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Review

A Review - Synthetic Polymers Used in Injectible Hydrogels for Cancer Treatment

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Abstract

Injectable hydrogels have become a promising platform for cancer treatment, especially for tissue engineering, tumour ablation, and localized drug delivery. These hydrogels, which offer a supporting matrix for drug release and cellular penetration, are usually made of biocompatible and biodegradable polymers that are simple to inject and then gel in place. Synthetic Polymers like poly(ethylene glycol) (PEG), poly(lactic-co-glycolic acid) (PLGA), and polycaprolactone (PCL), are important polymers utilized in injectable hydrogels.A cutting-edge development in cancer treatment, injectable hydrogels offer a flexible foundation for tissue regeneration, localized therapy, and targeted drug administration. These intelligent materials can be engineered to deliver chemotherapy drugs under controlled conditions, precisely targeting tumors and reducing systemic toxicity. Because they can be injected, less invasive administration is made possible, allowing for direct placement at the tumor site. This improves medication absorption and therapeutic efficacy. Because of its responsiveness, drug release can be synchronized with the course of the disease, potentially improving patient outcomes. Injectable hydrogels have the potential to revolutionize cancer therapy paradigms by fusing targeted delivery with regeneration capabilities. This offers hope for increased efficacy and better patient outcomes.

Keywords: Hydrogels, Tumour ablation, biocompatible biodegradable and chemotherapy.

INTRODUCTION

One of the most dangerous disease categories that affects people's health globally is cancer. 14.1 million new cases of cancer and 8.2 million deaths from cancer were reported globally in 2012. The number of new cases of cancer is predicted to reach 19.3 million by 2025. An authorized statistical research indicates that 1 in 8 males and 1 in 10 women are affected with these illnesses.[1]Therefore, cancer is a serious clinical issue that requires immediate attention.Cancer treatment choices vary and must be selected based on the kind, stage, and malignancy of the cancer. The rate of cancer is rising annually as a result of environmental degradation.Hydrogels innovation revitalizes classic chemotherapy approaches. Hydrogels based delivery system enable direct injection of drugs into tumors[2].

Definition of Hydrogels

Three-dimensional hydrophilic polymeric networks having a high affinity for bodily fluids are known as injectable hydrogels, and they can be directly injected into the body using a syringe or through a catheter. In the biomedical field, Injectible hydrogels have been proposed as a platform for therapeutic administration and tissue engineering (Figure 1) [3].

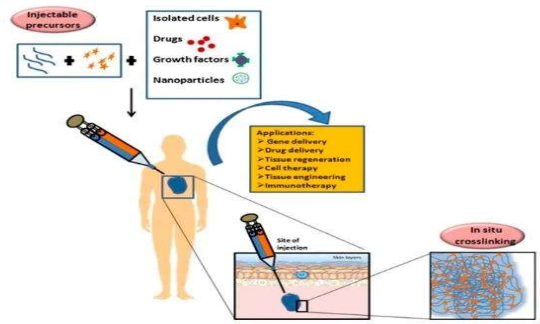

Fig 1: How injectable hydrogel systems are used in the biomedical industry. Reproduced from [4]with permission. Elsevier [2018].

The toxicity of the medication is restricted to the area where the tumour cells are found using injectable hydrogels. Continuous, efficient drug administration in the tumour location is demonstrated by a localized hydrogel [5]. To enhance this property, several system compositions have been developed, including polyphosphazene (PPZ), polyethylene glycol (PEG), and polylactate glycolic acid (PLGA)[6].Most of the hydrogel is insoluble in water, even if its capacity to absorb water varies from 10% to thousands of times its dry weight [7] (Figure 1). The body's stimulation is greatly reduced by the surface's softness, moisture content, and tissue affinity. Most of the materials used to make hydrogels are safe [8].Researchers and medical professionals throughout the world, particularly in the field of cancer therapy, have shown a great deal of interest in hydrogels with biodegradability, injectability, and stimuli (temperature, light, and pH) responsiveness for anticancer drug administration [9].

Hydrogel materials, a variety of sizes and delivery channels are available

Microgels (0.5–10 µm), macrogels, and nanogels (less than 200 nm) are among the various sizes of hydrogels. It can be administered by intravenous injection, oral administration, transdermal distribution, transarterial chemoembolization, pulmonary delivery, and in situ implantation (Figure:2) [10].

