparticles and DOX, were fabricated by radical photopolymerization [139], and proposed as a breast filler. This system, after heating in the sol state, was injected into the cavity of resected breasts, where a rapid gelation occurred during cooling to body temperature.

Table 4. Composition and anticancer performance of injectable hydrogels based on polyacrylates.

Ref	Composition		Carrier Properties		Delivery Properties		Cancer Model			Health Model	
	Hydrogel (Gelation Process)	Composite Component	Degradation Time (Days)	Smart Responsivity	Bioactive Agent (DL% <i>w/w</i>)	Release Time (Days)	Type	In Vitro	In Vivo	In Vitro	In Vivo
[132]	PEGDMA (Chemical – RP)	PEG–PCL	---	---	TMZ* (0.9–1.3)	12	Glioblastoma	---	U87	---	---
[133]	PEGDMA (Chemical – RP)	PLGA	---	---	PTX* (4.0)	7	Glioblastoma	U87	U87	---	Mice
[134]	PEGDMA (Chemical – RP)	TiO ₂ MWCNT	---	NIR	DOX* (10)	3	Breast	MCF7	MCF7	---	---
[135]	PEGDMA (Physical – T)	ZnFe ₂ O ₄	---	Magnetic	---	---	Breast	---	4T1	---	---
[136]	p(MEO ₂ MA-OEGMA-AA) (Chemical – RP)	---	---	---	BSA (1.6) Epo (1.6)	3 1.5	Prostate	---	PC3	3T3	---
[137]	PMNT–PEG–PMNT/PAA (Physical)	---	---	---	IL-12 (0.07)	15	Murine Colon	---	C26	---	---
[138]	p(NIPAAm-MPCD) (Chemical – RP)	AuNRs	---	pH NIR	DOX (6.6)	30	Breast	MCF7	---	---	---
							Cervix	HeLa	---		
							Murine sarcoma	---	S180		
[139]	PNAm (Chemical – RP)	PDA–AuNRs	---	NIR	DOX	2 [§]	Murine breast	---	4T1	---	---

* Loaded into Composite Component; DL: Drug loading; RP: Radical polymerization; AuNRs: Gold nanorods; BSA: Bovine serum albumin; DOX: Doxorubicin; Epo: Erythropoietin; IL: Interleukin; MEO₂MA: Methyl ether methacrylate; MPCD: Methacrylated poly- β -cyclodextrin; MWCNT: Multi-walled carbon nanotubes; NIPAAm: N-isopropyl acrylamide; NIR: Near-infrared; OEGMA: Poly(ethylene glycol) methyl ether methacrylate; PAA: Poly(acrylic acid); PCL: Poly(ϵ -caprolactone); PDA: Polydopamine; PEG: Polyethylene glycol; PEGDMA: Polyethylen glycole dimethacrylate; PLGA: Poly(lactide-*co*-glycolide); PMNT: Poly[4-(2,2,6,6-tetramethyl piperidine-*N*-oxyl)aminomethylstyrene]; PNAm: Poly(*N*-acryloylglycinamide-*co*-acrylamide); PTX: Paclitaxel; TMZ: Temozolomide.

2.5. Synthetic Polypeptide

Polypeptides (Pep) are synthetic protein-mimicking materials particularly attractive for their biocompatibility and biodegradability [140–142]. Another advantage of this class of compounds lies in the great chemical diversity due to the wide number of monomer sources from 21 natural amino acids and their synthetic derivatives (Figure 8).

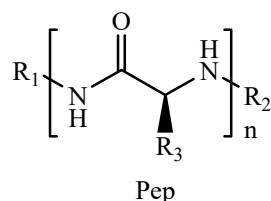


Figure 8. Schematic representation of synthetic polypeptides.

In addition, exploiting intramolecular hydrogen bonds within peptide backbones, polypeptides can adopt ordered secondary structures (i.e., α -helix and the β -sheet) that confer them the self-assembly behavior. Self-assembling polypeptides were employed as starting materials for the preparation of injectable hydrogels (Table 5) [143–145] via gelation processes of their aqueous solutions upon changes in pH, ionic strength, or temperature. The introduction of cytotoxic molecules into the solution led to the encapsulation of bioactive agents for the treatment of different tumors. In detail, ionic gelation was proposed for the preparation of Ce6 carrier system [146] for breast cancer, and stimulation of immune system in health mice [147,148]. Thermo gelation processes were used for the fabrication of injectable hydrogels for TMP-2 [149] and DOX-based therapy [150,151] of breast, cervix, and lung cancers, as well as for DOX or gene (CDN) administration with simultaneous stimulation of immune responses [152,153]. Furthermore, DOX@Liposome formulations were loaded in Pep hydrogels for an Losartan (LST) combination therapy [154]. Another approach for the preparation of starting materials for injectable hydrogels involves the conjugation of peptide moieties to oligoethylene glycol (OEG) [141] or PEG derivatives, with the formation of PEGylated [155–158] or block [15,159,160] copolymers. Such hydrogels were found to be suitable for the preparation of pro-drugs [160–162] and the delivery of different clinically relevant cytotoxic agents, with the possibility to trigger the releasing profile in response to physiological stimuli such as pH [155], temperature [158], and cell redox state [15,160–162], or stimulate the immune system (Figure 9) [157].

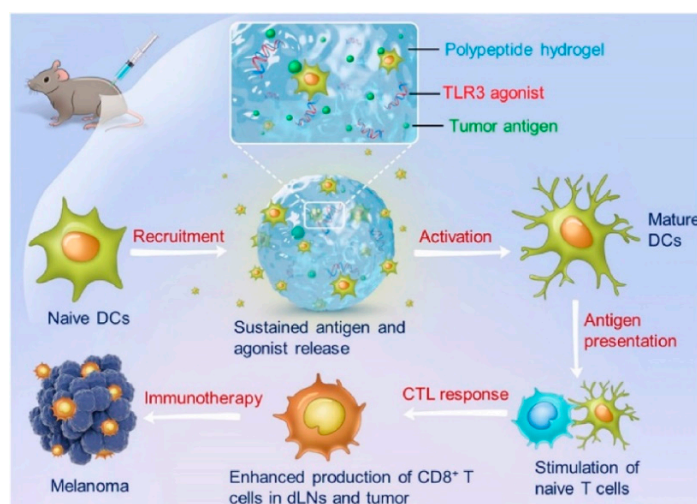


Figure 9. In vivo modulation of dendritic cells (DCs) by sustained release of tumor antigens and tumor cell lysates 3 (TLR3) agonist from a polypeptide hydrogel, evoking a strong cytotoxic T-lymphocyte (CTL) response. With permission from [157]; Elsevier, [2018].

Table 5. Composition and anticancer performance of injectable hydrogels based on synthetic polypeptide.

Ref	Composition		Carrier Properties		Delivery Properties		Cancer Model			Health Model	
	Hydrogel (Gelation Process)	Composite Component	Degradation Time (Days)	Smart Responsivity	Bioactive Agent (DL% w/w)	Release Time (Days)	Type	In Vitro	In Vivo	In Vitro	In Vivo
[146]	Fmoc-FF/PLL (Physical – I)	---	---	---	Ce6 (0.4)	14#	Breast	---	MCF7	---	---
[147]	Fmoc-FF/PLL (Physical – I)	---	---	---	---	---	---	---	---	---	Mice
[148]	RGD–PIC (Physical – T)	---	---	---	---	---	---	---	---	---	Mice
[149]	AcVES3 (Physical – T)	---	---	---	TIMP-2 (4.0)	28	Lung	A549	---	---	---
[150]	FEFFFFK (Physical – T)	---	---	---	DOX (0.5)	20#	Breast	MDA-MB 231	MDA-MB 231	---	---
							Murine breast	4T1	4T1		
[151]	Nap-GFFYGRGDH _n (n = 0–2) (Physical – T)	---	---	pH	DOX** (3.9–12.4)	7	Lung	A549	---	---	Mice
							Cervix	HeLa			
							Breast	MCF-7			
[152]	K ₂ (SL) ₆ K ₂ (Physical – T)	---	---	---	CDN (40)	1	Murine Oral	MOC2-E6E7	MOC2-E6E7	---	---
[153]	(RADA) ₈ (Physical – T)	---	10	---	MEL** DOX (16)	7	Murine Melanoma	B16F10	B16F10	---	---
[154]	C ₁₆ -GNNQQNYKD-OH (Physical – T)	Liposome	---	---	LST DOX*	9	Breast	---	4T1	---	---
[155]	PEG–PAH (Physical – T)	---	---	pH	DOX (1.7)	2	Fibrosarcoma	HT1080	HT1080	3T3	---
[156]	MPEG–(PELG–LG) (Physical – T)	---	28	---	CisPt (1.0)	7	Murine colon	C26	C26	---	---
							Cervix	HeLa	---		
							Breast	MCF-7	---		
[157]	MPEG–PV (Physical – T)	---	---	---	TCL (50)	21#	Murine Melanoma	---	B16	---	---
[158]	MPEG–PAF (Physical – T)	---	28	Temperature	DOX (6.0) CA4 (6.0)	28	Murine cervix	---	U14	---	---
[163]	MPEG–PLD–Arg–α–CD (Physical)	---	---	---	sRNA	6	Epithelium	HNE-1	HNE-1	3T3	---
[159]	PELG–PEG–PELG (Physical – T)	---	14	---	PTX (6.0)	21	Liver	HEPG2	HEPG2	---	Mice

