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# *In Vivo* Biocompatibility and Biodegradability of Dextrin-based Hydrogels

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**ABSTRACT:** The *in vivo* biocompatibility of dextrin hydrogels obtained by polymerization of dextrin-hydroxyethylmethacrylate (dextrin-HEMA) and dextrin-vinyl acrylate (dextrin-VA) are reported in this work. The histological analysis of subcutaneous implants of these hydrogels, featuring inflammatory and reabsorption events, were carried out over a 16-week period in mice. The dextrin-HEMA hydrogel was quickly and completely degraded and reabsorbed, whereas the dextrin-VA degradation occurred slowly and a thin fibrous capsule surrounded the nondegradable hydrogel. The dextrin-HEMA was degraded after 16 weeks with only mild inflammation and a few detectable foamy macrophages around the implant. These events were followed by complete resorption and no sign of capsule formation or fibrosis associated to the implants. The results indicate that the dextrin hydrogels are biocompatible because no toxicity on the tissues surrounding the implants was found. It may be speculated that a controlled degradation rate of the hydrogels may be obtained by grafting dextrin to HEMA and VA in different proportions.

**KEY WORDS:** hydrogels, dextrin, biocompatibility, degradability, HEMA, dextran-HEMA, dextran-vinyl acetate, *in vivo* assay.

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## INTRODUCTION

**H**ydrogels are water-swollen polymeric materials, with a stable 3D structure that provide scaffolds for tissue engineering and replacement, wound dressings, and drug delivery systems, among other applications [1]. They are also used to encapsulate cells that produce therapeutic agents, such as growth factors, to be released in the surrounding tissues [2–5]. Hydrogels must meet several strict requirements to be eligible for biomedical applications, such as biocompatibility, together with the nontoxicity of the leachable and degradation products. Therefore, a comprehensive characterization of the degradation processes and the biological effects of the by-products are crucial in determining the long-term success of a hydrogel application [6–9].

Natural polymers, modified using specific strategies, are an important source of hydrogel biomaterials [10–13]. We developed hydrogels made from dextrin, a polysaccharide obtained by partial hydrolysis of starch, composed of  $\alpha(1 \rightarrow 4)$  linked D-glucose residues [6,7]. It was found that the dextrin-based hydrogels have distinct degradation profiles, *in vitro*, depending on the acrylate ester used to functionalize the polysaccharide: dextrin-vinyl acrylate (VA) originates a nondegradable hydrogel, while polymerized dextrin-hydroxyethylmethacrylate (HEMA) is a degradable one [14]. Moreover, the degree of substitution (DS) of the polymer was shown to influence the degradation profile.

Although similar to previously developed dextran-VA and dextran-HEMA materials [10], the use of dextrin hydrogels represent, in our view, a better choice for biomedical applications. Dextrin is already used in clinical treatments, such as end-stage renal failure patients, peritoneal dialysis solution, and as a carrier for the anticancer agents [3,15–17] but is relatively unexploited in the biomaterials field. Dextrin presents excellent biocompatibility, nonimmunogenicity, and *in vivo* degradability by  $\alpha$ -amylases, yielding maltose and isomaltose. The molecular weight of dextrin is appropriate to ensure renal elimination, thus excludes the threat of progressive accumulation after repeated administration [2,17–19]. Due to the low molecular weight and readily degradation to glucose by the amylases present in the human fluids, it is expected to be completely metabolized or removed by renal filtration.

Biodegradability and resorption are highly desirable for tissue engineering and for other biomedical applications where a temporary use of a medical device is envisaged to avoid further surgery to extract it. Therefore, the degradation of the hydrogel used, under a set of conditions, must be thoroughly characterized to determine the suitability of the material for given bioapplications. In this work, the

*in vivo* biocompatibility and degradability of dextrin-HEMA and dextrin-VA are described.

## MATERIAL AND METHODS

### Reagents

Dextrin-Koldex 60 starch was a generous gift from Tate & Lyle (Decatur, IL, USA). All chemicals used in the preparation of the hydrogels, including VA, 2-HEMA, *N,N,N',N'*-tetramethylenediamine (TEMED), and ammonium persulfate (APS) were laboratory grade from Sigma-Aldrich, St. Louis, MO, USA.