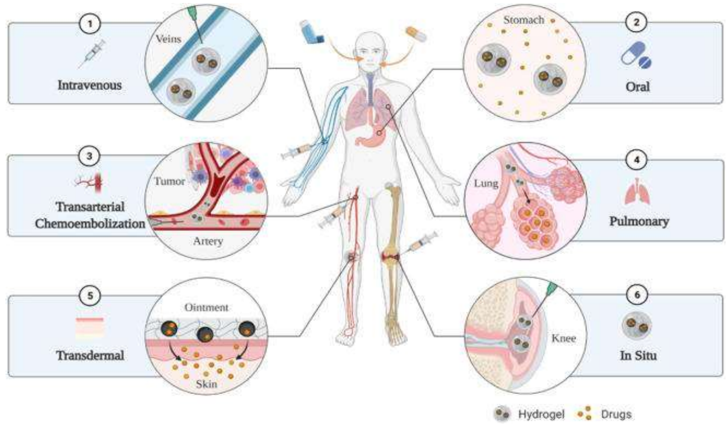

Fig 2: The hydrogels can be administered by intravenous injection, oral administration, transarterial chemoembolization, transdermal delivery, pulmonary administration, in situ injection, and in situ implantation, among other methods.

The structural properties of hydrogels

Hydrogels are networks of polymer chains connected by physical or chemical crosslinks. Non-covalent interactions include chain entanglement, weak molecular bonds (such as hydrogen bonding and the van der Waals interaction), and microcrystal areas, some of which are temporary and are created or destroyed in response to a situation [11].

Large volumes of water can be absorbed by the three-dimensional structures of hydrogels due to their crosslinked and insoluble network. Essentially, the non-covalent interactions between the structure's constituents dictate how crosslinked hydrogels are arranged [12].

Different types of Polymers used in synthetic injectable hydrogels for cancer care
Polyphosphazenes in Synthetic Injectables Hydrogels

The nitrogen and phosphorus atoms that repeat in a linear or branching skeleton with alternating single and double bonds make up the polyphosphazenes (PPZs) family of hybrid organic–inorganic macromolecules [13]. Each phosphorus atom is joined to two organic side groups that may be amino acids, aryl moieties, or alkyl moieties(Figure 3) [14].

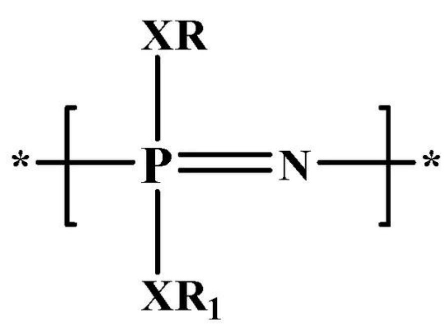

Fig 3:Polyphosphazenes represented. R and R1 = Alkyl, Aryl, amino acid; X = O, NH.

Properties

By altering the ratios of organic side groups or by joining multiple different side groups to the same backbone, a wide range of PPZs with precisely tuned mechanical and physical properties can be created [15]..At room temperature (or below), PPZs are in the sol state, but they truly gel at body warmth. This transition can be controlled by altering the ratio of hydrophobic to hydrophilic substituents [16].

Poloxamers

Tri-block amphiphilic polymers known as pluronics, or poloxamers, are composed of repeating units of poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO-PPO-PEO). The chemical and physical properties of these non-ionic surfactants are determined by their molecular weight and the ratio of hydrophilic (PEO) to hydrophobic (PPO) groups (Figure 4) [17].

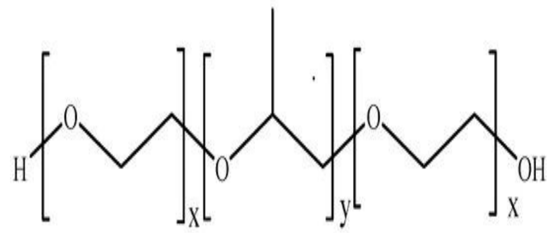

Fig 4: Poloxamer schematic representation: x = 2–130; y = 15–67

Properties

One of the most widely utilized poloxamers for biomedical applications is PF127 (PEO/PPO balance 70/30), which has the ability to create hydrogel networks after reverse thermal gelation or micellar nanocarriers for lipophilic medications (due to the PPO component). A low-viscosity condition is observed at 4 °C for PF127 water solutions (>20% by weight); nevertheless, heating to room temperature or body temperature produces semisolid gels, most likely due to micellar packing and tangling [18].

