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Drug absorption and release properties of crosslinked hydrogels based on diepoxy-terminated poly(ethylene glycol)s and aliphatic polyamines — a study on the effect of the gel molecular structure

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ABSTRACT

Crosslinked hydrogels with well-defined chemical structures and characteristics were prepared through the reaction between diepoxy-terminated poly(ethylene glycol)s of various molecular weights and aliphatic polyamines of different hydrocarbon chain length and functionalities, and the influence of some network parameters (molecular weight between crosslinking points, crosslinking degree, hydrophobic character) upon the absorption and release of drugs of different capacity to interact with the polymer chains was comparatively investigated. Diclofenac sodium (DCFNa) and 5-fluorouracil (5FU) were used as model drugs, based on their dissimilar hydrophobic character and ability of DCFNa to form crown ether-like complexes with PEG chains through the sodium cation. The experiments showed that the most important interactions occurring in these systems were mainly the hydrophobic ones and to a lesser extent the complexation of the Na^+ ion by the PEG chains. Both of them were in favor of DCFNa, resulting in a larger incorporation and a slower release of this one in comparison with 5FU. For both drugs, loading was larger for hydrogels with shorter PEG chains and/or crosslinked with amines with longer hydrocarbon chain or higher functionality. Drug release tests showed a lower rate for stronger drug–network interactions in agreement with the absorption experiments.

1. Introduction

Hydrogels have many uses in the biomedical field due to their water content and elasticity, which make them compatible with human tissue [1–3]. Among hydrogel bioapplications, the controlled-release drug delivery systems have attracted great interest, as they may solve the deficiencies of the conventional methods of drug administration. By achieving an almost constant release rate of the active principle over a longer period of time, these systems allow for the elimination of frequent dosing, and waste of drug and side effects due to too high drug concentration, and in some cases, protect the unstable bioactive compounds [4]. However, the duration and profile of the drug release from the hydrogel depend on some particular conditions like the amount of drug incorporated, drug solubility, drug–polymer interactions and hydrogel characteristics [5,6], which should be known in advance in order to design a drug release system with the desired properties [7].

There are many reports in literature connecting the duration and release rate of a drug from a hydrogel with some of the structural properties of the hydrogel network, like crystallinity, swelling degree, molecular weight (MW) between the crosslinking points, and chemical structure of polymer chains. Most of these reports investigate the influence of one or two of the network parameters upon the release of no more than one drug [8–14], while only some of them take into account more parameters [15–17], and even fewer additionally discuss comparatively the influence of the drug structure [18]. Also, in most cases the analyzed hydrogels have ill-defined network structure, made up of meshes of different sizes, as resulted from a statistical crosslinking process (for example crosslinking copolymerization or irradiation), and chains with functional groups randomly distributed, and therefore, conclusions based on average properties can only be drawn.

The present study aims at investigating the influence of the MW between the crosslinking points, crosslinking degree and increasing hydrophobic character, as well as the ability of the polymer chain to complex the drug, upon the absorption and release of drugs of different chemical structure and capacity to interact with the polymer chains, in the case of hydrogels with well-defined network. To the best of our knowledge this is the first paper discussing all these parameters influencing the drug absorption and release processes in the case of hydrogels with controlled structure. To carry out this study, we employed a novel class of hydrogels which we developed recently by crosslinking low-polydispersity diepoxy-terminated poly(ethylene glycol)s ($DEPEG_X$) with aliphatic polyamines (Scheme 1) [19,20], whose swelling and diffusion characteristics [19,20], mechanical [21] and thermal [22] properties and states of water contained [23] can be easily adjusted by varying the

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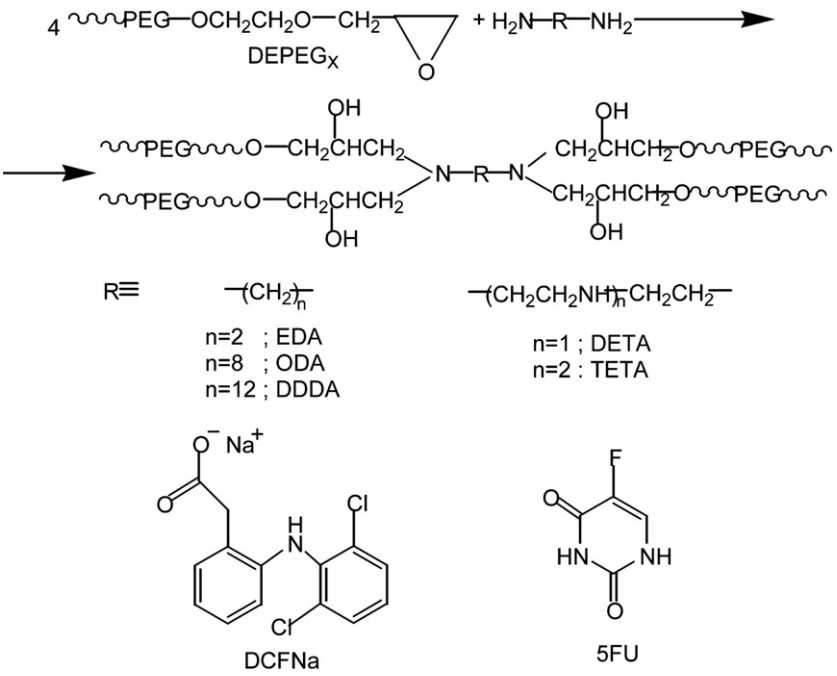

Scheme 1. Chemical structures of hydrogels and model drugs employed within this work.