Table 5. Cont.

Ref	Composition		Carrier Properties		Delivery Properties		Cancer Model		Health Model		
	Hydrogel (Gelation Process)	Composite Component	Degradation Time (Days)	Smart Responsivity	Bioactive Agent (DL% w/w)	Release Time (Days)	Type	In Vitro	In Vivo	In Vitro	In Vivo
[15]	(Me-D-1MT)–PEG–(Me-D-1MT) (Physical – T)	---	21	ROS	PD-1/PD-L1 CTLA-4	16#	Murine Melanoma	B16F10	B16F10	---	---
[160]	FFE–EE (Physical – Red)	---	---	Redox	SN-38**	3	Breast	MD-MBA-231	---	---	---
[161]	KE–EE/AcKE–EE/E–EE/R–EE/S–EE (Physical – Red)	---	---	Redox	DXM** TX**	1	Liver	HepG2	---	---	---

* Loaded to composite component; ** conjugated to hydrogel; # from in vivo experiments; DL: Drug loading; I: Ionic; T: Temperature; Red: Redox; Ac: Acetyl; AcVES3: Ac–VEVSVSVEV^DPPTEVSVEVEV–NH₂; Arg: Arginine; C₁₆: Palmitic acid; CA4: Combretastatin; CDN: Cyclic dinucleotides; CisPt: Cisplatin; CTLA-4: Cytotoxic T lymphocyte antigen 4; D-1MT: Dextro-1methyl tryptophan; DOX: Doxorubicin; DXM: Dexamethasone; Fmoc-FF: *N*-fluorenylmethoxycarbonyl diphenylalanine; LG: L-glutamic acid; LST: Losartan; MEL: Melittin; MPEG: Monomethoxy poly(ethylene glycol); Nap: Naphthylacetic acid; PAF: Poly(alanine-phenylalanine); PAH: α,β -polyaspartyl hydrazide; PD-1/PD-L1: Programmed cell death protein 1/programmed cell death-ligand 1; PEG: Polyethylene glycol; PELG: Poly(ethyl-L-glutamate); PIC: Tri-ethylene glycol-substituted polyisocyanopeptide; PLL: Poly-L-lysine; PTX: Paclitaxel; PV: Poly(L-valine); ROS: Reactive oxygen species; SN-38: 7-ethyl-10-hydroxycamptothecin; TIMP-2: Tissue inhibitor of metalloproteinase 2; TLC: Tumor cell lysates; TX: Taxol.

Disulfide bonds were also employed for the preparation of thermo-responsive injectable hydrogels. For example, PEGylated disulfide bond containing poly(L-cysteine) derivative (poly(L-EGx-SS-Cys)) possessed an irreversible thermo-responsive behavior in water, probably ascribed to chemical cross-linking caused by disulfide bond exchange. A thermogel consisting of PEG and poly(L-EG4-SS-Cys) diblock copolymer was used as reduction responsive injectable hydrogel [164]. Physical cross-linking approach was also employed for the preparation of injectable hydrogels with excellent shearing thinning features using PEG₄₄-NH₂ as a macroinitiator [165].

2.6. Dendrimers and Other Systems

Dendrimers are synthetic branched polymers with a globular structure, nanometric size, and low polydispersity index [166], fabricated via a sequence of reaction steps in which monomer units are added to a Generation 0 core [167]. This class of materials possesses unique features for drug delivery applications, including the high affinity of the inner hydrophobic environment for different drug molecules, the wide number of functional groups suitable for tailored functionalization [167], and the ability to cross the cell membrane via paracellular and endocytosis pathways [168,169]. Different injectable hydrogels based on dendrimers have been proposed in the literature for the treatment of solid cancers (Table 6), mainly consisting in modified PEG [170], poly(amine-ester) [171], and polyamidoamine (PAMAM) (Figure 10) [172,173].

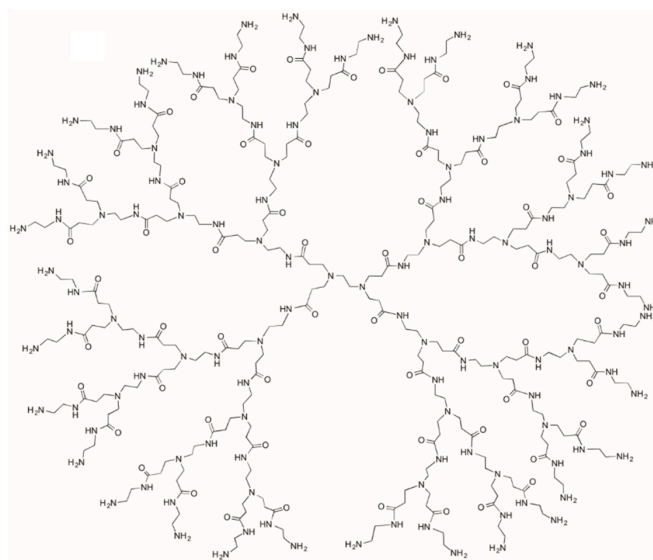


Figure 10. Schematic representation of polyamidoamine (PAMAM) dendrimer.

The main component of this class of materials enclosed PEG acrylate polymers (PEG-PA), which was designed to allow the insertion of PEG properties (e.g., non-cytotoxicity). PEG dendrimers were modified by insertion of disulfide bonds [174,175] or boronic acid moieties [176] to confer redox and pH responsivity, respectively. Boronic acid derivatives were also proposed to enhance the pH biodegradability patterns of injectable hydrogels employed for breast cancer treatment in mouse models [177], while the formation of Schiff's base with poly-L-lysine (PL) carried out to an effective MTF and 5-FU delivery system to colon C26 cells [34]. Targeting behavior can be conferred by derivatization with heparin residues [178]. PEGylated PAMAM injectable hydrogels with increased solubility and improved biodistribution characteristics [179] were tested as 5-FU carriers or as pH and redox responsive DOX delivery vehicles for head/neck and cervix cancer treatment, respectively [172,173]. Other examples of injectable hydrogels for cancer therapy consist in lipid nanocapsule-based hydrogels able to cross the blood–brain barrier [180], and in pH responsive PVA/GO hybrids loaded with a CPT-CD complex [181]. The latter systems take the advantages of the peculiar properties of the high biocompatible carbon nanostructures [182–184].

Table 6. Composition and anticancer performance of injectable hydrogels based on dendrimers and other systems.

