Controlled Release of Drugs from Multi-Component Biomaterials: drug release and mechanical properties studies

M. Alexandre[1], A. Zalfen[1], R. Riva[1], D. Nizet[2], B. Evrard[2], C. Jérôme[1]

[1]Center for Education and Research on Macromolecules, University of Liège, Liège 4000, Belgium; [2] Laboratory of Pharmaceutical Technology, Institut de Pharmacie, University of Liège, Liège 4000, Belgium
michael.alexandre@ulg.ac.be

ABSTRACT SUMMARY

Drug encapsulation into systems able to deliver at a certain site a given amount of drug over well defined periods is used for controlling the drug release. By encapsulating drugs in biodegradable polymeric microspheres, which in turn are embedded in a hydrogel body, several release mechanisms contribute to the tuning of the release profile of the drug. Mixed hydrogels, consisting of random copolymers of 2-hydroxyethyl methacrylate (HEMA) and methyl methacrylate (MMA) cross-linked by ethyleneglycol dimethacrylate (EGDMA), were chosen to serve as body of the device. Biodegradable poly-ε-caprolactone (PCL) microspheres, in which drugs such as levonorgestrel (LNG) were encapsulated, were physically embedded into hydrogels. The *hydrogel-microspheres* composites has been characterised in terms of water swelling and tensile properties. The release profile of the developed multi-component drug delivery biomaterial will be discussed.

INTRODUCTION

Controlled release systems based on microspheres are extensively studied drug delivery systems, due to their ability to maintain optimal drug concentration over a prolonged time, to protect and stabilize the drug and increase the patient compliance by reducing the administration frequency. Poly-ε-caprolactone (PCL) is one of the widely used biodegradable and biocompatible aliphatic polyester, having semicrystalline structure and a very low glass transition (-60 °C). Compared to other polymers, degradation of PCL is slow making it suitable for long-term delivery; due to its good drug permeability and biocompatibility, PCL microspheres including drugs dispersed in the polymer matrix have been extensively evaluated for the delivery of active compounds over long periods [1].

Hydrogels are polymers in three-dimensional network arrangements that are insoluble, but able to absorb and retain large amounts of water. In comparison with other synthetic biomaterials, hydrogels closely resemble natural tissues due to their relatively high water content and soft and rubbery consistency, being therefore frequently used for biomedical and pharmaceutical applications. The release of the drug from hydrogel controlled release systems is affected by the rate of water (body fluids) diffusion into the polymer, which in turn depends on the chemical structure of the polymer (polarity of the polymer segments, glass transition temperature, flexibility of the polymer backbone) and on the cross-link density and inter-chain interactions. The physico-chemical properties of the incorporated drug (size, shape, hydrophilicity) and the loading levels have an important contribution to the drug release from these systems [2]. Poly(2-hydroxyethyl methacrylate) (pHEMA) - based hydrogels have been investigated for several biomedical applications, such as substrates for cellular and tissue engineering and drug delivery devices, thanks to their ascertained non-toxicity and widespread use as soft contact lenses and intraocular lenses.

By embedding microspheres containing drugs into hydrogels, two different release mechanisms can be combined [3]: diffusion through the polymeric matrix for the microcarriers and diffusion through the hydrophilic matrix for the hydrogel. Combining hydrogels and microspheres lead to composites with unique release characteristics, whose mechanical properties could markedly differ from the properties of the initial hydrogel, affecting therefore the ability of the developed device to be used as an implant. For altering the mechanical properties of a hydrogel, the easiest way is to change the relative amounts of physically stronger co-monomer(s) - thus modifying the stiffness of the backbone polymer or its hydrophilicity - and cross-linking agents – changing the cross-linking density of the polymer network. Changes in the polymer will affect not only the mechanical properties, but also other behaviour of the material as well.

The softness, flexibility and mechanical integrity of drug delivery devices based on non-biodegradable materials used as implantable systems, which can be inserted and withdrawn on request, are of major importance with regard to the implantation issue.

EXPERIMENTAL METHODS

Hydrogels synthesis

After removal of dissolved oxygen – by nitrogen bubbling for 5 min - from monomer mixtures composed of HEMA and MMA, and containing 0.1 – 0.5% (w/w) EGDMA, into some monomer mixtures either LNG was added, or PCL microspheres (with drug or drug-free) were dispersed. Subsequently, the organic phases were mixed in reagent glasses in a ratio of 3:1 with aqueous solutions of redox initiators (6.4 mg $K_2S_2O_8$ and 3.2 mg $Na_2S_2O_5$ / ml water). The nitrogen bubbling continued for another 15 minutes, then the reagent glasses were closed and left under the nitrogen blanket at room temperature until the gelation of the reaction mass was visible. Subsequently, the viscous liquid was stirred to achieve uniform composition and was either aspirated into one-way plastic syringes or moulded between two glass plates spaced at

approximately 1 mm distance with a rubber spacer, and let to polymerise overnight at room temperature.
The hydrogel rods or membranes respectively obtained were washed for at least five days with distilled water, with daily water changes, to eliminate the unreacted monomer, and were stored in distilled water.