MW of PEG precursors, hydrocarbon chain length and functionality of the polyamine, the amine hydrogen/epoxy groups ratio, as well as by employing mixtures of oligomers with different MWs or mixtures of polyamines with various functionalities. By modifying some of these experimental parameters, polymer networks with well-defined chemical structure and characteristics can be obtained, as far as the MW of the chains between the crosslinking points, crosslinking points functionality (crosslinking degree) and content of hydrophobic/hydrophilic groups are concerned, which allows for a more accurate assessment of the hydrogel network–drug interactions.

Two hydrophilic drugs, diclofenac sodium (DCFNa) and 5-fluorouracil (5FU) (Scheme 1), were used as model drugs, from which we expected to interact in a different manner with the DEPEG-amine hydrogels as a function of their structure. Thus, DCFNa is able to form hydrophobic interactions, through the two benzene rings contained, as well as hydrogen bonds by means of the amino and carboxylate groups. In addition to these, DCFNa may interact with the PEG chains through the formation of a crown ether-like complex [24–26]. This last interaction seems to be less studied from the point of view of its influence upon drug loading and release in the case of PEG hydrogels, as we were not able to find any references on this subject. As compared to DCFNa, the 5FU molecule is smaller, and, according to its chemical structure, a lower ability to form hydrophobic interactions, but increased capacity to form hydrogen bonds is expected. We will show in this report that some of these interactions, promoted more or less through modifications of the structure of the DEPEG — aliphatic polyamines hydrogels as far as PEG chain length, crosslinking degree and hydrophobic character of the polymer network are concerned, may display a major influence upon drug absorption and release process in comparison with others.

2. Experimental

2.1. Materials

α,ω-Dihydroxy-PEG_{600}, -PEG_{1000}, -PEG_{2000} and -PEG_{4000} ($DHPEG_X$, Fluka) were used as received. Diepoxy-terminated PEG ($DEPEG_X$) were synthesized through the reaction of the corresponding $DHPEG_X$ and epichlorohydrin as previously described [19,27]. Ethylenediamine (EDA, Scharlau, 99%), 1,8-octanediamine (ODA, Acros, 99%), 1,12-dodecanediamine (DDDA), diethylenetriamine (DETA, Alfa Aesar, 99%), triethylenetetramine (TETA, Fluka, 97%), and all the other reagents were used without further purification. Diclofenac sodium (DCFNa, Sigma) and 5-fluorouracil (5FU, Sigma, 99%) were used as received.

The phosphate buffer saline solution (PBS, pH 7.4) was prepared by dissolving 8 g NaCl, 0.2 g KCl, 0.24 g KH_2PO_4 and 3.6 g $Na_2HPO_4 \cdot 12H_2O$ in distilled water up to 1 L solution. The pH value was always checked by means of a calibrated Consort C830 pH-meter. After preparation, the PBS solution was stored in the refrigerator until use.

2.2. Synthesis of hydrogels

The hydrogels from $DEPEG_X$ and aliphatic polyamines were synthesized at equimolar epoxy groups/amine hydrogen atoms ratio as previously described [19,20]. Briefly, a 30 wt.% $DEPEG_X$ solution was prepared by dissolving 0.5 g oligomer into the appropriate amount of distilled water, followed by the addition of the calculated volume of the aqueous solution of the polyamine. In the case of DDDA, whose solubility in water is very low, a 75/25 v/v ethanol–water mixture was used as the solvent instead. After vigorous stirring, the reaction mixture was transferred into a 10 mm diameter glass tube, which was sealed and kept in an oil bath at 60 °C for 140 h. At the end of the reaction time, the tube was broken and the resulting hydrogel rod was cut into small disk-shape pieces 1.5–2 mm thick. The disks were then placed into excess distilled water for 7 days at room temperature. The water was changed daily in order to remove unreacted amine and oligomer. The swollen disks were dried in a desiccator over anhydrous $CaCl_2$ until constant weight was obtained. Before loading with the drug, the xerogel disks of about 6 mm diameter were polished to reach 1.00 ± 0.05 mm thickness and dried again in a vacuum oven over anhydrous $CaCl_2$ at room temperature for two days.

2.3. Drug loading

Incorporation of drugs within hydrogels was carried out by soaking a weighed xerogel disk (W_x) in about 2 mL drug solution (2 mL solvent + drug), at room temperature, for 48 h. A diluted aqueous ammonia solution (pH 7.5–8) was employed in the case of DCFNa, due to its lower solubility in the slightly acidic distilled water (pH ≈ 5.5), while