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ScienceDirect
Acta Biomaterialia 4 (2008) 1788–1796
Acta BIOMATERIALIA
www.elsevier.com/locate/actabiomat

Controlled release of drugs from multi-component biomaterials

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Received 2 January 2008; received in revised form 24 April 2008; accepted 14 May 2008
Available online 5 June 2008

Abstract

In order to control their release, drugs are encapsulated into systems which are expected to provide a certain site with a predetermined amount of drug over a well-defined period of time. Here we report on a multi-component drug delivery biomaterial that consists of a hydrogel matrix in which drug-loaded biodegradable microcarriers are dispersed, and whose potential applications could be found in the design of implantable devices with long-term activity, as required by contraceptive and hormone replacement treatments. The release profile of the drug can actually be tuned by the complex interplay of several release mechanisms, including the permeability and eventually the degradation rate of the microcarriers and the diffusion through the hydrogel. The hydrogel consisted of 2-hydroxyethyl methacrylate cross-linked by ethylene glycol dimethacrylate. The microcarriers were biodegradable poly-ε-caprolactone (PCL) microspheres in which active molecules, such as levonorgestrel (LNG), were encapsulated. The hydrogels were characterized by water swelling, thermal properties, LNG diffusion through drug-free and drug-depleted hydrogel membranes and LNG release from devices with drug dispersed in the hydrogel. The PCL microspheres were observed by scanning electron microscopy; their size distribution, LNG loading and release were also investigated. The hydrogel-microsphere assemblies were characterized in terms of the distribution of the microspheres within the hydrogel, water swelling and the release of the encapsulated molecules. The developed device, due to its composite structure, has the ability to combine several release mechanisms, leading to drug release obeying zero-order kinetics for most of the time.

Keywords: Drug delivery; Controlled release; Hydrogel; Poly(2-hydroxyethyl methacrylate); Microspheres

1. Introduction

Theoretically, an ideal drug delivery system should deliver a drug to a specific site in a specific time and release pattern. After more than 40 years of research and development of a large number of systems, polymeric supports are integral to the design and preparation of controlled delivery formulations. In fact, the great versatility of polymers from a structural point of view, together with the possibility of combining hydrophilic and hydrophobic components, as well as polymer–polymer macromolecules, polymer–drug, polymer–solvent or polymer–physiological medium interactions, offers huge possibilities for the design and preparation of formulations with specific properties and functions.

Hydrogels are cross-linked polymer networks that are insoluble, but able to swell in water. Due to their close resemblance to natural tissues, they have been frequently used for tissue engineering and drug delivery [1–5]. Due to their biocompatibility, hydrogels based on poly

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doi:10.1016/j.actbio.2008.05.021

(2-hydroxyethyl methacrylate) (pHEMA) are commercially employed as soft contact lenses and intraocular lenses, and have been investigated for several biomedical applications, such as substrates for cellular and tissue engineering [6,7] and drug delivery devices [8–11]. The release of the drug from hydrogel controlled release systems is affected by the rate of water diffusion into the polymer, which in turn depends on the chemical structure of the polymer (polarity, glass transition temperature, flexibility of the polymer backbone) and on the cross-link density and inter-chain interactions [3,11,12].