Ref	Composition		Carrier Properties		Delivery Properties		Cancer Model			Health Model	
	Hydrogel (Gelation Process)	Composite Component	Degradation Time (Days)	Smart Responsivity	Bioactive Agent (DL% w/w)	Release Time (Days)	Type	In Vitro	In Vivo	In Vitro	In Vivo
Dendrimers											
[170]	PGA-MA/PEG-4-SH (Chemical – MR)	---	---	---	TZB (1.0–13)	42	Breast	BT474	BT474	---	---
[171]	HPAE (Chemical – RP)	---	7	---	DOX (0.05) 5-FU (0.5) LC (0.2)	5	Breast	MCF7	---	L929	---
[172]	PAMAM(G4)/PEG-PDBCO (Physical)	---	---	---	5-FU (4)	0.5	Head/Neck	HN12	HN12	3T3	---
[173]	PEGDA-PAMAM (Chemical – MR)	---	14-22 1.4-2.0	pH Redox	DOX (4)	2	Cervix	HeLa	---	---	---
[174]	PEG-4-SH/PDMA-PEGMA (Physical)	p(AA-co-4-VPBA)	21	pH Redox	CA4P (0.05) DOX* (14.3–96.3)	3 14	Breast Liver	MCF-7 ---	--- HepG2	3T3	---
[175]	PEG-4-SH/PEG-2-MI (Physical – pH)	---	2.7	Redox	BSA (1.2)	7	---	---	---	---	---
[176]	PEGBA-4/PEGBA-8 (Chemical – RP)	PEGBA-4/PEGBA-8	---	pH	PLP*	20	Oral	CAL-27	---	---	---
[177]	PBA-PEG (Physical)	---	---	pH	DOX (1.2)	5	Murine Breast	4T1	4T1	3T3	---
[34]	PEG-4-SH/PLL (Chemical – C)	---	14	pH	MTF (5.0) 5-FU (0.5)	14	Colon	C26	C26	---	---
[178]	Hep-PEG-4-SH (Physical)	---	---	---	DOX (0.004–0.08)	4	Breast	MCF-7 MDA-MB-231	MDA-MB-231	---	---
Other systems											
[181]	PVA/GO (Physical)	β-CD	---	pH	CPT (5.0)	5	---	---	---	---	---

Table 6. Cont.

Ref	Composition		Carrier Properties		Delivery Properties		Type	Cancer Model		Health Model	
	Hydrogel (Gelation Process)	Composite Component	Degradation Time (Days)	Smart Responsivity	Bioactive Agent (DL% w/w)	Release Time (Days)		In Vitro	In Vivo	In Vitro	In Vivo
[180]	GemC ₁₂ LNC (Physical – PI)	---	---	---	---	---	Glioblastoma	U251	---	---	---
								T98-G	---	---	---
								9L-LacZ	---	---	---
								U-87	U87		

* Loaded into composite component; DL: Drug loading; MR: Michael reaction; RP: Radical polymerization; 4-VPBA: 4-vinylboronic Acid; 5-FU: 5-Fluoruracil; CD: Cyclodextrin; AA: Acrylic acid; BSA: Bovine serum albumin; CA4P: Combrestatin A4 phosphate; DOX: Doxorubicin; GO: Graphene oxide; Hep: Heparin; HPAE: Hyperbranched poly(amine-ester); LC: Leucovorin calcium; LNC: Lipod nanocapsule; MPEG: Monomethoxy poly(ethylene glycol); MTF: Metformin; PAMAM: Polyamidoamine; PBA: Phenylboronic acid; pDMA: Poly(3,4-dihydroxyphenethyl)-methacrylamide; PEG-4-SH: 4-arm PEG; PEGBA-4: 4-arm PEG-boronic acid; PEGBA-8: 8-arm PEG-boronic acid; PEGDA: PEG-based diacrylate; PGA-MA: Maleimide-modified c-polyglutamic acid; PEGMA: Methoxypoly(ethylene glycol) monomethacrylate; PEG-2-MI: Maleimide-functionalized linear PEG; PLD-Arg: Arginine-poly(L-lysine) dendron; PLL: Poly-L-lysine; PLP: Polyphenols mixture; PVA: Polyvinyl alcohol.

3. Natural Polymers

3.1. Polysaccharides

Polysaccharides are widely employed for the fabrication of injectable hydrogels, owing to their outstanding advantages consisting in water affinity, biocompatibility, biodegradability, non-immunogenicity, and non-fouling features. Furthermore, the presence of multiple chemical functionalities (e.g., acid, amine, hydroxyl, and aldehyde groups) allows easy chemical modifications with the obtainment of a plethora of biomedical devices. They exert biological activities such as cell recruiting, cell adhesion, and modulation of the inflammatory process, and the pharmacokinetic profiles can be tailored by choosing the appropriate molecular weight distribution [185,186].

Polysaccharides are obtained from renewable plant and animal sources, including algae (e.g., dextran, alginate), plants (e.g., cellulose, agarose), microbes (e.g., dextran, gellan gum), and animals (e.g., hyaluronic acid, chitosan). In this review, when polysaccharides are mixed with synthetic polymers to further modify their physical, mechanical, and chemical properties, the resulting systems are referred as N/S hybrids.

Chitosan (CS, Figure 11), the *N*-deacetylated derivative of chitin, is a biomaterial with a wide range of biomedical applications due to its high biocompatibility and biodegradability.

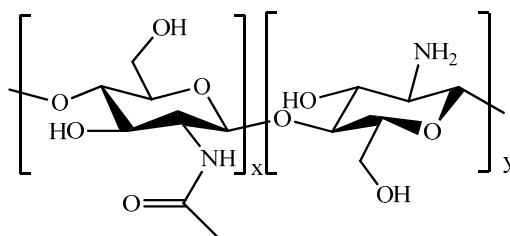


Figure 11. Schematic representation of chitosan (CS).

In addition, the wound-healing, anti-tumor, and antimicrobial activities, make CS an ideal starting material for designing pharmaceutical injectable formulations (Table 7) [187–189]. A CS prodrug of a photosensitizing agent was used as base material to obtain an injectable pH-responsive hydrogel to be used in breast cancer and melanoma therapy [190], whereas the chemical cross-linking of CS with β -GP was proposed in several research works as a valuable strategy to obtain thermo-responsive materials for the treatment of a number of cancer diseases. In more detail, CS/ β -GP systems were either employed as platforms for the release of antineoplastic drugs [191–194] or loaded with nanoparticles bearing the anticancer agent, in order to obtain a more sustained drug release in the site of interest [195–198]. Other applications involved the possibility to combine chemo- and radio-therapy [195,199], and produce local hyperthermia for different types of cancer [200–202]. Thermal gelation of CS in the presence of G carried out to injectable hydrogels for the treatment of breast cancer [203], while mixed polysaccharide hydrogels, including CS-ALG [204] and CS-HA-NIPAAm [205,206] complexes, were designed to produce targeted delivery of anti-VEGF antibody [204], as well as pH-responsive systems for the DOX [205] and DOX@GO [206] vectorization to colon and breast cancer, respectively. Injectable hydrogels were also prepared using CS hydrophilic derivatives [207]; for example, CS modified with glycol moieties was covalently linked with PEG to obtain hydrogel materials for the release of self-healing [208] and photosensitizing [209] agents. In another approach, DOX@PLGA nanoparticles were inserted into the hydrogel structure, together with magnetic nanoparticles, to raise a more sustained release profile combined with magnetic ablation of breast cancer [210]. Furthermore, supramolecular hydrogels composed of GCS, PF127, and α -CD were proposed as DOX delivery platforms in the treatment of liver carcinomas [211]. Different modifications involved the bonding of hydroxybutyl [212], hydroxypropyl [7], carboxymethyl [213,214], and carboxyethyl [215–217] groups.

Table 7. Composition and anticancer performance of injectable hydrogels based on chitosan.