Applications

For the treatment of solid and blood malignancies, PF127 injectable hydrogels have currently been proposed as drug and drug crystal delivery systems [19].Co-delivering 5-fluoruracil (5-FU) and doxorubicin-loaded Poly(d,l-lactide-co-glycolide) nanoparticles (DOX@PLGA) for the treatment of melanoma in vitro and in vivo was made possible by this technique [20].

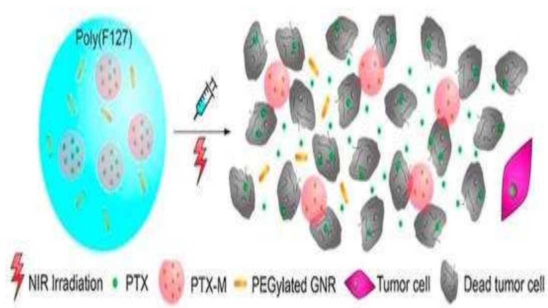

Fig 5: Diagram illustrating the gel-mediated photothermal–chemotherapy in combination with PTX-NPs and AuNRs. Paclitaxel is PTX; gold nanorods are GNR; near infrared is NIR.
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Finally, it should be noted that cyclodextrins (α-CD) are used in hydrogel networks to create effective depot systems for the treatment of cervical and breast cancer [22]. A further enhancement was the development of hybrid hydrogels with longer-lasting drug delivery behaviour with the incorporation of graphene oxide (GO) or reduced graphene oxide (rGO) materials [23].

Polyester based materials

In the last several decades, thermosensitive in-situ gels of amphiphilic copolymers based on biodegradable polyesters and polyethylene glycol (PEG) have become a feasible alternative for systemic drug delivery of hydrophobic therapies. These gels avoid the problems usually related to systemic medication administration while still enabling the recovery of high drug concentration at the tumour site.

Drawback

However, the main drawback of these materials is that their acidic breakdown byproducts have a significant impact on the pH value of the surrounding environment, which may limit their use in biomedical applications [24].

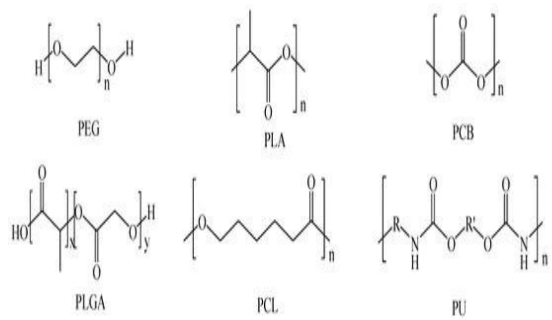

Fig 6: A schematic illustration of the primary biodegradable polyesters and poly(ethylene glycol) (PEG). PLGA stands for poly(lactide-co-glycolide), PCL for poly(ε-caprolactone), PU for poly(urethane), and PLA for polylactide.

Applications

Gemcitabine (GEM) and cisplatin (CisPt) were locally delivered using injectable thermosensitive PLA–PEG–PLA to enable synergistic combination therapy against pancreatic cancer [25]. As an alternative, poly(d,l-lactide) PLA was combined with pluronic L (PL) moieties to create three-block hydrogels (PLA–PL–PLA), which were then proposed for intraperitoneal treatment of colon cancer [26].

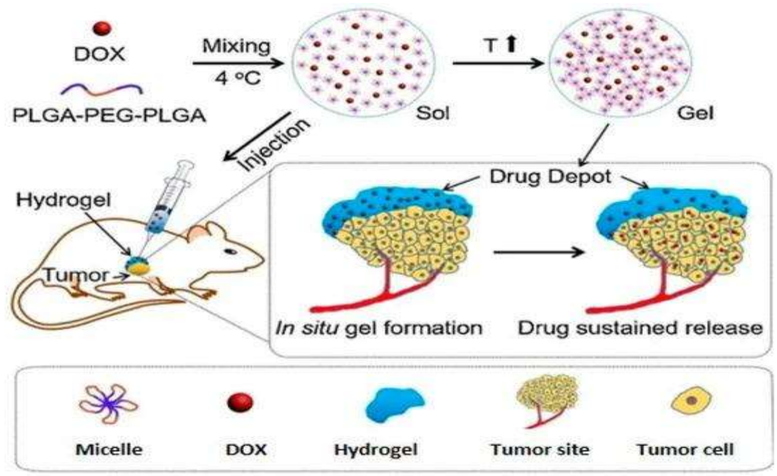

Fig 7: Diagrammatic representation of drug release and localized hydrogel development. Reproduced with permission from Elsevier, [2018] and [28].

