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Review article

Engineered *in-situ* depot-forming hydrogels for intratumoral drug delivery

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ABSTRACT

Chemotherapy is the traditional treatment for intermediate and late stage cancers. The search for treatment options with minimal side effects has been ongoing for several years. Drug delivery technologies that result in minimal or no side effects with improved ease of use for the patients are receiving increased attention. Polymer drug conjugates and nanoparticles can potentially offset the volume of drug distribution while enhancing the accumulation of the active drug in tumors thereby reducing side effects. Additionally, development of localized drug delivery platforms is being investigated as another key approach to target tumors with minimal or no toxicity. Development of *in-situ* depot-forming gel systems for intratumoral delivery of immuno-oncology actives can enhance drug bioavailability to the tumor site and reduce systemic toxicity. This field of drug delivery is critical to develop given the advent of immunotherapy and the availability of novel biological molecules for treating solid tumors. This article reviews the advances in the field of engineered *in-situ* gelling platforms as a practical tool for local delivery of active oncolytic agents to tumor sites.

Contents

Abbreviations: C/GP, chitosan/β-glycerophosphate; CMC, Carboxymethyl chitosan; DMSO, Dimethylsulfoxide; HA, hyaluronic acid; HEM, 2-hydroxyehthyl methacrylate; HPC, Hydroxypropylcellulose; HPMC, Hydroxypropylmethylcellulose; IL-2, interleukin-2; MA, maleic anhydride; MC, Methylcellulose; MM, methyl methacrylate; mPEG, Methoxy poly(ethyl glycol); mPEG-b-(PCL-ran-PLLA), Methoxypolyethylene glycol-b-polycaprolactone-ran-polylactide; NMP, N-Methyl-2-pyrrolidone; PAA, Poly(acrylic acid); PAH, α,β-polyaspartylhydrazide; PCL, Poly(ε-caprolactone); PDEAEM, Poly(N,N′-diethylaminoethyl methacrylate); PEEU, Poly(ether ester urethane); PEG, Poly(ethylene glycol); PEG–PAA, Poly(ethylene glycol)-b-poly(acrylic acid); PEG–PDLA, Poly(ethylene glycol)-poly(D-lactide) acid; PEG–PLA, Poly(ethylene glycol)-poly(lactic) acid; PEO, Poly(ethylene oxide); PHA, Poly (α-hydroxy acids); PLA, Polylactic acid; PLGA, Poly (lactic-co-glycolic acid); PMA, Poly(methacrylic acid); PNIPAAM, Poly(N-isopropyl acrylamide); Poly(HPMAL), Poly(N-(2hydroxypropyl) methacrylamine lactate); POPS, Poly(organophosphazene).

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1. Introduction

The most effective treatment for cancers for localized solid tumor is to remove the tumor by surgery followed by post-operative chemotherapy or radiation treatment. However, this approach is not suitable for many cancers since many patients are not candidates for surgical procedure due to tumor size, location of tumor, and stage of cancer. In some cases, even after the surgery, the overall survival rates for some patients are not promising [1]. While an anticancer drug is administrated intravenously (IV), high plasma concentrations in the systemic circulation can result in undesirable side effects with just a portion of the entire administrated dose reaching the tumor [1–3]. Additionally, several anticancer drugs have rapid plasma clearance resulting in minimal tumor exposure that is not sufficient to build an effective treatment. To enhance efficacy of chemotherapy and reduce systemic side effects, new drug delivery approaches are being developed and have received significant attention in recent years [1,4].

One such approach is the advancement of drug delivery depot technologies for localized intratumoral delivery of anticancer drugs to achieve greater efficacy and minimize systemic side effects. Several configurations, such as gels, wafers, particles, rods, and films, have been evaluated for direct distribution of anticancer drugs to the tumor site [5–7]. In most cases, these platforms are made from biodegradable polymeric materials such as natural polymers including polysaccharides and polypeptides, and synthetic polymers such as PLA and PLGA [1,5,8]. These biopolymers are shown to be biocompatible *in-vivo* and applicable as *in-situ* depot-forming systems for localized intratumoral drug delivery [5,9–23].

Hydrogel depot systems are three-dimensional networks of polymers with high capacity to hold water and biological fluids [24]. Hydrogels are classified into two categories with regard to the cross-linking type used for the three dimensional depot formation: 1) depot-gelling systems in which the network is formed by covalent bond formation (chemical cross-linking); and 2) depot-gelling systems in which the network is formed by physical association between the components (physical cross-linking) [24,25]. Both categories have been investigated as injectable sustained release drug delivery systems that form a depot gel *in-situ* [24,26–28].