Ref	Composition		Carrier Properties		Delivery Properties		Cancer Model			Health Model	
	Hydrogel (Gelation Process)	Composite Component	Degradation Time (Days)	Smart Responsivity	Bioactive Agent (DL% w/w)	Release Time (Days)	Type	In Vitro	In Vivo	In Vitro	In Vivo
Naturals											
[190]	CS (Chemical – C)	TA-ZnPc	1	Light pH	TA-ZnPc (6.0)	8	Breast Melanoma	MDA-MB-231 A435	---	---	---
[191]	CS/ β -GP (Physical – T)	---	---	---	CisPt (1.0)	15	Colon Breast	HCT-116 MCF7	---	---	---
[193]	CS/ β -GP/HA (Physical – I)	---	---	pH	DOX (0.016–0.033)	5	Cervix	HeLa	---	---	---
[194]	CS/ β -GP/CNT (Physical – T)	---	21	---	MTX	7	Breast	MCF7	---	3T3	---
[196]	CS/ β -GP (Physical – T)	MPEG	---	---	MEL** (4.6–10.6)	4	---	---	---	---	---
[198]	CS/ β -GP (Physical – T)	Liposome	---	pH	TPT* (0.97)	2	Murine Liver	---	H22	---	---
[197]	CS/ β -GP (Physical – T)	Liposome	---	---	DOX* (4.5)	7	Ovarian	A2780	---	---	---
[195]	CS/ β -GP (Physical – T)	Liposome	---	---	DOX* (0.2) ¹⁸⁸ Re*	21	Murine Breast	---	4T1	---	---
[199]	CS/ β -GP (Physical – T)	Sn	---	---	DOX (0.025) ¹⁸⁸ Re	2	Liver	N1-S1	N1-S1	---	---
[200]	CS/ β -GP (Physical – T)	Fe ₃ O ₄	48	Magnetic	BCG	---	Bladder	---	Mice	---	---
[201]	CS/ β -GP (Physical – T) ALG (Physical – T)	F ₃ O ₄	---	Magnetic	---	---	Breast Ovarian Glioblastoma Colon	---	SK-BR-3 SKOV-3 LN229 Co112 T380	---	---
[202]	CS/ β -GP (Physical – T)	GO/PEI-Fe ₃ O ₄	---	pH Magnetic	DOX* (200)	0.5	Breast Murine Sarcoma	MCF7 ---	---	S180	---
[203]	CS/G (Physical – T)	---	21	---	MTX (0.0125)	7.5	Breast	MCF7	---	---	---

Table 7. Cont.

Ref	Composition		Carrier Properties		Delivery Properties		Cancer Model			Health Model	
	Hydrogel (Gelation Process)	Composite Component	Degradation Time (Days)	Smart Responsivity	Bioactive Agent (DL% w/w)	Release Time (Days)	Type	In Vitro	In Vivo	In Vitro	In Vivo
[204]	CS-ALG (Physical – I)	---	31	---	anti-VEGF (0.018)	---	---	---	---	HUVECs	---
[212]	HBCS (Physical)	---	45	---	DOX (2.5–10)	3	Murine Breast	4-T1	---	HUVEC	---
[214]	CMCS-oxALG (Chemical – C)	---	---	---	HDBP	---	Liver Murine Liver	Bel-7402 H-22	---	L02	---
[216]	CECS-oxALG (Chemical – C)	MGM	14	Magnetic	5-FU* (4.0)	35	---	---	---	---	---
[217]	CECS/HA (Chemical – C)	---	10	pH	DOX (0.3)	3.5	Cervix	HeLa	---	---	---
[218]	CS-oxDEX (Chemical – C)	PF127	10	pH Redox	5-FU (2.5) CUR* (7.6)	10	Cervix	HeLa	---	---	---
[219]	PBCS-oxDEX (Physical – T)	---	---	pH Glucose	DOX (1.0)	0.5	---	---	---	L929	---
[220]	CS-DA/oxPLN (Chemical – C)	---	---	pH	DOX (0.01–0.32) AMX (0.5)	2.5 1.5	Colon	HCT116	---	---	---
[221]	SCS-oxCS (Chemical – C)	---	11	pH	DOX (3.0) FeG1 (5.0)	6 2	---	---	---	MSC	---
[222]	SCS-oxALG (Physical)	---	---	pH	DOX** (7.6)	2	Breast	MCF7 MDA-MB-231	---	---	---
[223]	GTMACS/ePC/LA (Physical)	---	---	---	DTX	---	---	---	---	---	mice
[224]	CS-CAT (Physical – I)	---	---	---	DOX DTX (2.5)	18	Murine Lung Murine Breast	---	LLC 4T1	C212	---
[225]	CS-TRIPOD (Chemical – C)	---	---	Light pH	TPP**	12	Breast Liver	MCF7 HepG2	---	---	---

Table 7. Cont.

Ref	Composition		Carrier Properties		Delivery Properties		Cancer Model			Health Model	
	Hydrogel (Gelation Process)	Composite Component	Degradation Time (Days)	Smart Responsivity	Bioactive Agent (DL% w/w)	Release Time (Days)	Type	In Vitro	In Vivo	In Vitro	In Vivo
N/S Hybrids											
[192]	CS/ β -GP/NIPAAm-IA (Physical – T)			pH Thermo	DOX (3.0)	8	Breast	MCF7	---	---	---
[205]	CS-HA-NIPAAm (Chemical – C)	---	40	pH	DOX (10)	12	Murine Colon	CT-26	CT-26	---	---
[206]	CS-HA-NIPAAm (Physical – T)	GO	60	pH	DOX* (14.20)	9	Breast	MCF7	MCF7	---	---
[207]	GCS/GMA (Chemical – IRD)	---	---	---	DOX (1.0)	7	Breast	MCF7	MCF7	---	---
[208]	GCS-PEG (Physical – T)	---	---	---	CRB (2.0)	0.25	---	---	---	---	mice
[209]	GCS-PEG (Physical – T)	---	---	---	TMPyP (0.05–0.2)	7#	Cervix	U14	U14	---	---
[210]	GCS-PEG (Chemical – C)	PLGA-F ₃ O ₄	---	Magnetic	DTX* (9.0)	30	Breast	MDA-MB-231	MDA-MB-231	---	Mice
[211]	GCS/PF127/ α -CD (Physical)	---	11	pH	DOX (1.0–5.0)	8	Liver	HepG2	---	---	---
							Murine Liver	---	H22		
[7]	PPLG-HPCS-PPLL (Physical – I)	oxDEX	21	---	DOX* (22.1) IL-2* (8.3) IFN- γ * (8.7)	24#	Breast	MCF7	---	---	---
							Cervix	HeLa			
							Lung	A549	A549		
[213]	CMCS-NIPAAm (Chemical – RP)	---	---	pH Thermo	5-FU (6.2–8.9)	2	Breast	MCF-7	---	L929	---
							Cervix	HeLa			
[215]	CECS-PEG (Chemical – C)	---	8	pH	DOX	7.5	Liver	HepG2	---	L929	---
[226]	TCS-PEGDMA (Chemical – MR)	STC	---	Enzyme	CUR (3.8) LSZ*	7 0.5	Liver	HepG2	HepG2	---	---

* Loaded in composite component; ** conjugated to composite component; # from in vivo experiments; C: Condensation; I: Ionic; IRD: Irradiation; MR: Michael reaction; RP: Radical polymerization; T: Temperature; 5-FU: 5-Fluorouracil; CD: Cyclodextrin; β -GP: β -Glycerophosphate; ALG: Alginate; AMX: Amoxicillin; BCG: Bacillus Calmette–Guérin; CAT: Catechol; CECS: Carboxyethyl chitosan; CisPt: Cisplatin; CMCS: Carboxymethyl chitosan; CNT: Carbon nanotubes; CRB: Carbazochrome; CS: Chitosan; CUR: Curcumin; DA: Dihydrocaffeic acid; DOX: Doxorubicin; DTX: Docetaxel; ePC: Egg phosphatidylcholine; FeG1: Non-hormonal contraceptive; G: Graphene; GCS: Glycol chitosan; GMA: Glycidyl methacrylate; GO: Graphene oxide; GTMACS: Glycidyltrimethylammonium chitosan; HA: Hyaluronic acid; HBCS: Hydroxybutyl chitosan; HDBP: Hydrogel degradation by-product; HPCS: Hydroxypropyl chitosan; IA: Itaconic acid; IL: Interleukin; IFN: Interferon; LA: Lauric aldehyde; LSZ: Lysozyme; MEL: Melfalan; MGM: Magnetic gelatin microspheres; MPEG: Monomethoxy poly(ethylene glycol); MTX: Methotrexate; NIPAAm: N-isopropyl acrylamide; oxALG: Oxidized alginate; oxCS: Oxidized chitosan; oxDEX: Oxidized dextran; oxPLN: Oxidized pullulan; PBCS: Phenylboronic-modified chitosan; PEG: Polyethylene glycol; PEGDMA: Polyethylen glycol dimethacrylate; PEI: Poly(ethylene imine); PF: Pluronic F; PLGA: Poly(lactide-co-glycolide); PPLG: 4-Arm PEG-polyglutammic acid; PPLL: 4-arm poly(ethylene glycol)-poly(L-lysine); SCS: Succinate chitosan; STC: Starch; TA-ZnPc: Tetra-aldehyde functionalized zinc phthalocyanine; TCS: Thiolated chitosan; TMPyP: Meso-tetrakis(1-methylpyridinium-4-yl) porphyrin; PP: Tetrakis(4-aminophenyl)porphyrin; TPT: Topotecan; TRIPOD: 2,4,6-tris(p-formylphenoxy)-1,3,5-triazine; VEGF: Vascular endothelial growth factor

In more details, carboxymethyl chitosan (CMCS) was copolymerized with NIPAAm [213] to obtain pH- and thermo-responsive depots for the on-off release of 5-FU to cervix and breast cancers. hydroxypropyl chitosan (HPCS) was condensed with PPLL dendrimers by Schiff's bases and subjected to an ionic gelation process in the presence of PEG dendrimers and oxDEX nanoparticles bearing DOX, IL-2, and IFN- γ for a synergistic anticancer therapy.