Properties

At a polymer content of 15-20% wt, the transition temperatures of PLGA–PEG–PLGA gels varied between 10 and 40 °C, according to data from the literature [27].Topotecan (TPC), DOX, CisPt, and methotrexate (MTX) were proposed to be carried by PLGA–PEG–PLGA gel for the treatment of osteosarcoma in in vivo experiments [29].

Applications

After being loaded with 5-FU and PXT, PEG-PCL-PEG-based drug delivery systems were studied in vivo for the treatment of breast and colon malignancies, respectively [30].

Novel drug delivery systems that might combine the advantages of radiation and chemotherapy while avoiding damage to healthy tissue and boosting therapeutic efficacy were developed by using the co-delivery of radiosensitizer isotopes and anticancer medications [31]. More specifically, multifunctional devices that administered DOX and β-emitter species, specifically rhenium-188 and iodine-131, to treat hepatocellular carcinoma were developed using PEG–PCL-based hydrogels [32].

Poly-acrylates

Photo-induced radical polymerization, which employs acrylate monomers and/or functionalized macromers, is an alternative to thermal gelation for the synthesis of injectable hydrogels that can self-assemble following injection following UV light (Figure 8) [33].

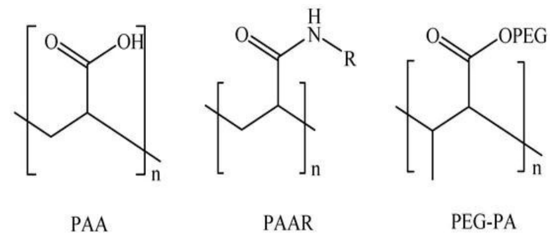

Fig 8: Diagram illustrating the primary acrylate polymers. PEG-PA is PEGylated poly(methacrylic acid); PAA is poly(acrylic acid); PAAR is N-alkyl poly(acrylic amide).

Properties

The main component of this class of materials, PEG acrylate polymers (PEG-PA), were designed to allow the insertion of PEG properties (such as non-cytotoxicity, non-immunogenicity, and the ability to reduce opsonization) within a hydrogel network, exhibiting improved mechanical properties, extended drug retention durations, and increased drug loading capability.

Applications

This method was investigated in the treatment of glioblastoma, using a polyethylene glycol dimethacrylate (PEGDMA)-based approach. In the brain tumour resection bed, the photopolymerizable monomer—which was subjected to UV light—was used to provide temozolomide (TMZ) and paclitaxel (PTX).

Generic Polypeptide

Polypeptides (Pep) are synthetic polymers that mimic proteins and are especially attractive due to their biocompatibility and biodegradability [34]. This class of molecules also has the advantage of having a high degree of chemical diversity because of the wide range of monomer sources that may be obtained from the 21 natural amino acids and their synthetic derivatives (Fig 9).

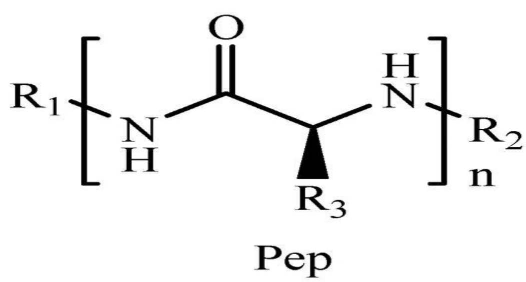

Fig 9: A schematic illustration of artificial polypeptides.

Applications

Thermogelation techniques were used to create injectable hydrogels for TMP-2 and DOX-based therapy for lung, cervix, and breast cancers as well as for the delivery of DOX or gene (CDN) with simultaneous immune response stimulation. Additionally, DOX@Liposome formulations were loaded onto Pep hydrogels in order to provide a combination therapy that included Losartan (LST).