### Animals

The *in vivo* biocompatibility studies were performed using male BALB/c mice (8 weeks old) purchased from Charles River (Barcelona, Spain). The animals were kept at the Institute Abel Salazar animal facilities during the experiments. All procedures involving the mice were performed according to the European Convention for the Protection of Vertebrate Animals used for Experimental and Scientific Purposes (ETS 123) and 86/609/EEC Directive and Portuguese Rules (DL 129/92).

### Preparation of Dextrin-based Hydrogels

The functionalization of the dextrin with VA and HEMA was achieved as described by Carvalho et al. [2,14]. Dextrin-VA and dextrin-HEMA monomers were synthesized in DMSO with specific amounts of dextrin and VA or HEMA monomers. The DS was determined by proton nuclear resonance spectroscopy ( $^1\text{H-NMR}$ ) in  $\text{D}_2\text{O}$  as previously described [2,14]. Hydrogels with different DS were prepared by radical polymerization of dextrin-VA (or dextrin-HEMA). For implantation, 300 mg of dextrin-VA (DS = 20 or 70) were dissolved in 1 mL of phosphate buffered saline (PBS); 30  $\mu\text{L}$  of this solution was cast into the circular discs (5 mm in diameter and 5 mm thick). After polymerization, by adding 3  $\mu\text{L}$  of TEMED (13.3%, v/v) and 3  $\mu\text{L}$  APS (80%, w/v) to the dextrin solution, the discs were transferred to an Eppendorf vial with PBS buffer and sterilized (121°C, 1 atm, 20 min). The dextrin-HEMA hydrogel with DS 20 was prepared using two concentrations, 300 and 150 mg/mL, respectively.

### **MALDI-TOF Analysis**

The molecular weight of the dextrin used in the hydrogel preparation was evaluated by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF), using a 4700 MALDI-TOF Proteomics Analyzer (Applied Biosystems) and a matrix of 2, 5-dihydroxybenzoic acid.

### **Cryo-SEM Analysis**

The cryo-scanning electron microscopy (cryo-SEM) analysis of the polymerized hydrogels was performed using a JEOL JSM 6301F/Oxford INCA Energy 350/Gatan Alto 2500, 15 kV, WD 15 mm.

### **Subcutaneous Implantation**

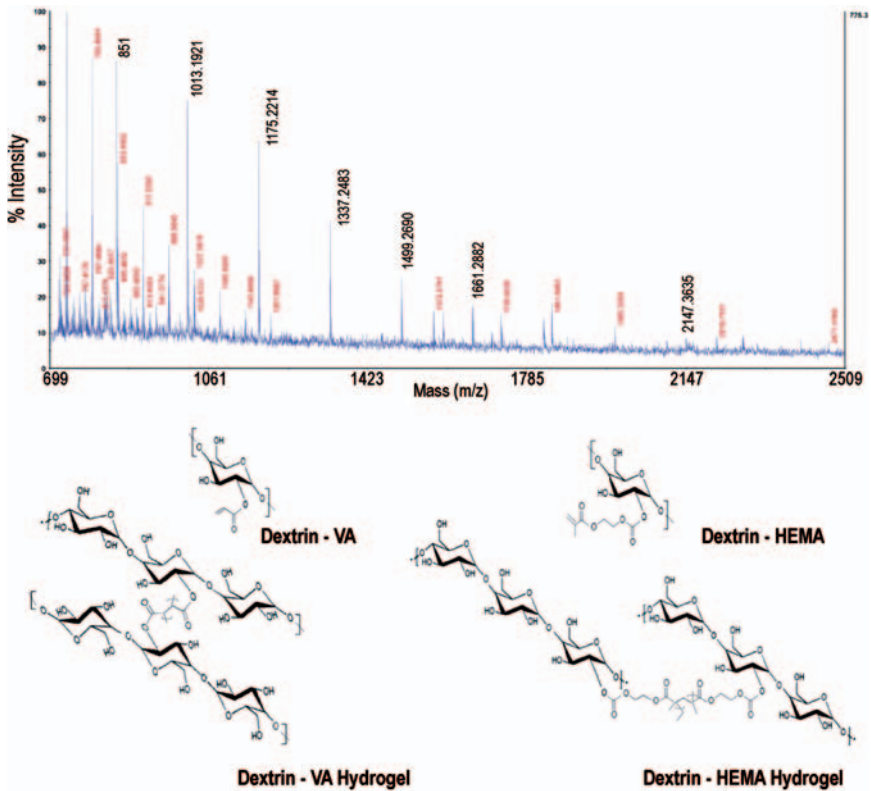
The hydrogels were surgically implanted subcutaneously in the backs of the mice with each mouse receiving two implants. The mice were anesthetized by an intramuscular injection of a ketamine (Imalgene 1000, Material) and Bompun 2% (Bayer Healthcare) mixture, at a 50 and 10 mg/kg dose, respectively. The hair was removed and two small incisions were made in the skin as bilateral subcutaneous pockets along the backbone and the hydrogel discs implanted and the incisions closed with stitches. The control animals received no implants. For each type of implant, two animals were used for each postimplantation period analyzed.