In another approach, CS [218], PBCS [219], CS-DA [220], or CS alkyl derivatives [214,216,217] were condensed with oxidized polysaccharides, including DEX [218,219], ALG [214,216], HA [217], and PLN [220].

SCS was combined with oxCS [221] or oxALG [222] to obtain pH-responsive injectable hydrogels for DOX sustained release. Other examples of CS derivatives include GTMACS [223] and CS-CAT [224], used for DTX or DOX/DTX combination therapy, respectively. TCS was employed to produce an enzyme-responsive CUR delivery vehicle [226], and CS-TPP was proposed for photothermal therapy in breast and liver cancers [225].

Hyaluronic acid (HA, Figure 12), a non-sulfated glycosaminoglycan, is one of the major components of connective tissues and synovial fluid.

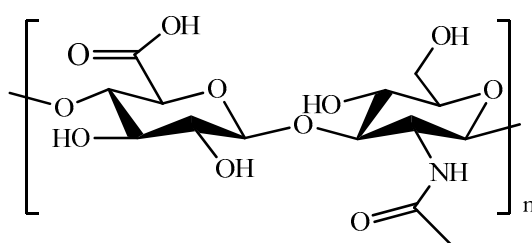


Figure 12. Schematic representation of hyaluronic acid (HA).

It is able to interact with cell surface receptors (e.g., CD44), thus promoting cell migration, and, in virtue of its high biocompatibility, has been extensively exploited as a starting material for the fabrication of different injectable hydrogel systems (Table 8) [227–230]. The thermo-gelation of HA in the presence of PF127 carried out to injectable hydrogels suitable for DOX release to breast [231] and colon cancers [68], or for the DOX-DTX synergistic treatment of CT26 cancer cells [67]. Oxidized HA was chemically cross-linked to obtain an injectable biomaterial mimicking embryonic microenvironments, thus exerting and controlling the phenotype of aggressive cancer cells [232]. Injectable HA hydrogels obtained with the same approach were either physically loaded with, or chemically conjugated to, CisPt-loaded HA nanogels for gastric cancer treatment [233]. Different cross-linking strategies involved the preliminary derivatization of HA with Tyr residues [234–236], or the insertion of thiol groups [237]. In the first case, horseradish peroxidase (HRP) catalyzed the coupling reaction between HA-Tyr chains with the formation of injectable hydrogels for the delivery of IFN- α to Kidney cancer (Figure 13) [236], while the incorporation of hyaluronidase allowed the selective vectorization of conjugated IFN- α [234] and loaded TZB [235] to liver and breast cancer, respectively.

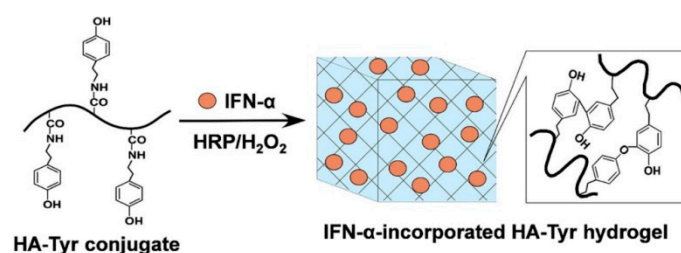


Figure 13. Schematic illustration of in situ formation of IFN- α -incorporated HA-Tyr hydrogels through enzymatic cross-linking reaction. HRP: horseradish peroxidase. With permission from [236]. Elsevier, [2016].

Table 8. Composition and anticancer performance of injectable hydrogels based on hyaluronic acid.

Ref	Composition		Carrier Properties		Delivery Properties		Cancer Model			Health Model	
	Hydrogel (Gelation Process)	Composite Component	Degradation Time (Days)	Smart Responsivity	Bioactive Agent (DL% w/w)	Release Time (Days)	Type	In Vitro	In Vivo	In Vitro	In Vivo
Naturals											
[232]	oxHA (Chemical – C)	---	10	---	Anti-2B11	24#	Breast	MCF7	---	---	---
								MDA-MB-231	MDA-MB-231		
							Murine Breast	---	BT-474	---	---
							Murine Melanoma	---	B16		
[233]	oxHA (Chemical – C)	HA-IDA HA-MA	---	---	CisPt* (200)	7.5	Stomach	---	MKN45P	---	---
[236]	HA-Tyr (Chemical – HRP)	---		---	IFN- α	1	Kidney	ACHN	ACHN	---	---
[234]	HA-Tyr (Chemical – HRP)	---	---	Enzyme (HAse)	IFN- α	1	Liver	HAK-1B	HAK-1B	---	---
[235]	HA-Tyr (Chemical – HRP)	---	28	Enzyme (HAse)	TZB (0.3)	28	Breast	BT474	BT474	---	---
[237]	HA-SH (Chemical – Red)	---	---	Redox	DOX (1.0) DOX/SRB (1.0/1.0)	21	Breast	MCF7	---	---	---
								MDA-MB-231			
							Murine Breast	4T1	4T1		
[238]	HA (Physical – pH)	MSNs	---	Enzyme (HAse)	DOX* (27)	6	Breast	SKBR3	---	293T	---
[239]	HA- α CD (Physical)	AuBNs-MSNs	7	Enzyme (HAse)	DOX* (11.1–32.0)	7	Squamous Carcinoma	SCC	---	HaCaT	---
N/S Hybrids											
[231]	HA/PF127 (Physical – T)	---	31	---	DOX (0.5)	31	Breast	MCF7	---	---	mice

Table 8. Cont.

Ref	Composition		Carrier Properties		Delivery Properties		Cancer Model			Health Model	
	Hydrogel (Gelation Process)	Composite Component	Degradation Time (Days)	Smart Responsivity	Bioactive Agent (DL% w/w)	Release Time (Days)	Type	In Vitro	In Vivo	In Vitro	In Vivo
[68]	PF127/HA (Physical – T)	---	---	---	DOX (1.0)	1	Murine colon	C26	C26	---	---
							Colon	HT29	---		
							Breast	MCF7	---		
[67]	PF127/HA (Physical – T)	PF127_PL121	---	---	DOX (1.0) DTX* (1.6)	3	Colorectal	---	CT26	---	---
[240]	HA–Gln/PEG-8–SH–Lys (Chemical – E)	---	---	---	---	---	Breast	MCF7	---	C2C12	---

* Loaded in composite component; # from in vivo experiments; C: Condensation; E: Enzymatic; Red: Redox; T: Temperature; CD: Cyclodextrin; AuBNs: Gold nanobipyramids; CisPt: Cisplatin; DOX: Doxorubicin; DTX: Docetaxel; Gln: Glutamine substrate peptide; HA: Hyaluronic acid; HAase: Hyaluronidase; HA-IDA: HA-iminodiacetic Acid; HA-MA: HA-malonic acid; HRP: Horseradish peroxidase; IFN: Interferon; Lys: Lysine; MSNs: Mesoporous silica nanoparticles; MTF: Metformin; oxHA: Oxidized HA; PEG-8-SH: 8-arm PEG; PF: Pluronic F; PL: PLuronic L; SRB: Sorafenib; Tyr: Tyramine; TzB: Trastuzumab.

