



Agarose drug delivery systems upgraded by surfactants inclusion: Critical role of the pore architecture



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ABSTRACT

Anionic or non-ionic surfactants have been introduced in agarose-based hydrogels aiming to tailor the release of drugs with different solubility. The release of a hydrophilic model drug, Theophylline, shows the predictable release enhancement that varies depending on the surfactant. However, when the hydrophobic Tolbutamide is considered, an unexpected retarded release is observed. This effect can be explained not only considering the interactions established between the drug loaded micelles and agarose but also to the alteration of the freeze-dried hydrogels microstructure. It has been observed that the modification of the porosity percentage as well as the pore size distribution during the lyophilization plays a critical role in the different phenomena that take place as soon as desiccated hydrogel is rehydrated. The possibility of tailoring the pore architecture as a function of the surfactant nature and percentage can be applied from drug control release to the widespread and growing applications of materials based on hydrogel matrices.

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1. Introduction

Among the different polysaccharides in the biomaterials and biotechnological world (Borgogna, Bellich, & Cesaro, 2011; Coviello, Matricardi, Marianecci, & Alhaique, 2007; Laurienzo, 2010; Malafaya, Silva, & Reis, 2007; Murano, 1998; Oliveira & Reis, 2011), agarose is gaining several applications (Rinaudo, 2008) further than its traditional and extensive utilization in molecular biology separation techniques such as gel electrophoresis or gel filtration chromatography (Punna, Kaltgrad, & Finn, 2005; Stellwagen, 2009). In addition agarose is employed as an alternative to agar in particular situations as culture media, microorganism motility assays or food texture modifications. Besides its utilization in different aspects within the biotechnology field (Renn, 1984), agarose is being employed in the biomaterial field as a matrix to regenerate a damaged tissue or forming part of a drug controlled release device. Both functions are being combined, in what can be termed as functional scaffolds, aiming to achieve a better integration of a scaffold by the inclusion of biomolecules that avoids the immunological reactions, facilitate the cell colonization while

avoiding a possible bacterial infection. ... In this sense agarose has been considered as a potential candidate to regenerate different types of tissues, especially hard (bone and cartilage (Chung & Burdick, 2008; Ge, Li, Heng, Cao, & Yang, 2012)), pancreas (Bloch et al., 2005; Iwata et al., 1992; Teramura & Iwata, 2010) and nervous system (Bellamkonda, 2006; Cao, Gilbert, & He, 2009; Khaing & Schmidt, 2012; Stokols & Tuszynski, 2006). Many of these studies are based on the facility of this substance to form hydrogels that can be used to shape pieces in the required form for an actual case. Indeed, the relatively low gelling temperatures allow the direct inclusion of thermal labile biomolecules or even cells during the fabrication procedure (Cabanas, Pena, Roman, & Vallet-Regi, 2009; Pena, Roman, Cabanas, & Vallet-Regi, 2010). In such a way a system with a high content in water and a chemical composition that resembles that of extracellular matrix can be obtained and tailored by the inclusion, besides the already mentioned biomolecules, of structural components that contribute to improve the mechanical performance (Delair, 2012; Gupta, Vermani, & Garg, 2002; Jeong, Kim, & Bae, 2002; Lee & Mooney, 2001; Lin & Metters, 2006; Pena et al., 2010; Peppas, Bures, Leobandung, & Ichikawa, 2000; Slaughter, Khurshid, Fisher, Khademhosseini, & Peppas, 2009).

However it must be taken into consideration that this type of matrixes requires, due to their high water content and presence of labile components, the employment of a preservation technique that facilitates its off-the-shelf application. Freeze-drying

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has been extensively employed in different industries to eliminate water from solid, semisolid or liquid systems, thus enabling their conservation and ulterior application after a rehydration process (Claussen, Ustad, Strommen, & Waide, 2007; Sanchez, Hernandez, Auleda, & Raventos, 2011; Wang, 2000). At the same time this technique has been employed as a tool to generate a characteristic honeycomb pore architecture that consist on uniaxial parallel pores of around 100–200 μm that have been generated during the water extraction (Gutierrez, Ferrer, & del Monte, 2008; Lozinsky et al., 2003). This range of porosity is of critical importance for the fluid migration containing nutrients and metabolic waste throughout the whole matrix volume; in addition it facilitates the capillary vascularization.

Nevertheless, despite their several benefits the highly hydrophilic environment within hydrogels supposes a disadvantage to entrap homogeneously poorly soluble drugs and may not ensure an adequate protection even causing a premature degradation. In this sense several strategies are being developed in order to optimize the performance of these compounds as drug delivery devices or functional scaffolds (Alvarez-Lorenzo & Concheiro, 2003; Bai, Thomas, Rawat, & Ahsan, 2006; Coviello et al., 2007; Tadros, 2009). On one side, a better release control can be achieved by including the drug molecules in structures of greater size and lower diffusivity, while it can also be regulated through the incorporation of additives, especially surfactants (Alvarez-Lorenzo & Concheiro, 2008; Kawakami, Oda, Miyoshi, Funaki, & Ida, 2006; Paulsson and Edsman, 2001).

