Effect of Zwitterion Concentration on the Biocompatibility of Perfluoropolyethers implants

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Introduction: A significant proportion of the world's population have a vision disability. Whilst spectacles and contact lenses provide a functional solution to this problem, many people would prefer a permanent and convenient means of correcting refractive error. A biocompatible and biostable synthetic lens implanted within the cornea (corneal inlay) may alter the curvature of the cornea and thereby correct for refractive error.[1].

Perfluoropolyether (PFPE) polymers are good candidate materials for ophthalmic implants since they are non-cytotoxic, biocompatible, biostable and transparent.[2] PFPE implants have previously shown their utility as ophthalmic implants *in vivo.*[3] However, these implants lost some optical clarity due to fouling of the membranes. Here we report on the effect of zwitterion comonomer concentration to reduce fouling, the characterisation of the resulting polymers and data from the testing of the improved PFPE formulation in both *in vitro* and *in vivo*.

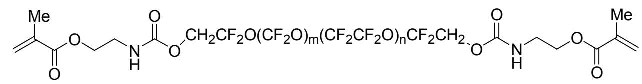
Materials and Methods: PFPE porous membranes were prepared by photo-copolymerisation of the PFPE macromonomer (1) with a zwitterionic comonomer ([2-(methacryloyloxy)ethyl]diethyl-(3-sulfopropyl)-ammonium hydroxide, inner salt) (2) dispersed in a microemulsion.[4] PFPE membranes were surface modified with collagen as previously reported.[5]

Equilibrium water content (EWC), permeability and modulus measurements were recorded as previously reported.[6] Optical haze was measured using a Gardner PG5500 photometric unit. Cell growth inhibition, bovine corneal epithelial cell and tissue assays were performed as previously reported.[7] AFM analyses were performed on a Digital Instruments Nanoscope III in tapping mode. Scanning electron micrographs of platinum coated membranes were made on a Phillips XL-30 SEM.

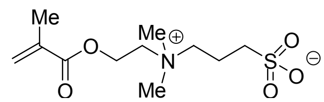
PFPE polymers were evaluated *in vivo* by implantation of lenticules in rabbits under a corneal flap generated by a microkeratome incision of the stroma (inlay surgical model).[8] Optical clarity of all corneas was evaluated using back scattering under slit-lamp biomicroscopy.

Results and Discussion: In an attempt to improve biocompatibility of the PFPE polymers the zwitterionic monomer (2) was copolymerized with the PFPE macromonomer (1) in varying ratios (2 to 40%). The influence of zwitterionic comonomer on the physical characteristics was analysed. Typically optically clear membranes were prepared having EWC between 20% and 80%. The membranes were permeable to bovine serum albumin. The level of porogen in the formulation had more effect on EWC and permeability of the membranes than the level of zwitterionic comonomer.

The zwitterionic PFPE comonomer materials were found to be non-cytotoxic. However, materials with high levels of zwitteronic comonomer (>7%) were found to be poor supporters of cell and tissue growth. The inhibitory effect *in vitro* of high zwitterion comonomer levels could be overcome by covalent attachment of collagen.



PFPE Macromonomer (1)



Zwitterionic Monomer (2)

Unlike typical hydrogels, PFPEs are hydrophobic having sessile contact angles greater than 90^o and are hydrated from the anhydrous state by a gradient exchange from 100% ethanol to 100% water. PFPEs prepared with high zwitterionic comonomer levels have hydrogel-like properties and can be hydrated quickly by simply placing them in water.

Long term implantation of these materials within rabbit cornea using an inlay surgical model was used to evaluate the materials. PFPEs containing high zwitterion concentration maintained optical clarity (90 to 100% clarity by backscatter) *in vivo* for 12 months compared to those with low concentration (80-95% clarity by backscatter).

Conclusion: New PFPE polymers with a variety of zwitterion concentration were prepared which have hydrogel-like properties. The polymer was not cytotoxic but at high zwitterion content does not support epithelial cell attachment and growth or corneal tissue migration. The higher levels of zwitterionic comonomer were shown to reduce fouling of the membrane *in vivo* compared to low concentrations. Hydrogel-like PFPE membranes are promising candidates for corneal inlay applications.

References

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