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Oil-in-microgel strategy for enzymatic-triggered release of hydrophobic drugs

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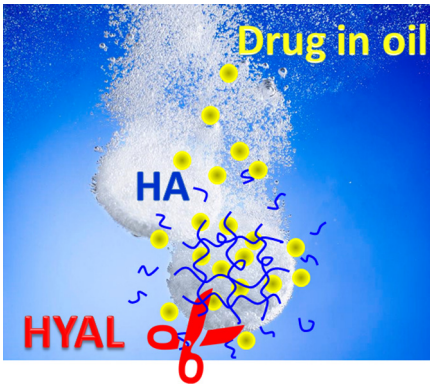
GRAPHICAL ABSTRACT



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ABSTRACT

Polymer microgels have received considerable attention due to their great potential in the biomedical field as drug delivery systems. Hyaluronic acid (HA) is a naturally occurring glycosaminoglycan composed of *N*-acetyl-D-glucosamine and D-glucuronic acid. This polymer is biodegradable, nontoxic, and can be chemically modified. In this work, a co-flow microfluidic strategy for the preparation of biodegradable HA microgels encapsulating hydrophobic drugs is presented. The approach relies on: (i) generation of a primary oil-in-water (O/W) nanoemulsion by the ultrasonication method, (ii) formation of a double oil-in-water-in-oil emulsion (O/W/O) using microfluidics, and (iii) cross-linking of microgels by photopolymerization of HA precursors modified with methacrylate groups (HA-MA) present in the aqueous phase of the droplets. The procedure is used for the encapsulation and controlled release of progesterone. Degradability and encapsulation/release studies in PBS buffer at 37 °C in presence of different concentrations of hyaluronidase are performed. It is demonstrated that enzymatic degradation can be used to trigger the release of progesterone from microgels. This method provides precise control of the release system and can be applied for the encapsulation and controlled release of different types of hydrophobic drugs.

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1. Introduction

Among different types of drug delivery systems, polymeric hydrogels hold great promise thanks to their hydrophilic three-dimensional network which offers large water-retaining property and excellent biocompatibility. Moreover, particles made of hydrogels, namely microgels or nanogels, exhibit good colloidal stability and are injectable. All these lightly cross-linked polymers are porous and can be loaded with drugs. Stimuli-responsive hydrogels are fascinating materials because they swell or shrink in response to an external stimulus such as temperature, pH, irradiation or even the presence of a biomolecule in solution [1–4]. In this case, drug release can be additionally controlled by stimuli [5]. Microgels also offer opportunities as surface coatings when adhered to biomaterials or surgical implants to reduce infection and inflammation and to improve biocompatibility, particularly when containing antimicrobial and anti-inflammatory drugs [6–8]. Therefore, responsive hydrogels allow a fine tuning of drug release rate with tailored properties.

For most therapeutic applications, the drug delivery system needs to be readily biodegradable in order to avoid accumulation-related adverse effects. Biodegradability of the matrix can also be used as the trigger to control the release of the drug. HA is a naturally occurring glycosaminoglycan composed of N-acetyl-D-glucosamine and D-glucuronic acid, which exhibits biocompatible and biodegradable properties. This linear polysaccharide is ubiquitous in all tissues, as a major component of the extracellular matrix (ECM) in animal tissues [9]. Advantageously, chemical modification of HA is relatively easy [10,11]. Being non-toxic and non-immunogenic, it has been widely used as a building block to design cross-linked architectures with a potential application in tissue regeneration [12,13] and drug delivery [14] or cell growth [15]. Enzymatic degradation of HA occurs *in vivo* via hyaluronidases (Hase), which are present in both intra- and extracellular space [16]. Therefore, HA-based microgels are expected to deliver their payload after injection in the body by progressive enzymatic erosion of the matrix. In general, members of HA signaling pathway (receptors such as CD44 and CD168 [17,18], Hase [19,20]) are also overexpressed in a variety of carcinomas. HA has been used in drug delivery formulations for the targeted delivery of chemotherapy drugs and other anticancer compounds to tumor cells through interaction with cell-surface HA receptors [21]. Furthermore, Hase-responsive containers appear as emerging technologies to deliver anticancer drugs since the high concentration of Hase in the tumor cells can increase the release efficiency [22–26].