Swelling behaviour

Freeze-dried rods of pHEMA-based hydrogels were immersed in distilled water at room temperature. At certain time intervals, the hydrogel pieces were extracted from the water, blotted dry with paper towel and weighed.

Tensile measurements

Specimens were cut from every pHEMA-based hydrogel membrane in a dumbbell shape with a custom-made steel knife. The dimensions of the swollen samples were L = 40 mm and w = 4 mm, with variable thicknesses as a function of the spacer thickness and hydrogel composition. Hydrated grease-covered samples were mounted on the Instron equipped with a 10 N load cell, and a pretension of 0.2 N was applied at a rate of the cross-head displacement of 20 mm / min. During the measurements, a constant displacement of the cross-head of 10 mm / min was used. The rate of displacement produced fracture in the specimen within 1/2 to 5 min of test initiation, as suggested by ASTM D 638-99.

RESULTS AND DISCUSSION

Different hydrogel formulations manifested different swelling ratios and tensile parameters, as a function of their hydrophobic co-monomer and cross-linker content. The elasticity modulus strongly increased with the increase of the cross-linker content, but this component brought about also the side effect of increased brittleness.

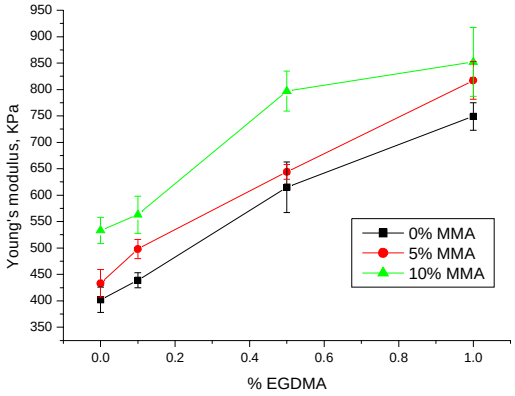

Figure 1. Young's modulus values for pHEMA-based hydrogel membranes with different compositions

As shown in Figure 1, The increase of the hydrophobic co-monomer content lead to an increase of the elasticity modulus and to an improvement of the parameters at break (not shown). Embedding microspheres into the hydrogel – for a certain loading range - did not negatively influence the tensile parameters of the materials; on the contrary, a slight increase of the elasticity modulus was registered. The increase of MMA content lead, as expected, to a progressively slow down of LNG diffusion through pre-formed hydrogel membranes; the LNG release out of hydrogel devices with dissolved drug was influenced mainly during the first release days, but was relatively similar for the following release stage.
Drug-loaded PCL microspheres, dispersed in a pHEMA-based hydrogel, form composites where the hydrogel is not only a physical support for the drug loaded microspheres, but it also acts as an additional diffusion barrier. This ability of the hydrogel could be further developed by performing the polymerisation of the HEMA with a hydrophobic co-monomer, such as MMA. Potential applications of this drug delivery system could be found in the design of implantable devices with long-term activity as required by contraceptive and hormone replacement treatments.

CONCLUSION

The developed multi-component material has the ability to preserve in a high degree the mechanical properties characteristics for hydrogels upon embedding the microspheres into the hydrogel body, allowing their use as implantable drug delivery devices. These multi-component devices are of particular interest in drug eluting implants used for contraception or for hormone replacement treatments.

REFERENCES

1. Buntner, B., et al., *The application of microspheres from the copolymers of lactide and e-caprolactone to the controlled release of steroids.* Journal of Controlled Release, 1998. 56: p. 159-167.
2. Hill, D.J.T., et al., *Copolymer hydrogels of 2-hydroxyethyl methacrylate with n-butyl methacrylate and cyclohexyl methacrylate: synthesis, characterization and uptake of water.* Polymer, 2000. 41: p. 1287-1296.
3. Zalfen, A.M., et al., *Controlled release of drugs from multi-component biomaterials.* Acta Biomaterialia. 2008, 4 (6), 1788-1796

ACKNOWLEDGMENTS

The authors wish to thank to the Walloon Region for the financial support accorded in the framework of the IMPUT, IMPEIOSE project through the DGO6. CERM is also grateful to the “Interuniversity Attraction Poles: Functional Supramolecular Systems (FS2)” (IAP 6/27).