On the other hand, the oxidation of thiol groups was exploited to generate disulfide bonds acting as cross-links of the hydrogel. The resulting redox-responsive material was employed as a delivery vehicle of DOX and the combinations of DOX–SRB and DOX–SRB–MTF [237]. HA was also employed as a functional element for the enzymatic synthesis of PEGylated dendrimers able to modulate the cellular phenotype of human mammary cancer epithelial cells and mouse myoblasts [240].

Finally, the incorporation of MSNs [238] and α -CD–AuBNs–MSNs [239] within HA hydrogels allowed the fabrication of hybrid systems suitable for photothermal DOX combination therapy of mammary and squamous carcinoma, respectively.

Cellulose (CL, Figure 14) is a polysaccharide consisting of repeating β -D-glucopyranose units obtained from different sources, including wood pulp, cotton, tunicates, fungi, bacteria, and algae [241].

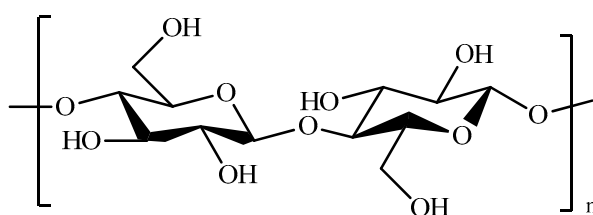


Figure 14. Schematic representation of cellulose (CL).

The superior biological features, together with the large availability and low cost, make CL-based materials suitable for a wide range of applications, including biomedicine (Table 9) [242].

Hydrophilic CL derivatives, such as quaternized cellulose [243] and hydroxypropyl methyl cellulose [244], were investigated for the DOX-based and PTX/TMZ therapy of hepatocellular carcinoma [243] and glioma [244], respectively. Pristine CL was also tested as a base material for the fabrication of hybrid hydrogels for the photothermal treatment of melanoma and hepatic cancer, both *in vitro* and *in vivo* [245], with black phosphorus nanosheets acting as active agent.

Alginate (ALG, Figure 15), an anionic biopolymer consisting of units of mannuronic acid and guluronic acid in irregular blocks [246], is widely used in biomedical field due to its several favorable properties, including biocompatibility, hydrophobicity, and availability of hydroxyl and carboxyl groups for tailored chemical modifications (Table 9) [247].

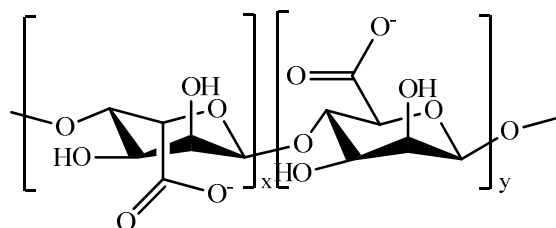


Figure 15. Schematic representation of alginate (ALG).

Injectable hydrogels prepared by ionic gelation were proposed for the delivery of CisPt dendrimers to breast and lung cancer cells with high efficiency [248], as well as for the incorporation of magnetic nanoparticles for the thermal ablation of different types of cancers, including breast, ovary, glioblastoma, and colon [201]. The insertion of NIPAAm moieties carried out the formation of thermo-responsive vehicles of gene [249] and DOX@micelles [250] to prostate cancer and osteosarcoma. Further modifications of ALG chains involved the oxidation to aldehyde derivatives, suitable for coupling with PEI polymers. The obtained *in situ* gelling systems were proposed as delivery systems for core-shell nanoparticles loaded with CisPt and PTX, and found to be effective in the treatment of breast, skin, and liver neoplasia [251,252].

Table 9. Composition and anticancer performance of injectable hydrogels based on other polysaccharides.

Ref	Composition		Carrier Properties		Delivery Properties		Cancer Model			Health Model	
	Hydrogel (Gelation Process)	Composite Component	Degradation Time (Days)	Smart Responsivity	Bioactive Agent (DL% w/w)	Release Time (Days)	Type	In Vitro	In Vivo	In Vitro	In Vivo
Naturals											
[243]	QCL-CCNCs (Physical - I)	---	18	---	DOX (0.5)	21	Murine Liver	---	H22	COS-7	---
[245]	CL (Chemical - C)	BPNs	---	---	---	---	Murine Melanoma	B16	---	J774A.1	---
							Liver	SMMC-7721	SMMC-7721		
[248]	ALG (Physical - I)	PAMAM	---	---	CisPt* (37.0)	30#	Breast	MFC7	---	3T3	---
							Lung	PC9	PC9		
[253]	oxDEX-SRC (Chemical - C)	---	70	---	HRP (0.39-1.36) DOX (0.39-1.36)	50 30	Melanoma	---	B16F10	C2C12 HL7702	mice
[254]	oxDEX (Chemical - C)	PAMAM	14	---	Pt*	9#	Breast	MDA-MB-231	MDA-MB-231	---	mice
[255]	MADEX-SH/MAHA (Chemical - Red)	Bi NPs	---	---	DOX* (3.1)	7.5	Murine Breast	4T1	4T1	---	---
[256]	GG (Physical)	Liposome	---	---	PTX (33)	2	Bladder	T24	---	---	mice
							Murine Bladder	NBT-II			
[257]	GG (Physical)	CuS NPs	---	NIR	DOX* (0.1)	0.2	Murine Breast	4T1	4T1	---	---
[258]	AGR (Physical)	---	7	pH NIR	DOX (4.5)	2	Murine Breast	4T1	4T1	L929	---
							Cervix	HeLa	---	HUVEC	
[259]	AGR (Physical)	DEX-SH	---	---	DOX* (20-50)	80	Breast	MDA-MB-231	---	3T3	---
N/S Hybrids											
[244]	HPMCL/PF127/ALG (Physical)	MPEG-DPPE	---	---	PTX* (5.1) TMZ* (5.3)	3	Murine Glioma	C6	C6	---	---
[249]	ALG-NIPAAm (Physical - T)	---	365	Thermo	DNA	29	Prostate	PC3	---	---	---
[250]	ALG-NIPAAm (Physical - T)	---	---	Thermo	DOX (1.2)	21	Prostate	AT3B-1N AT3B-1	---	---	---

Table 9. Cont.

Ref	Composition		Carrier Properties		Delivery Properties		Cancer Model			Health Model	
	Hydrogel (Gelation Process)	Composite Component	Degradation Time (Days)	Smart Responsivity	Bioactive Agent (DL% w/w)	Release Time (Days)	Type	In Vitro	In Vivo	In Vitro	In Vivo
[251]	oxALG-PEI (Physical)	PLGA-PLA	---	---	CisPt* (0.01–2.48) PTX* (1.0–1.7)	45	Breast	MDA-MB-231	---	---	---
[252]	oxALG-PEI (Physical)	PLGA-PLA	---	---	CisPt* (0.01–2.48) PTX* (1.49–1.70)	45	Liver	HepG2	---	MRC-5	---
[260]	DEX-HEMA/PEI-MA (Chemical – RP)	---	9–17	---	sRNA	9–17	---	---	---	HEK 293	---

* Loaded in composite component; # from in vivo experiments; C: Condensation; I: Ionic; T: Temperature; Red: Redox; RP: Radical polymerization; AGR: Agarose; ALG: Alginate; BPNs: Black phosphorus nanosheets; CCNCs: Cationic cellulose nanocrystals; CisPt: Cisplatin; CL: Cellulose; DEX: Dextran; DOX: Doxorubicin; DPPE: Dipalmitoylphosphatidylethanolamine; GG: Gellan gum; HPMCL: Hydroxypropyl methyl cellulose; HRP: Horseradish peroxidase; MADEx: Methacrylated DEX; MAHA: Methacrylated HA; MPEG: Monomethoxy poly(ethylene glycol); NIPAAm: N-isopropyl acrylamide; NIR: Near-infrared; NPs: Nanoparticles; oxALG: Oxidized alginate; oxDEX: Oxidized dextran; PAMAM: Polyamidoamine dendrimer; PEI: Poly(ethylene imine); PF: Pluronic F; PLA: Polylactide; PLGA: Poly(lactide-co-glycolide); PTX: Paclitaxel; QCL: Quaternized cellulose; SRC: Sericin; TMZ: Temozolomide.

Dextran (DEX, Figure 16) consists of glucose monomers linked via α -1,6 glycosidic bonds, with branches originating from α -1,3 linkages. It finds a wide range of applications in the biomedical field, due to its high availability, low cost, and easy chemical modification.

