Biocompatibility and Biodegradation of NovoSorb™ Biodegradable Polyurethanes

Adhikari, R , Mayadunne RTA, Houshyar S, Hanu L, Field JR*, McGee M*, Werkmeister J, Wickramarathna M, Menzis D, Moore T, Griffiths IM, Gunatillake PA PolyNovo Biomaterials Pty Ltd, Bag 10, Clayton South, Victoria 3168, Australia. * Orthopeadic Unit, Repatriation General Hospital, Flinders University of South Australia

Introduction

The interest in polyurethanes for biomedical applications is due to their excellent mechanical properties, good biocompatibility and structural versatility in tailoring polymer structure to meet the needs of many biomedical applications. We have developed a family of biodegradable polyurethanes (NovoSorb™) with properties suitable for implants and tissue engineered products and therapies in orthopaedic, and cardiovascular applications. NovoSorb™ can be formulated as *in-situ* curable (ISC) or cure on demand (COD) gels[1]. Biodegradable polymers that can be formulated as injectable liquids and cured *in-situ* to form high strength solid materials have a number of advantages over those currently used. A key advantage is arthroscopic delivery to the defect site. This paper reports on the *in-vivo* evaluation of biocompatibility and biodegradation of injectable and pre–cured NovoSorb™ polymers formulated for orthopaedic applications.

Experimental

Ten formulations, five each from ISC (P1 to P5) and COD (P6 to P10) methods were investigated. ISC polymers were prepared by reacting two prepolymers (A and B). ISC polymers were prepared by reacting two prepolymers with stannous octoate as catalyst. A was prepared from pentaerythritol (PE) and ethyl 2,6-diisocyanatohexane (ELDI) and B was a mixture of polyols PEDLLA (PE and l-lactic acid) and PEGA (PE & glycolic acid). The polyols PEDLLA and PEGA were prepared by acid-catalysed condensation polymerisation. P1, P2, P6, P7 were injectable polymers. Polymers P3 and P4 were porous cylindrical solids with and without β-tri-calcium phosphate (5 μm), respectively. And P5 was based on PELLA-ELDI as prepolymer A. COD polymers were based on isocyanatoethylmethacrylate (IEM) functionalized four-arm star polyols prepared from glycolic acid, l-lactic acid and PE. COD polymers P8 and P9 were porous cylindrical solids with and without β-tri-calcium phosphate, respectively. P10 was based on a terpolymer polyol of PE, l-lactic acid, GA and caprolactone.

A bilateral sheep model was used in the study. Six implant sites per femur (3 cortical and 3 cancellous regions) were created using a electric drill. Precured polymer plugs were implanted as solid cylindrical plugs (6mm D x12mmL) [Figure 1(a)]. Injectable polymers were delivered into the sites by a syringe and allowed to cure in-situ over 10-15 minutes. COD gels were cured for 2 minutes using a light source (Elipar™ FreeLight 2). Flurochrome dyes were injected at 1, 2 and 3 weeks prior to sacrifice to assess bone apposition. Femurs were retrieved at 6, 12 and 24 weeks postoperatively. Untreated drill sites, Purasorb™ and PMMA bone cement were used as controls in the study.

Results and Discussion

The mechanical properties of the pre-cured polymers were reported previously[2]. The porosity of solids formed by ISC injectable gels was on average 60%, whereas that for COD was 30%. In the former case porosity was achieved by carbon dioxide released during curing, and in the latter water used as porogen created porosity.

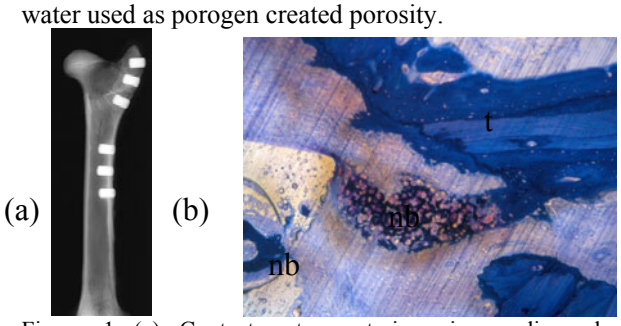

Figure 1 (a) Contact anteroposterior view radiograph of retrieved femur showing location of implants (b) Photomicrograph of ground section of longitudinal section of P8 plug six weeks after implantation showing new bone (nb) formation extending from thickened trabeculae (t) to the plug (p) interface and new bone formed within the plug composite (100x mag, tol blue stain).

At the 6 and 12 week time points, no adverse tissue reaction to the polymers was noted histologically. Implants were covered with surrounding new bone with no evidence of polymer degradation in bone sites but there had been break down in intramedullary sites. Fluorescent microscopy demonstrated new bone formation within the plug sites and at the plug-bone interface in cortical and cancellous bone sites as early as three weeks post-implantation. New bone formation continued to occur at later time periods up to 11 weeks. Purasorb™ control which is a copolymer of glycolic and lactic acid had completely degraded at 6 week time point, and had been partially or completely replaced by new bone within cortical sites. Figure 1 (b) illustrates new bone formation within the porous scaffold and at the cancellous bone-plug interface of COD polymer P8. Evaluation of explanted polymers after 6 and 12 weeks will be presented including histology results.

Conclusions

Preliminary histological evaluation of NovoSorb samples has shown no adverse tissue reactions to the biomaterials after 6 and 12 weeks implantation suggesting biocompatibility of NovoSorb in both injectable and prefabricated solid form in this sheep implant study.

References

1. (a) Gunatillake PA and Adhikari R. Int. PCT Application PCT/AU03/00935 (b) 7th World Biomaterial Congress, Sydney May 2004, p703.
2. Adhikari R, Gunatillake, Mayadunne RTA, et al, Proceedings 30th Annual meeting, Society For Biomaterials, Memphis, TN. USA, 2005, p442.