Poly-ε-caprolactone (PCL) is a biodegradable and biocompatible aliphatic polyester with a semicrystalline structure and a very low glass transition temperature. Due to its slow degradation [13–15], high permeability to many drugs and low toxicity [16], PCL microcarriers consisting of a drug dispersed in spherical polymer matrix have been extensively evaluated for the administration of active compounds over long periods [17–20]. In these systems, the drug release is governed by factors depending on the polymer (molecular weight, crystallinity), the drug (solubility in water/biological fluids) and their interactions, as well as on the microcarrier's characteristics (drug loading, particle size, porosity) [21]. Previous studies have indicated that PCL could retain its integrity in the body over long periods before being metabolized and completely excreted [22,23]. The fact that the degradation rate of PCL is relatively slower than those of other known biodegradable polymers makes it suitable as a long-term device. By embedding PCL microspheres containing drugs into hydrogels, two different release mechanisms can be combined: diffusion through the polymeric matrix for the microcarriers and diffusion through the hydrophilic matrix for the hydrogel. With the aid of the different parameters mentioned above, the release profile of drugs encapsulated into PCL microspheres, which in turn are embedded in pHEMA-based hydrogels, can be tuned to an apparent zero-order and maintained over a long period. Low-dose drug delivery devices releasing active principles over a long period could find their application in the field of contraceptives and hormone replacement treatments. Intrauterine devices and intrauterine drug delivery devices act locally, avoiding systemic effects, and are therefore particularly attractive for contraception or hormone replacement therapy in postmenopausal women [24,25].

2. Experimental

2.1. Materials

2-Hydroxyethyl methacrylate (HEMA) and ethylene glycol dimethacrylate (EGDMA) were purchased from Sigma Aldrich and distilled under vacuum or used as received. Freshly prepared aqueous solutions of potassium persulfate, $K_2S_2O_8$ (Sigma Aldrich) and sodium disulfite dry $Na_2S_2O_5$ (Merck) were used together as redox initiators.

Levonorgestrel (LNG) was purchased from Industriale Chimica (Saronno, Italy). PCL (mol. wt. = 50,000) was received as a free sample from Solvay. Poly(vinylalcohol) (PVA) (Mowiol 3-83, mol. wt. = 18,000 g/mol) was supplied from Calbiochem, and the Carbomer 980 was from Certa (Belgium). All other chemicals were analytical grade and were used as received.

2.2. Preparation of multi-biomaterial delivery systems

2.2.1. Microspheres

PCL microspheres, blank and loaded with drug, were prepared by the oil in water (o/w) emulsion-solvent evaporation method, a technique commonly used for the microencapsulation of water-insoluble drugs within hydrophobic polymers [26,27]. PCL and LNG were dissolved in 5 ml dichloromethane, forming the oil phase. This organic phase was gradually added into a 250 ml beaker containing 125 ml of 0.27% PVA aqueous solution, maintained at room temperature and stirred at 300 rpm to form an o/w emulsion. The emulsion system was continuously stirred at room temperature and ambient pressure to allow the evaporation of dichloromethane and to let the droplets harden into microspheres. The microspheres were collected by filtration on a filter paper, washed three times with distilled water and freeze-dried to obtain free flowing PCL microspheres.

2.2.2. Hydrogels

Dissolved oxygen was removed from monomer mixtures composed of HEMA with 0–0.5 vol.% EGDMA by nitrogen bubbling for 5 min. For the preparation of drug-loaded substrates, either appropriate amounts of drug were dissolved or appropriate amounts of PCL microspheres encapsulating drug were dispersed in the monomer mixture. Subsequently, the organic phase was mixed in reagent glasses in a volume ratio of 3:1 with aqueous solutions of redox initiators (6.4 mg of $K_2S_2O_8$ and 3.2 mg of $Na_2S_2O_5$ per ml of water). The nitrogen bubbling continued for another 15 min, then the reagent glasses were left at room temperature under the nitrogen blanket until the gelation of the reaction mass was visible. Finally, the viscous liquid was stirred to achieve a uniform composition and was then either aspirated into 1 ml one-way plastic syringes or poured between two glass plates kept approximately 1 mm apart by the use of a rubber spacer and left to polymerize overnight at room temperature. A series of pHEMA rods embedding increasing amounts of blank PCL microspheres was also prepared.

The pHEMA-based rods and membranes synthesized as above were washed for 5 days with distilled water, with daily water changes, for the removal of unreacted monomer (the residual HEMA was less than 5 ppm after 5 days' washing as determined by high-performance liquid chromatography, HPLC), and then stored either freeze-dried (rods) or in distilled water (membranes).

pHEMA-based drug-depleted membranes, used for drug diffusion experiments, were prepared in the presence

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