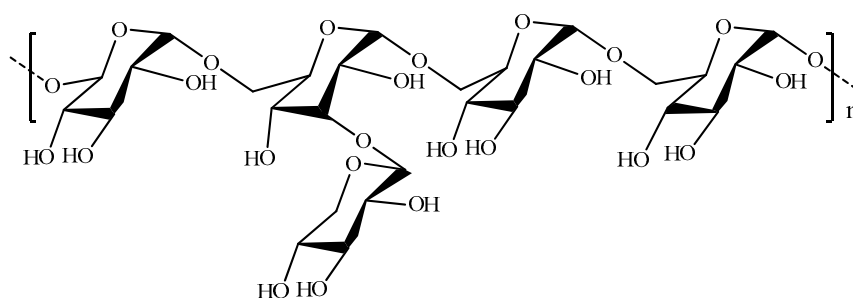


Figure 16. Schematic representation of dextran (DEX).

Moreover, its high stability, hydrophilicity, absence of toxicity, and biodegradability make this polysaccharide an ideal drug delivery carrier (Table 9) [261]. It is able to promote the penetration of chemotherapeutic agents in tumor masses [262], thus allowing the fabrication of effective delivery vehicles for cancer treatment [263]. Preliminary derivatization of dextran, including oxidation [253,254] and conjugation to acrylic [260] or thiol groups [255], was carried out to obtain effective carriers for the delivery of cytotoxic drugs [253,254], gene [260], or DOX in combination with Bismuth Nanoparticles in a combined X-ray radio- and chemo-therapy [255].

Gellan gum (GG, Figure 17) is a linear anionic polysaccharide approved by the FDA as an additive in food and pharmaceutical formulations (Table 9) [264].

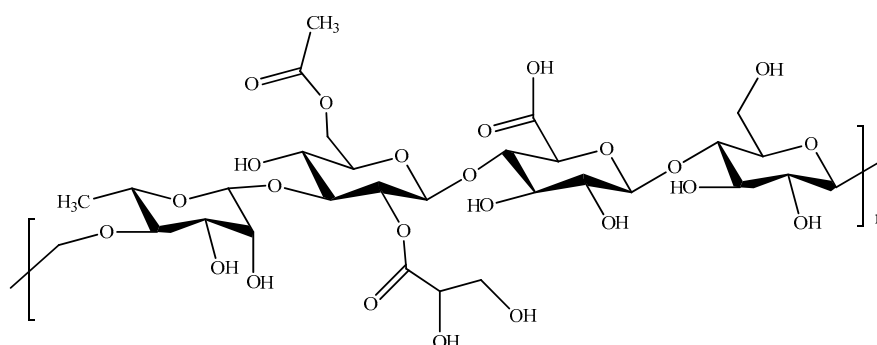


Figure 17. Schematic representation of gellan gum (GG).

Its biodegradability, mucoadhesivity, and thermo-reversible gelling properties make it the ideal candidate for the preparation of injectable matrices to be employed in tissue engineering and wound healing. Injectable nanocomposites, consisting of GG hydrogels incorporating drug-loaded nanoparticles, were proposed for the treatment of different cancer diseases. More closely, PTX-loaded liposomes were loaded on a GG hydrogel matrix and the overall system directly instilled in the urinary bladder [256]; whereas, in another work, DOX-loaded CuS nanoparticles were embedded in GG injectable hydrogels for NIR-triggered chemo-photothermal therapy of breast cancer [257].

Agarose (AGR, Figure 18) is an FDA-approved linear polysaccharide derived from marine algae. A robust injectable thermo-responsive AGR hydrogel incorporating sodium humate and DOX was proposed as a valuable tool for chemo-photothermal treatment of breast cancer [258]. Furthermore, DOX@nanoparticles were encapsulated in AGR injectable hydrogels for sustained local drug delivery (Table 9) [259].

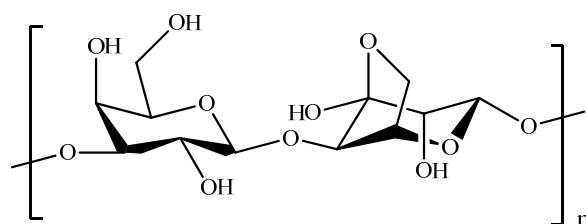


Figure 18. Schematic representation of agarose (AGR).

3.2. Proteins

The integration of the structural and functional properties of proteins in injectable hydrogels was also tested, thanks to the high biocompatibility, biodegradability, non-toxicity, and non-immunogenicity of such materials, as well as by virtue of their similarity to naturally occurring components of organs, tissues, and cells (Table 10) [25,265–268].

Serum albumins, from both bovine and human serum, are the most abundant protein in blood plasma (40–50 mg/mL) and the primary transport proteins of various endogenous and exogenous substances in plasma, including cations, bilirubin, fatty acids, and drugs [269,270].

Albumin from bovine serum (BSA) was proposed as polymeric support in the synthesis of injectable hydrogels for cancer therapy. BSA was added to the cross-linking agent epichlorohydrin to prepare a gel with suitable mechanical strength, viscoelastic behavior, shear thinning, injectability, and self-healing properties useful as DOX delivery vehicles to cervix and breast cancer [269]. Alternatively, an injectable hydrogel consisting of PEG-modified BSA- and PTX-encapsulated red blood cell membrane nanoparticles was proposed to improve the intraperitoneal retention of PTX in the treatment of human gastric cancer [271]. Finally, human serum albumin (HSA) chemically conjugated to PEG dendrimers was suggested as a functional biomaterial for the induction of apoptosis in pancreatic cancer [270].

Gelatin (GEL) represents another interesting protein material able to spontaneously undergo the gel–sol transition process at body temperature. Despite its good biological properties, gelatin hydrogel cannot be used in biomedical applications without chemical modifications, due to its instability under physiological conditions and, also, poor mechanical properties [272]. Different approaches were proposed to improve its performance in the biomedical field [273]: GEL–dendrimer [274], GEL–pectin [275], and GEL–CS [276] composites, cross-linked by means of HRP chemistry [274,275] or ionic gelation [276], were successfully employed in lung and skin carcinomas studies, and for the controlled release of DOX@Liposome. In addition, GEL injectable hydrogels were proposed as DOX carriers in the treatment of prostate cancer [277] in a multifunctional system, also acting as regenerative matrix with pronounced adhesion to abdominal tissue that, by *in situ* polymerization, allow to overcome the inconvenience usually related to radical prostatectomy. Moreover, due to its surfactant properties [278], GEL was also employed for the fabrication of thermo-responsive hybrid hydrogels for the controlled release of DOX to gastric cancer [279], with improved efficiency due to the incorporation of rod-like-shaped nanoparticles, such as carbon nanotubes [280,281]. Finally, an injectable and colloidal hydrogel composed of amphoteric GEL nanoparticles and polydopamine (PDA) nanoparticles was developed to realize multi-stimuli (pH, enzymes, and near-infrared light)-responsive drug delivery properties and combined chemo-photothermal cancer treatment [282]. Due to the sensitivity of GEL nanoparticles to the tumor microenvironment and PDA nanoparticles to the NIR laser, DOX-loaded hydrogel could show multiple responsivity to acidic pH and NIR laser irradiation, resulting in controlled and sustained anticancer release profiles.

Silk fibroin (SF) was proved to be a biodegradable and biocompatible native natural material derived from *Bombyx mori* silkworm with safe record *in vivo* [283,284]. SF hydrogels developed by the protein conformation transition from amorphous to β -sheet induced by physical cross-linking, including the ultrasound assisted processes, possess injectability as well as biocompatibility and safety features [285]. SAL–PTX-loaded silk fibroin hydrogel was fabricated by ultrasound-assisted cross-linkage, without toxic organic solvents and surfactants, for loco-regional tumor treatment and

cancer stem cell inhibition *in vivo* [286]. Additionally, self-assembling pH-responsive silk nanofiber hydrogels with thixotropic properties were proposed to support the injectable delivery DOX for the treatment of breast cancers in mouse models [287]. The possibility to obtain benefits from a photothermal treatment was exploited in the synthesis of SF nanofiber hydrogel systems complexed with lanthanide-doped rare-earth up-conversion nanoparticles and nano-graphene oxide for breast cancer treatment [288]. In this case, a synergistic effect of combined up-conversion luminescence imaging diagnosis and photothermal therapy was confirmed to decrease dosage-limiting toxicity and tissue damage by over-heating and improve the therapeutic efficiency. An innovative approach that drastically reduces gelation times involved an enzyme-mediated cross-linking strategy to produce fast-gelled SF-based injectable hydrogels at physiological conditions [289].