In spite of the great interest for HA-based hydrogel materials, these systems are generally limited to water-soluble drugs, most often peptides and proteins [27–30], whereas many drugs are hydrophobic, such as anticancer drugs. The encapsulation of a hydrophobic drug has been reported using different strategies of functionalization of the micro- or nanogels: (1) via the incorporation of a hydrophobic core in a hydrogel shell [31] or hydrophobic domains in the hydrogel matrix [32,33,36] and (2) via the introduction of cyclodextrin (CD) moieties, that can bind hydrophobic molecules through inclusion complexes [34]. However, the loading efficiency is often poor. Alternately, hydrophobic drugs can be solubilized in non-polar solvent that can further be dispersed in a hydrogel matrix. This latter solution offers the advantage of incorporating high payloads of drugs in a dissolved form. The concept has been explored recently using alginate matrices [35,36] and thermoresponsive poly(*N*-isopropylacrylamide) (pNIPAM) ones [37,38], where burst release could be achieved by collapsing the hydrogel upon heating.

In this paper, we focus on the preparation of a biocompatible system that could be used *in vivo* to deliver a hydrophobic drug upon Hase degradation (Fig. 1). We demonstrate the concept using progesterone (PGR), a lipophilic steroid hormone with a low molecular weight. This drug requires long-time controlled delivery system to induce estrus and ovulation in production animals [39,40]. Several progesterone delivery systems for estrus synchronization have been reported but they are based on non-biodegradable polymers [41]. HA microgels would provide a controlled release of the hormone after subcutaneous administration. Once the microgel is degraded and the oil droplets are dissolved, progesterone could be absorbed to systemic circulation and could reach sites of action thanks to its extensively binding to plasma proteins, primarily albumin.

Thus, we report the preparation of oil-in-microgel containers, made of fully biocompatible ingredients, encapsulating PGR. The materials are prepared by a two-step method which allows a fine and robust control of the structural parameters: the drug is incorporated in an oil-in-water nanoemulsion, that is further incorporated within monodispersed HA microgels prepared by microfluidic approach. The enzymatic degradability of the microgels and their ability to release the PGR-loaded oil nanodroplets upon enzymatic degradation is finally presented.

2. Experimental

2.1. Materials

All the reagents were purchased from Sigma-Aldrich unless otherwise noted. Methacrylic anhydride (AMA), *N*,*N*-dimethylformamide (DMF), ethanol, *n*-hexadecane, octadecyltrichlorosilane (OTS), chloroform, toluene, soybean oil, sunflower oil, sorbitan monooleate (Span 80), polysorbate 80 (Tween 80), hyaluronidase from bovine testes (type I-S), *N*,*N*′-methylenebisacrylamide (BIS), sodium caseinate (SC), 1-[4-(2-hydroxyethoxy)-phenyl]-2-hydroxy-2-methyl-1-propan-1-one (Irgacure 2959), 2,2′-azobis(2-methylpropionamidine) dihydrochloride, Nile Red (NR), progesterone (PGR) and phosphate buffered saline (PBS) were used without any further purification. NIPAM was recrystallized from *n*-hexane. Hyaluronic acid (M_w = 60,000 g mol^{-1}) was purchased from Lifecore (USA).

2.2. Synthesis of methacrylated hyaluronic acid macromer (HA-MA)

The synthesis of hyaluronic acid modified with methacrylates is fully reported by Hachet et al. [42]. In brief, 1 g of hyaluronic acid (2 wt%) was solubilized for 4 h at room temperature in ultrapure water. Then, DMF was added dropwise to the solution (volume ratio 3:2 water–DMF) and the mixture was cooled down to 4 °C. The reaction medium was cooled after addition of DMF to avoid a temperature increase upon addition of the anhydride in the hydro-alcoholic medium that could promote side reactions (hydrolysis of esters formed and hydrolysis of the anhydride). Then, AMA (1 M equivalent with respect to the moles of the repeating unit of HA) was added dropwise and the pH was maintained between 8 and 9 for 4 h by the addition of 0.5 M NaOH. The reaction was run overnight and then, 0.5 M NaCl was added to the mixture. The polymer was precipitated by the addition of ethanol (with a water–EtOH volume ratio of 2:3). After the removal of the supernatant, the precipitate was successively washed with mixtures of water–EtOH using volume ratios of 3:7, 1:4 and 1:9. The final precipitate was dissolved in ultrapure water and further dialyzed against ultrapure water by diafiltration (ultramembrane Amicon YM10). The purified macromer was recovered by freeze-drying and characterized by ^{1}H NMR analysis.

^{1}H NMR spectra of HA-MA in D_2O (C = 8 mg mL^{-1}) were recorded at 80 °C with 128 scans using a Bruker 400 MHz

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