### **Histological Analysis**

Aspects of the wound and the presence of edema were observed before removing the implants. Two animals, each one containing two implants, were sacrificed sequentially at 1, 2, 4, 8, and 16 weeks after implantation. The implantation sites were completely excised for histological analysis. Samples were fixed in 10% neutral buffered formalin for 24 h and paraffin embedded. Sections 4- $\mu$ m thick were obtained and used for hematoxylin and eosin (H&E), Schiff's periodic acid (PAS), and Masson's trichrome stains. Slides were examined under a light microscope (Nikon E600), and photographs were obtained using a digital camera (Nikon DS-5M).

## RESULTS

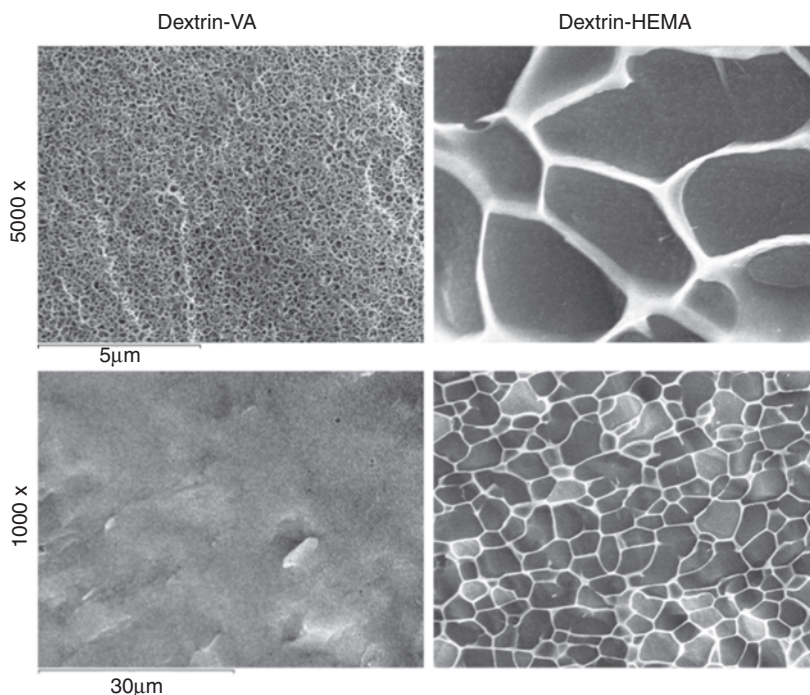
Previously, we have described the structure, rheology, and *in vitro* biocompatibility of dextrin hydrogels [2,14,19] and further characterization is provided in this work. The dextrin MALDI-TOF mass spectrum, the chemical structures of dextrin-VA, dextrin-HEMA, and the corresponding hydrogels are presented in Figure 1. MALDI-TOF analysis is not quantitative, the lower molecular weight oligomers producing a stronger signal. The dextrin mass spectrum data supports the gas chromatography methylation analysis that the polymer has very low molecular weight and is highly polydisperse. Peaks corresponding to a degree of polymerization up to 15 are detected, confirming the previously determined average degree of polymerization of 13. This is a



**Figure 1.** Dextrin MALDI-TOF mass spectra and chemical structure of dextrin substituted with VA or HEMA and its structure following polymerization.

relevant finding since the dextrin low molecular weight fractions are pertinent to the efficient clearance of the hydrogel degradation products.