A key requirement of *in-situ* depot-forming systems for local delivery and more specifically intratumoral delivery is the injectability using standard gauge needles in either a vial/syringe or a pre-filled syringe configuration. The injection should be easy to administer and also provide minimal discomfort to the patient. Intratumoral injections based on *in-situ* gelling polymers are solutions that have low viscosity and can easily flow during administration but rapidly form gel networks once injected. This article focuses on the approaches for *in-situ* gelation for local intratumoral drug delivery, and the application of *in-situ* gelling formulation as a practical tool for improved local biodistribution and potential uptake of anticancer drugs to the tumor via intratumoral injection.

2. Advantages of intratumoral cancer therapy

Several anticancer drugs have low aqueous solubility that limits IV administration; chemical modifications have been introduced to convert these drugs to produce water soluble prodrugs for administration [5]. However, some of these systems are prone to poor bioavailability, cause sensitization and other adverse reactions [5,29,30]. Additionally, IV administration of anticancer drugs does not specifically target the tumor site, resulting in less than optimum drug concentration in the tumor. Moreover, large quantities of anticancer drugs are distributed to healthy tissues resulting in acute adverse effects and toxicity. For example, during the first 24 h after IV administration of free paclitaxel, almost 50% of the administrated dose is eliminated and only less than 0.5% of the administrated dose is bioavailable locally at the tumor site within the lung [5,31].

The high prevalence of systemic side effects for current treatment in the early and intermediate cancer stages indicates that improvements are required on treatment approaches [5]. Intratumoral drug delivery can be a tool to enhance the current cancer treatment approaches via local delivery. At each stage of cancer, there are potential intervention points in which intratumoral cancer therapy could be implemented or completely replace existing treatments. There are numerous potential advantages of intratumoral drug delivery, and it is applicable to both improving effective treatment and lowering patient morbidity. When compared to traditional IV administration of anticancer drugs (Fig. 1), intratumoral drug delivery systems have the potential to (a) provide controlled and sustained drug distribution ensuring sufficient drug transport and diffusion into cells, (b) enable the loading and release of insoluble anticancer drugs through novel solvent/polymer combinations, (c) deliver anticancer drugs locally to the tumor site leading to low dose requirements, (d) reduce multiple drug administration cycles, and (e) reduce or eliminate adverse effects of the drug due to local delivery, and prevention of systemic drug uptake [5,32,33].

3. Engineering *in-situ* depot-forming systems for intratumoral drug delivery

Injectable gelling depots and pre-shaped implant systems are two types of intratumoral delivery systems for anticancer drugs [5]. Injectable biodegradable *in-situ* forming depots are shown to be less invasive and have less pain upon injection as compared to pre-formed implants, making them desirable systems for local administration of anticancer drugs [8]. Injectable biomaterials are suitable for development as delivery systems to localize the drug molecules at the tumor site [8]. According to the mechanism of depot formation, engineered *in-situ* gelling depots can be classified into two categories: (1) platforms based on *in-situ* cross-linking, and (2) platforms based on *in-situ* phase separation (Table 1) [8,34–37].

3.1. Platforms based on in-situ cross-linking

In this platform, *in-situ* gels form by either photo-polymerization, chemical cross-linking, or physical cross-linking (Fig. 2) [8,38–41].

3.1.1. Photo-polymerization

In the photo-polymerization approach, the starting materials are liquid solutions that can be injected into the tumor site. Upon exposure to light, the injected materials polymerize to form the depot matrix *in-situ*. Monomers with a minimum of two free radicals (or cross-linkable polymer), a photo-initiator, and visible or ultraviolet (UV) light are required for *in-situ* depot formation (Fig. 2) [8,42–47].

Examples of polymers used for *in-situ* photo-polymerization are triblock copolymerized materials of poly(HPMAL) and PEG, di-block copolymerized materials of PEG and PHA containing acrylated terminal groups, and modified chitosan [8,45,48].

Obara and his colleagues showed slow paclitaxel release from photocrosslinked chitosan based hydrogels [49]. The *in-vivo* results indicated that the paclitaxel incorporated gel prevented the expansion of subcutaneously induced tumors more effectively compared to free paclitaxel group.

In another attempt, Sharifi et al. employed modified PCL to develop *in-situ* depot forming system based on photocrosslinking for sustained release of tamoxifen citrate as a potential treatment for breast cancer [50]. Results showed a slow release of drug *in-vitro* resulting in death of cancer cells.

The main concern for applying this approach is the presence of reactive species generated by photo-polymerization. The reactive species can expose free radicals to the surrounding tissues and affect incorporated anticancer drugs. Moreover, performance of depot formation based on photo-polymerization is limited by the penetration depth of visible