ENGINEERING OF DEXTRAN-BASED MATRICES FOR SOFT TISSUE REGENERATION

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Introduction

Dextran is a non-toxic, bacterial polysaccharide mainly composed of linear α-1-6,linked D-glucopyranose residuals with a low content of α-1-2, α-1-3 and α-1-4-linked side chains [1]. Its biocompatibility and biodegradability is well documented, thus dextran has been extensively explored in the field of biomaterials [2]. Dextran is able to decrease vascular thrombosis, reduce inflammatory response and promote vascularization, hence it is a promising candidate for soft tissue regeneration. This biopolymer has been clinically used for more than five decades as a plasma volume expander and nowadays its applications extend to new biomedical applications including hydrogel-like scaffolds for tissue engineering [2,3]. Particularly, dextran hydrogels have been investigated for applications as 3D scaffolds to support and promote regeneration of tissue, mainly due to their capacity to be designed to mimic the mechanical properties and water content of native tissues.

Chemical structure of dextran enables wide range of chemical modification. Incorporation of crosslinkable moieties (e.g. methacrylic groups, -MA) into dextran structure allows to obtain derivatives capable for crosslinking initiated by UV or ionizing radiation [4-6].

The radiation technique is very efficient and clean tool for modifying polymers. Unquestionable advantages of using radiation include possibility of processing materials in any physical state, at a convenient temperature (usually room temperature), typically with no need of application of additional chemicals, i.e. potentially toxic initiators or catalysts [7]. Moreover, if sufficient dose is applied (typically 25 kGy) sterilization can be accomplished simultaneously with the processing. In our recent study we have demonstrated possibility of radiation synthesis of hydrogels based on biocompatible dextran methacrylate (Dex-MA) [6].

The current work was aimed at synthesizing a dextran derivative having substituents capable of covalent crosslinking (Dex-MA – dextran methacrylate), and to develop conditions suitable for formation of macroscopic hydrogels using radiation technique.

Materials and Methods

Dextran derivatives have been synthesized using the procedure of van Dijk-Wolthuis by coupling glycidyl methacrylate with this polysaccharide, yielding Dex-MA of various degrees of methacrylate substitution (DS) [8]. Dextran (from *Leuconostoc ssp*., Mr = 25,000; 70,000 and 500,000) was purchased from Sigma-Aldrich (Canada), dimethyl sulfoxide (DMSO, 99.5%) and hydrochloric acid (HCl, 36-38%) were obtained from Chempur (Poland). Glycidyl methacrylate (GMA 97%, stabilized by 0.005% hydroquinone monomethylether) was purchased from Sigma Aldrich, 4-(*N,N*-dimethylamino)pyridine (DMAP) were obtained from Sigma Aldrich (USA). Synthesized dextran derivatives were characterized using FTIR and NMR spectroscopy. Dextran-based hydrogels were manufactured in aqueous solutions of Dex-MA through polymerization/crosslinking of methacrylic groups with radiation initiation. Aqueous solutions of 1, 2, 3 and 5% Dex-MA with different DS were prepared, saturated with argon and subsequently irradiated by electron beam (0.5 – 25 kGy). Following the irradiation, the samples of permanent chemical hydrogels underwent sol-gel analysis to determine equilibrium degree of swelling in deionized water (EDS) and gel fraction (GF). Moreover, for selected samples (3%, 25 kGy) cytotoxicity evaluation based on XTT test was performed. The targeted cells used were mouse fibroblasts L929 (European Collection of Authenticated Cell Cultures (ECACC)).

Results and Discussion

The main goal was detailed study on radiation-initiated synthesis of dextran-based hydrogels. Crosslinking of Dex-MA in aqueous solutions was found to be an efficient process yielding gels with high insoluble fraction content (up to 100 %). The equilibrium swelling encompasses a wide range of 20 – 120 g of water absorbed per g of dry crosslinked polymer. Based on collected data it can be concluded that the utility characteristics of hydrogels can be tailored by appropriate selection of parameters such as dextran's initial molecular weight, DS, concentration and irradiation conditions. Moreover, XTT tests have shown that cell viability maintained the level of positive controls for gels of Dex-MA of low DS, 0.15. Hydrogels manufactured from Dex-MA of the lower DS under applied experimental conditions have no negative impact on cell proliferation and viability, therefore can be regarded as non-cytotoxic.

Conclusions

In this work a series of Dex-MA was synthesized by reaction of the polysaccharide with GMA. Irradiation of aqueous solution of Dex-MA in absence of low-molecular-weight additives (crosslinkers) resulted in formation of permanent macroscopic hydrogels even at doses as low as 0.5 kGy. Thus, obtaining hydrogel of this natural polymer using ionizing radiation, i.e. crosslinking through unsaturated C=C bonds of -MA substituents, seems to be interesting alternative in comparison to other methods (chemical and UV-crosslinking). End-characteristics of hydrogels can be tailored by manipulation of crosslinking conditions. Moreover, lack of toxicity of synthesized hydrogels was proved. This, combined with well-known biological activity and functionality of dextran, implies possibility of biomedical applications of these dextran-based hydrogels, especially in the field of soft tissue regenerative medicine.

Acknowledgments

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