Engineering the Performance of Biomaterials through Understanding and Optimisation of Their Viscoelastic Properties

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ABSTRACT

Biomaterials are materials that are employed to replace or enhance a bodily function and, as such, are commonly used in modern medicine. The performance of these systems is directly related to their viscoelastic properties. This paper provides an overview of the importance of such properties and how they may be manipulated to achieve optimal performance.

INTRODUCTION

In recent years medicine has benefited from the use of polymeric-based biomaterials, e.g. as medical devices/artificial organs, implantable drug delivery systems and biosensors. The importance of biomaterials in clinical medicine cannot be ignored and indeed, it has been reported that "ultimately, almost every human in technologically advanced societies will host a biomaterial". Unfortunately, the design of many clinical biomaterials is inadequate and limitations associated with their use have been reported[1].

The design of medical devices/bioactive implants/drug delivery systems is performed according to key product requirements. For example, in the design of medical devices, the ability to undergo stresses in situ and maintain structural integrity is vital to their performance. Similarly the mechanical/rheological properties of coatings for medical devices directly affect key properties including, lubricity, encrustation and drug release[2].

The rheological properties of drug delivery systems (particularly those designed as implants) are key to their subsequent clinical (and indeed non-clinical) performance. Examples of properties that are directly consequences of the rheological properties include ease of spreading to and retention at the site of application, removal from the container, drug release kinetics and the resistance to removal from the site of application following dilution with body fluids. Therefore, when designing such systems, consideration of these properties is essential to the development of biomaterials that exhibit optimal in vitro and in vivo performance

EXAMPLES OF THE IMPORTANCE OF RHEOLOGICAL PROPERTIES TO BIOMATERIAL PERFORMANCE

This paper will use a series of examples to highlight the importance of rheological properties on biomaterial performance.

Bioadhesive drug delivery systems designed for the treatment of local disorders

Periodontal disease is an inflammatory disease of the oral cavity that affects the supporting structures of the teeth and which

if left untreated results in tooth loss[3-5]. Treatments involve the use of implantable drug delivery systems within the periodontal pocket (the space formed between the tooth and the gingiva) to eradicate the pathogenic microorganisms that have colonised this environment. Ideally, the implantable drug delivery system should offer key rheological properties, notably ease of administration and retention within the pocket for a period to offer controlled release of the antimicrobial agent at the required rate and for the required period. One strategy that may be employed to achieve these aims is by the use of bioadhesive, interactive polymer blends[4, 6-8]. In this strategy, a primary network is established through polymer-polymer (hydroxyethylcellulose-polyvinylpyrrolidone) interactions following which the strongly bioadhesive polymer and antimicrobial agent are dispersed. Using this approach the flow and viscoelastic properties may be engineered to meet the specific clinical demands. Correlations have been observed between the elasticity, bioadhesive properties, drug release and retention time in vivo. Conversely, the work of syringeability and elasticity were inversely related. Selection of formulations for clinical evaluation was performed based on a compromise between these positively and negatively correlated parameters. Clinically, the optimised formulation successfully resolved the pathogenic microorganisms (enabling a return to the normal microbiological ecology) and a reduction in the depth of the periodontal pocket: all indicators of clinical improvement[4, 8].

Despite the clinical efficacy of these systems, the required compromise between formulations that offer ease of administration and those that offer optimal retention/drug release properties restricts their clinical utility and application to the treatment of other conditions, e.g. other conditions within the oral cavity, vaginal drug delivery. Therefore to address this imbalance, newer interactive platforms have been developed that are non-aqueous with primarily Newtonian flow properties but undergo rheological structuring in the presence of biological fluids. Examples of the systems under consideration include Tetronic/poly(acrylic acid) dispersions[9] and other surfactant/bioadhesive polymeric systems that undergo a phase transition in the presence of body fluids. Following the ingress of moisture these platforms become highly elastic (high G', low loss tangent) and, in this state, offer high retention and controlled drug release properties.

Of great importance to the clinical performance of such systems is their resistance to rheological destructuring upon dilution with body fluids. To understand this process, a creep model has been developed in which a residence time, based on the time for the system to enter the terminal Newtonian region of the creep curve was constructed. Following validation using the reported retention times for commercial formulations, this approach may be successfully used to predict in situ retention. This model is under subsequent evaluation to understand retention in a range of body cavities, notably the periodontal pocket, the vagina and the oral cavity.

Optimisation of rheological properties of medical devices

As previously detailed, medical devices are frequently used to replace a mechanical function, e.g. to facilitate fluid flow and, as a result, their rheological/mechanical properties are of great importance. One concern regarding the use of medical devices is the subsequent morbidity and mortality associated with medical device related infection. Therefore, there have been considerable efforts to design systems that exhibit resistance to this phenomenon. One approach involves the use of bioactive platforms, in which there is controlled release or stimulus responsive release of antimicrobial agents. The traditional

incorporation of antimicrobial agents into medical device biomaterials, whilst seeming obvious, has not been successful due to problems associated with inappropriate release properties and, in addition, the effects of the incorporated drug on the mechanical properties. For example we have shown that the incorporation of hexetidine, a model antimicrobial agent, into endotracheal tube PVC may reduced the incidence of microbial colonisation on this material however the elastic modulus of such systems is inappropriate for clinical use[10].

Due to their biocompatibility, hydrogels have been frequently used as medical device biomaterials[11] however, their use as bioactive platforms is compromised by the associated relatively rapid release, which in turn renders their use only suitable for short term implantation, e.g. contact lenses. To overcome this problem, we have designed rheologically structured hydrogel systems based on interpenetrating network systems. Examples of these include poly(methylmethacrylate)/poly(hydroxyethylmethacrylate) networks, poly(caprolactone)/poly(hydroxyethylmethacrylate) networks. More recently we have designed thermoresponsive networks that allow drug to be absorbed into the polymer matrix at temperatures below the sol-gel transition temperature (Tm). Raising the temperature above the Tm may then be effectively used to release drug in a stimulus responsive manner directly to the surface of the device. The rheological properties of these materials both before and after the Tm are of great significance to the resulting drug release and mechanical properties. This particular application has shown great promise for the treatment of ventilator-associated pneumonia in association with conventional treatments, e.g. nebulisation with gentamicin

CONCLUSIONS

The mechanical and rheological properties of biomaterials are essential determinants of their performance (both in vitro and in vivo). To optimise biomaterial performance it is essential that due consideration of these properties is given. In so doing these systems may be rationally designed and engineered to provide the appropriate physicochemical and biological properties.

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