In both cases, the polymer was functionalized by transesterification with acrylate esters to yield water-soluble functionalized dextrin-VA or dextrin-HEMA. Gelation was achieved by polymerizing the double bonds in the presence of TEMED and APS to form cross-links. Shown in Figure 1 is the schematic representation of the dextrin substituted with VA and HEMA as well as their structures after polymerization, based on the dextran-HEMA and dextran-VA structures previously reported [20–22]. The ester bonds obtained behaved differently; the VA cross-links were resistant to hydrolysis, while HEMA were hydrolysable in an enzyme-free system (shown elsewhere [14]). The structural patterns of the hydrogels, obtained by cryo-SEM analysis, are shown in Figure 2. The dextrin-VA and dextrin-HEMA hydrogels exhibited distinct porosities; the former was more compact and less porous for



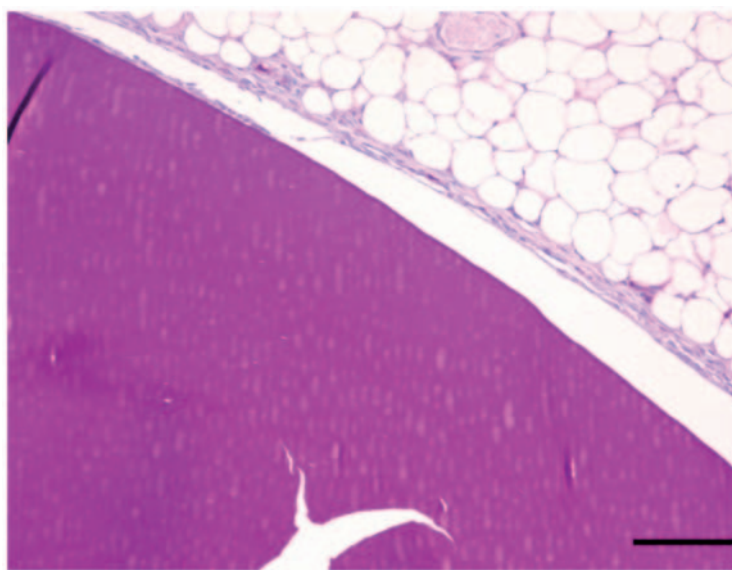
**Figure 2.** Cryo-SEM analysis of polymerized hydrogels: dextrin-VA and dextrin-HEMA (DS 20%, 300 mg/mL). Analysis performed at 15 kV; amplification: 5000 $\times$  and 1000 $\times$ .

the same DS (20%) and concentration (300 mg/mL). The hydrogels also presented distinct mechanical properties differences that were noticed by visual evaluation [14].

### **Dextrin-VA is a Nondegradable Hydrogel *In Vivo***

To evaluate the biocompatibility of dextrin-based hydrogels and its degradation behavior *in vivo*, BALB/c mice were implanted subcutaneously with dextrin-VA or dextrin-HEMA hydrogels. The implanted tissue was removed at specific times and histological analyses were carried out. After 1 week postimplantation, a mild to moderate subacute focal inflammatory response was observed at the surgical sites on both the control and implanted animals. Both groups showed marked vascular congestion and interstitial edema, with moderate infiltration of neutrophils, a few macrophages and lymphocytes, together with proliferation of fibroblastic and endothelial cells (Figure 3). This was interpreted as a reaction to surgical trauma rather than to the implants since both the treated and control animals responded similarly.

From 2 to 4 weeks postimplantation, the vascular phenomena decreased. Macrophages progressively became more predominant within the cellular infiltrate and concentrated around the implanted material.