Finally, silk–elastin-like protein (SELP), genetically engineered materials composed of tandem repeats of a six amino acid sequence commonly found in silkworm silk fibroin and a five amino acid sequence commonly found in mammalian elastin, was proposed in the synthesis of injectable hydrogels. This combination of silk and elastin molecular properties results in a polymer which is responsive to temperature increases and irreversibly forms hydrogels at physiological temperature. Gelation occurs without the need of chemically-induced cross-linking, because this phase transition spontaneously occurs when elastin-like units collapse thermodynamically aligning the silk-like units that form hydrogen-bonded beta sheets, and results in a physically cross-linked matrix. SELP-based carriers were applied as a platform for drug delivery with negligible toxicity for the radiation treatment of prostate and pancreas cancers [288,290], for localized delivery in transarterial chemoembolization to treat intermediate stage hepatocellular carcinoma [290,291], or as gene-directed enzyme prodrug therapy [292]. In particular, injectable brachytherapy polymers [290,291] composed of SELP labeled with the radionuclide ^{131}I exhibit a gelling transition as a result of two independent mechanisms, firstly involving SELP moieties that, at the body temperature, are rapidly converted into an insoluble material. Afterwards, the high energy β -emissions of ^{131}I further stabilize the depot by introducing cross-links within the SELP depot over 24 h. Additionally, SELP-based hydrogel was proposed to overcome the limitations usually associated with the commercial embolic liquids that discourage their employment in transarterial chemoembolization. To this regard, DOX and SRB, two chemotherapeutics used in the treatment of hepatic carcinoma, were incorporated into the *in situ* gelling liquid embolic composed of SELP polymer [290,291]. Due to its pore size and *in vivo* gelation properties, SELP restricts the distribution and controls the release of therapeutic viruses, such as herpes simplex virus, for up to one month, representing a valuable approach which may also have significant potential for increasing the safety of adenoviral gene delivery, while not sacrificing efficacy is spatial and temporal delivery of viruses following injection into a localized area [292]. In this way, gene expression levels at the site of interest were localized, prolonged, and significantly increased.

4. Conclusions and Future Perspectives

Hydrogel systems represent a relevant class of healthcare products with applications ranging from tissue engineering, bio-sensing, and bio-imaging, to drug delivery [293]. The huge interest in hydrogels is underlined by the worldwide market, estimated at around US\$10 billion in 2017 and expected to grow up to US\$15 billion by 2020 [294]. Injectable hydrogels have been proved to be a valuable tool for the delivery of anticancer drugs, providing temporal and spatial control over the releasing rate, thus improving the therapeutic index of commonly used chemotherapeutics [29]. To date, a few products are currently available on the market, including CS/Organophosphate (BST-Gel[®]), PLGA–PEG–PLGA (ReGel[®]), Poloxamer 407 (LeGOO[®]), Poly(vinyl methyl ether co maleic anhydride) (Gantrez[®]) hydrogels, available as cartilage repair [295] hydrogel market, tumors [296], vascular injury [297], and vaccine adjuvants [298].

Table 10. Composition and anticancer performance of injectable hydrogels based on proteins.

Ref	Composition		Carrier Properties		Delivery Properties		Cancer Model			Health Model	
	Hydrogel (Gelation Process)	Composite Component	Degradation Time (Days)	Smart Responsivity	Bioactive Agent (DL% w/w)	Release Time (Days)	Type	In Vitro	In Vivo	In Vitro	In Vivo
Naturals											
[269]	BSA (Chemical – CR)	---	3	---	DOX (0.11–0.14)	5	Cervix Breast	HeLa MCF-7 MDA-MB 231	---	---	---
[277]	GEL (Chemical – E)	---	---	---	AraC	---	Prostate	DU-145	---	L929	mice
[274]	GEL–HPA (Chemical – HRP)	---	---	Enzyme (COLase)	DCs Ad	19#	Murine Lung	---	LL	---	---
[275]	GEL–SBP (Chemical – HRP)	---	---	---	DOX (0.9)	6	Murine Melanoma	---	B16F10	---	---
[276]	GEL–CS (Chemical – C)	Liposome	---	---	CAL (0.39–0.47) CAL*	7 21	---	---	---	---	---
[282]	GEL (Physical – T)	PDA	7	pH Enzyme NIR	DOX*	7	Murine Breast	---	4T1	---	---
[286]	SF (Physical – US)	SF NPs	---	---	SAL* (12) PTX* (12)	5 28	Murine Liver	---	H22	---	mice
[287]	SF (Physical – CDP)	---	---	pH	DOX (8–24)	56	Breast	MDA-MB-231	MDA-MB-231	---	---
[288]	SF (Physical – T)	GO	---	---	NaLuF ₄ :Er ³⁺ ,Yb ³⁺	---	Murine Breast	4T1	4T1	---	---
[290]	SELP (Physical – T)	---	---	---	¹³¹ I	---	Prostate Pancreas	---	PC3 BxPc3	---	---
[291]	SELP (Physical – T)	---	---	---	DOX (21–28) SRB (21–28)	15-30	---	---	---	---	---
[292]	SELP (Physical – T)	---	---	---	HSVtk/GCV	---	---	---	---	---	mice
N/S Hybrids											
[270]	HSA–SH/PEG–4–SH (Physical – T)	---	21	---	TRAIL (5.8)	7	Pancreas	Mia PAca-2	Mia PAca-2	---	---
[271]	PEG–BSA (Physical – T)	PRNP	50	---	PTX* (22.1)	6	Stomach	MKN45	MKN-45	---	---
[279]	GEL–SWCNT–pNIPAAm (Chemical – RP)	---	---	Temperature	DOX (1.11)	28	Stomach	BGC-823	BGC-823	---	---

* Loaded in composite component; # from in vivo experiments; C: Condensation; CDP: Concentration dilution process; CR: Cross-linking; E: Enzyme; US: Ultrasound; RP: Radical polymerization; T: Temperature; Ad: Oncolytic adenovirus; AraC: Cytosine arabinoside; BSA: Bovine serum albumin; CAL: Calcein; COLase: Collagenase; CS: Chitosan; DCs: Dendritic cells; DOX: Doxorubicin; GCV: Ganciclovir; GEL: Gelatin; HPA: Hydroxyphenyl propionic acid; GO: Graphene oxide; HPA: Hydroxyphenyl propionic acid; HRP: Horseradish peroxidase; HSA: Human serum albumin; HSVtk: Herpes simplex virus thymidine kinase; PDA: Polydopamine; PEG-4-SH: 4-arm PEG; pNIPAAm: Poly(N-isopropyl acrylamide); PRNP: Red blood cell membrane nanoparticles; PTX: Paclitaxel; SAL: Salinomycin; SBP: Sugar beet pectin; SELP: Silk–elastin-like protein; SF: Silk fibroin; SRB: Sorafenib; SWCNT: Single-walled carbon nanotubes; TRAIL: Tumor necrosis factor-related apoptosis-inducing ligand.

The main limiting issues, concerning sterilization, scale-up, shelf-life, and user compliance (professional and/or patient), must be addressed before the benefits afforded by injectable hydrogels can be translated into clinical practice. Some formulations are currently in clinical trials, mainly consisting in radiopaque PEG hydrogels (TraceIT[®] and SpaceOAR[®]) useful to improve the target definition of radiotherapy, thus reducing the radiation doses [299,300].

The scientific community recognizes great potential to the use of injectable systems for anticancer delivery, but to definitely replace the conventional therapies with the injectable systems, continuous innovation in the development of new architectures and design strategies is required. For a more effective translation of injectable hydrogels from research into clinical reality, future attempts should be done to explore the possibility of combining chemotherapy, hyperthermia therapy, immunotherapy, and radiotherapy, by selecting appropriate materials and evaluating the biological effects on metabolic and cellular mechanisms, both in the normal and diseased states.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

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