Other Systems and Dendrimers

Artificially produced branching polymers with a low polydispersity index, globular structure, and nanometric size are known as dendrimers [35]. They are made by introducing monomer units via a sequence of reaction stages into a Generation 0 core.

Application

They are perfect for medication delivery applications because of these special qualities. Numerous injectable hydrogels based on dendrimers have been proposed in the literature for the treatment of solid tumors; these primarily consist of modified PEG, poly(amine-ester), and polyamidoamine (PAMAM).

Organic Polymers

Polysaccharides

In order to create an injectable pH-responsive hydrogel for application in the treatment of melanoma and breast cancer, a CS prodrug of a photosensitizing agent was utilized as the basis material [36]. Additionally, a number of research studies have suggested that chemically cross-linking CS with β-GP is a useful method for producing thermoresponsive materials that can be used to treat a variety of cancer disorders. Among these extra advantages of CS include its capacity to eradicate microbes, fight cancers, and mend wounds.[37].

Applications

Other applications included the induction of localized hyperthermia for different forms of cancer and the possibility of combining chemotherapy and radiation [38]. More precisely, carboxymethyl chitosan (CMCS) was copolymerized with NIPAAm to form pH- and temperature-responsive depots for the on-off release of 5-FU to cervix and breast cancer.Its high biocompatibility and capacity to connect with cell surface receptors (such CD44) that stimulate cell migration have made it a popular starting material for the development of different injectable hydrogel systems [39].

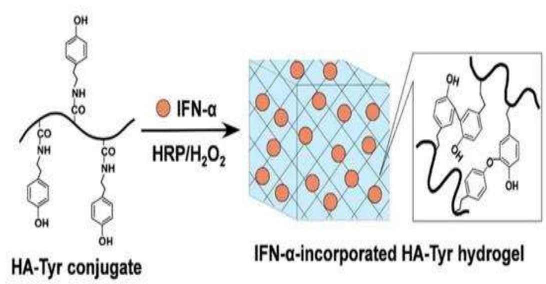

Fig 10: Diagrammatic representation of the enzymatic cross-linking reaction used to generate IFN-incorporated HA–Tyr hydrogels in situ. Horseradish peroxidase, abbreviated HRP. Permission granted by [40]. 2016; Elsevier.

Proteins

The integration of the structural and functional properties of proteins in injectable hydrogels has also been tested because of the materials' high biocompatibility, biodegradability, non-toxicity, and non-immunogenicity, as well as their similarity to naturally occurring organ, tissue, and cell components [41].

Applications

It was proposed to employ bovine serum albumin (BSA) as the polymeric foundation for injectable hydrogels meant to be used in cancer treatment. BSA was added to the cross-linking agent epichlorohydrin to produce a gel that possessed the required mechanical strength, viscoelastic behaviour, shear thinning, injectability, and self-healing properties for use as DOX delivery vehicles to treat breast and cervix cancer [42].

Alternatively, an injectable hydrogel containing BSA-modified PEG and PTX-encapsulated red blood cell membrane nanoparticles was created in order to improve the intraperitoneal retention of PTX in the treatment of gastric cancer in humans. Finally, human serum albumin (HAS) chemically bonded to PEG dendrimers was proposed as a functional biomaterial for inducing apoptosis in pancreatic cancer.

CONCLUSION

The creation of injectable hydrogels specifically for cancer therapy relies heavily on synthetic polymers, which offer a number of benefits that improve treatment effectiveness. The mechanical and physical features of polymers like polyethylene glycol (PEG), polycaprolactone (PCL), and polylactic acid (PLA) are versatile, allowing for exact customization to meet the specific needs of different cancer therapies.In conclusion, synthetic polymers play a critical role in developing injectable hydrogels for cancer treatment, which enhances treatment options and improves patient outcomes.Injectable hydrogels are transforming the way we treat tumors and aid in patient recovery because they are at the cutting edge of innovation and effectiveness in cancer care. These flexible materials enable tailored and responsive treatment plans by responding dynamically to the distinct features of the tumor microenvironment in addition to delivering medicines directly to the site of malignancy.Essentially, injectable hydrogels represent a paradigm change toward more intelligent, efficient, and compassionate care, signaling a time when cancer therapy will be as unique to each patient as it is. They are more than just another tool in the fight against cancer.

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