**Figure 3.** DS 20 dextrin-VA implant, 1 week postimplantation. The implant (\*) is intact (PAS, bar = 50  $\mu$ m).



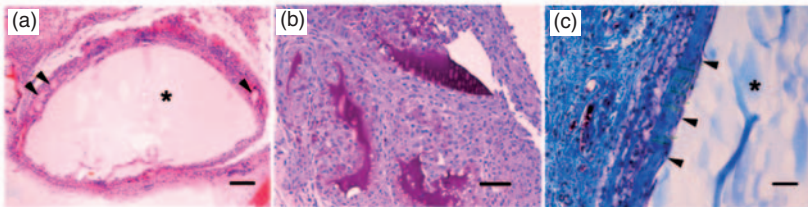
Some smaller hydrogel particles were observed to be surrounded by foamy macrophages, which showed moderate amounts of intracytoplasmic PAS-positive hydrogel material. This was more evident with the DS 20 hydrogels since these were softer and easily fragmented during surgery.

By week 16 postimplantation, the inflammatory reaction had subsided, with only a thin macrophagic ring surrounding the implants. Although small hydrogel fragments seemed to be amenable to phagocytosis, the main bulk of the implants showed no signs of resorption (Figure 4(a) and (b)). Using Masson's trichrome stain, thin fibrous capsules were observed at 16 weeks postimplantation around both DS 20 ( $30.78 \pm 1.79 \mu\text{m}$ ) and DS 70 ( $34.78 \pm 2.64 \mu\text{m}$ ) implants (Figure 4(c)).

### Dextrin-HEMA is a Degradable Hydrogel *In Vivo*

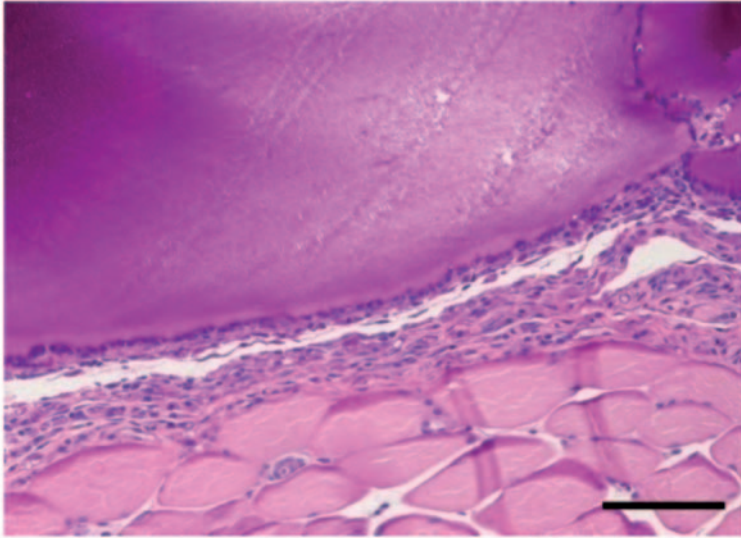
After 1 week postimplantation, the control animals showed identical changes to those described for dextrin-VA, while the dextrin-HEMA implanted animals presented a moderate to intense subacute inflammatory response, focused around the implanted material. There was moderate vascular congestion and mild interstitial edema, with moderate to intense, mixed infiltration of neutrophils and less macrophages. Both 150 and 300 mg/mL implants showed mild signs of resorption, with a few foamy macrophages exhibiting intracytoplasmic PAS-positive material (Figure 5).

From week 2 to 4, the number of neutrophils progressively decreased and foamy macrophages became largely predominant. At week 4, there were no signs of extracellular 150 mg/mL material left, but variably sized

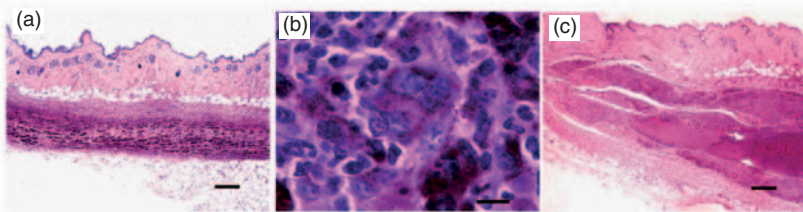


**Figure 4.** DS 20 dextrin-VA implant, 16 weeks postimplantation. The implant (\*) is generally intact. (a) Note a ring of macrophages around the implant and a few scattered fragments (arrows) in its vicinity (H&E, bar =  $200 \mu\text{m}$ ); (b) Small DS 20 dextrin-VA fragments surrounded by numerous macrophages showing small amounts of intracytoplasmic PAS-positive material (PAS, bar =  $50 \mu\text{m}$ ); (c) The implant (\*) is surrounded by a fibrous capsule (arrows), showing five consecutive measurements (Masson's trichrome stain, bar =  $20 \mu\text{m}$ ).