Surfactants are compounds very used in different industrial fields. In pharmaceutical technology may act as wetting agents, emulsifiers, foaming and dispersant agents in order to stabilize different systems (solutions, suspensions, emulsions, aerosols) (Eeckman, Moes, & Amighi, 2003; Moffat, Osselson, Widdop, & Clarke, 2004; Tadros, 2009). Moreover, their micelle-forming capability increases the solubility of poorly soluble drugs as well as hydrophobic organic compounds (Bromberg, Hatton, Barreiro-Iglesias, Alvarez-Lorenzo, & Concheiro, 2007; Kawakami et al., 2006; Laha, Tansel, & Ussawarujikulchai, 2009; Lin, Lin, & Yang, 2009). Sodium lauryl sulphate, an anionic surfactant, has been used to enhance water solubility of Camptothecin, Mefenamic acid, Nimesulide or Ibuprofen (Liu & Li, 2005, 2007; Park & Choi, 2006). Tween 80[®], hydrophilic nonionic surfactant, has demonstrated its capability as stabilizing agent of solid lipid nanoparticles or in the water insoluble suspensions of Itraconazole and Budesonide (Olbrich & Muller, 1999; Owen, Graham, Werling, & Carter, 2009). Pluronic F-68[®], non-ionic surfactant consist of polyethylene oxide–polypropylene oxide–polyethylene oxide (PEO–PPO–PEO) block copolymers has been incorporated to chemotherapeutic micelles formulation to enhance their effectiveness (Kabanov, Batrakova, & Alakhov, 2002a; Kabanov, Lemieux, Vinogradov, & Alakhov, 2002b; Tadros, 2009).

Besides their applications in the drug delivery field, the combination of polysaccharides and surfactants are being applied for different uses such as nanopore matrixes for separation (Sitaras, Naghavi, & Herrington, 2011; Stellwagen, 2009), generation of nanoparticles (Chatterjee, Chatterjee, & Woo, 2010), homogeneous dispersion of a compound within the gel matrix (Guo et al., 2013), unusual texture properties for food ingredients (Chhatbar, Godiya, & Siddhanta, 2012; Maurer, Junghans, & Vilgis, 2012), creation of superporous adsorbents (Shi, Wang, & Wang, 2013; Zohuriaan-Mehr, Omidian, Doroudiani, & Kabiri, 2010).

Initially the aim of this research was to study the possible benefits of incorporating a surfactant within agarose matrixes with the objective of facilitating the release of poorly soluble drugs such as Tolbutamide in comparison with a model drug highly water soluble (Theophylline) (Alvarez-Mancenido, Landin, Lacik, & Martinez-Pacheco, 2008; Kondo, Niwa, Okamoto, & Danjo, 2009;

Luo, Zhang, Wei, Liu, & Chen, 2009; Shaheen & Yamaura, 2002). However, the unexpected results obtained induced us to characterize the microstructural changes caused in the agarose matrixes by the surfactants presence and how do these alterations affect to the behavior of these materials when immersed in an aqueous medium. In this sense it should be remarked that part of this characterization must be carried out in a dry state, that is, freeze-dried. Considering this, the objective of this work is to characterize the microstructure, focusing specially on the porosity, of freeze-dried samples and try to correlate it with their behavior in a fluid, specifically with the release of a substance initially included in the formulation. Such characterization results of considerable interest taking into account the great number of hydrogels employed in applications related to the controlled release of active substances, and that these formulations are usually preserved by freeze-drying before administration or implantation.

2. Materials and methods

2.1. Materials

Theophylline (**THE**) (Lot: 093K0122), Tolbutamide (**TLB**) (Lot: 16H0898), Tween 80[®] (**T**) (Lot: 83H0550) and Pluronic F-68[®] (**P**) (Lot: 100K0199) were purchased from Sigma Chemical (St. Louis, MO, USA). Sodium lauryl sulphate (**L**) (Lot: 252368CS) was purchased from Panreac, (Barcelona, Spain). Agarose (**A**) for routine use (Lot: 085K0062) with a sulphate content <0.15%, E.E.O. 0.09–0.13 a gel point at 36 °C and a gel strength >1200 g/cm² was also purchased from Sigma Chemical (St. Louis, MO, USA). Water was purified with the Milli-Q reagent system (Millipore). The physico-chemical properties of the surfactants employed in this work are detailed in Table 1.

2.2. Preparation of freeze-dried hydrogels

As shown in Table 2, the different amounts of surfactants or drugs previously sieved to a particle size <100 μm were dissolved in demineralized water. Subsequently, the agarose was added into this solution/suspension and slowly heated at 90 °C (± 0.1 °C) on a water bath under agitation until the agarose in completely hydrated. At that moment, each system was poured into PVC blisters (1 mL of capacity) and allowed to gel at room temperature for 24 h. Finally, as schematized in Fig. 1 all the systems were freeze dried (Lia-bor) reaching a freezing temperature, a sublimation temperature and a sublimation pressure into a chamber of –45 °C, from –45 to 25 °C and 4.54×10^{-4} atm, respectively.

2.3. Systems characterization

All samples were analyzed by X-ray diffraction (XRD) in a Philips X-Pert MPD diffractometer with Bragg–Brentano geometry, operating with CuK α radiation ($\lambda = 1.5406$ Å) at 40 kV and 20 mA. The X-ray diffraction patterns were collected over the range between 4° and 40° 2 θ with a step size of 0.02° 2 θ and a contact time of 5 s per step. Thermogravimetric Analysis (TGA) and differential thermal analysis (DTA) were performed in a TA instruments TG/DTA analyser, with 10 °C/min heating ramps. In order to observe the behavior showed for every sample during its heating, thermomicroscopic examinations were carried out using a Thermogalen Hot Stage Microscope (HSM) fitted with a Kofler stage; every sample was heated at a rate of 2 °C/min between 30 and 350 °C. An Hg intrusion porosimetry study was carried out using a Micromeritics AutoPore III 9410 porosimeter between 0.1 and 30,000 psi.

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