accumulations of foamy macrophages laden with PAS-positive material were present, forming a subdermal band (Figure 6(a) and (b)). Fragments of the 300 mg/mL implants were still partially visible (Figure 6(c)). By week 8 postimplantation, both groups already showed complete implant resorption and neither group presented any signs of capsule formation or, indeed, fibrosis associated with the implants (data not shown).



**Figure 5.** Dextrin-HEMA 300 mg/mL implant, 1 week postimplantation. The implant is generally intact and surrounded by macrophages with PAS-positive material (PAS, bar = 10  $\mu$ m).



**Figure 6.** Dextrin-HEMA (a, b) 150 mg/mL, and (c) 300 mg/mL implant, 4 weeks postimplantation. (a) There are no visible extracellular fragments of the implant. Numerous macrophages containing abundant intracellular PAS-positive material form a subdermal band located at the implantation site (PAS, bar = 200  $\mu$ m); (b) Variably abundant, intracytoplasmic, globular, PAS-positive material is present in macrophages (PAS, bar = 10  $\mu$ m); (c) Large, extracellular implant fragments remain in the deep dermis, surrounded by a thick macrophagic ring (PAS, bar = 200  $\mu$ m).

## DISCUSSION

The results obtained with dextrin-VA hydrogels indicate its apparent nondegradability *in vivo*, irrespective of the DS of the polymer used. This hydrogel was rendered degradable *in vitro* by the incorporation of amylase, which proved to be effective in modulating the gel degradation and release of entrapped molecules [18]. However, *in vivo* insignificant degradation was observed for the dextrin-VA hydrogels, as described for dextran-MA (methacrylated) hydrogels [10]. In the vicinity of the implanted DS 20 hydrogel, some macrophages, positively stained with PAS, were observed; however, the bulk material remained intact. This suggests that, while the smaller hydrogel fragments (probably from mechanical fragmentation during implantation) were being reabsorbed, the hydrogel was basically nondegradable. Similar findings were described for dextran-MA hydrogels [10,23].

Due to its high stiffness, the dextrin-VA DS 70 hydrogel implants were always damaged during the process of inclusion for histological analysis. Nevertheless, fibrous capsules were identified at the implant site. By week 16, after implantation, only a thin macrophagic ring surrounding the implants was observed together with the fibrous capsule. Since the material did not induce detectable necrosis, immunotoxicity, or damage to muscle tissue, the dextrin-VA hydrogels presented biocompatible behavior *in vivo* [24].

The dextrin-HEMA was previously shown to be degradable *in vitro*, in PBS, with rate depending on the polymer DS [14]. Similar to dextrin-VA, the dextrin-HEMA hydrogels presented biocompatible behavior. The histological analysis after 1 week postimplantation, inflammatory responses due to implantation, macrophages were observed indicating resorption, which increased during the time course of the experiment, with complete degradation at week 4 postimplantation, for the 150 mg/mL hydrogels. The 300 mg/mL hydrogel required more time for complete resorption; thus, the degradation rate is controllable by appropriate selection of the polymer concentration.

## CONCLUSIONS

The *in vivo* biocompatibility of dextrin hydrogels obtained by polymerization of dextrin-HEMA and dextrin-VA were evaluated. Both presented biocompatible behavior, as none induced necrosis, immunotoxicity, or damage to muscle tissue. Thus, both can be used in different applications and their degradation profile can be controlled by selecting

the polymer DS and its concentration. Based on these results, dextrin hydrogels with mixed reticulation chemistry, such as HEMA or VA in different proportions, may be used to fine-tune degradation rates.

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