Composition–Property Relationships of Chitosan-Egg Phosphatidylcholine Films For Use in Drug Delivery

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Statement of Purpose: In this study, relationships were established between the composition and properties for films composed of a hybrid mixture of polymer and lipid. Specifically, the ratio of the polysaccharide chitosan and the lipid egg phosphatidylcholine (ePC) was related to the stability, morphology, thermal and mechanical properties of the blends. These relationships can be used to tailor the biological performance of the chitosan-ePC system for use in drug delivery. Previous studies have demonstrated the film is a biocompatible, biodegradable implant and provides sustained release of the hydrophobic anticancer agent, paclitaxel [1,2].

Methods: Films were prepared by blending a 2% solution of 85% deacetylated chitosan of medium molecular weight (purchased from Fluka BioChemika, Buchs, Switzerland) with ePC (obtained from Northern Lipids Inc. British Columbia, Canada). The ratio of chitosan to ePC investigated in this study varied from 1 : 0.2 to 1 : 2.5 (wt/wt). The solutions were poured into teflon-coated dishes and dried in a dessicator for five days. Thermal analysis of chitosan, ePC and chitosan-ePC blends were evaluated using a DSC Q100 system (TA instruments, USA). X-ray diffraction patterns were obtained using a Siemens D5000 2diffractometer with Cu-Kα source operating at 50 kV, 35 mA. The morphology of the chitosan-ePC films were imaged on a Zeiss LSM 510 laser scanning fluorescence confocal microscope (Zeiss, Germany). The storage moduli of the chitosan-ePC films were measured with a DMA Q800 V3.13 (TA Instruments, USA). The mechanical response of dry and wet chitosan-ePC films at high deformations was measured using a universal Instron testing apparatus according to the ASTM D638 protocol. Finally, the percent weight loss of the chitosan-ePC films were evaluated over a six week incubation period in a 0.01M phosphate buffer solution containing 10% fetal bovine serum at 37 ˚C.

Results / Discussion: The relationships between composition and properties of chitosan-ePC blends were evaluated by various methods. Thermal analysis of the chitosan-ePC films revealed that chitosan caused the main endothermic peak for ePC to split into two components that were higher and lower in temperature in comparison to the T_m for pure ePC. Furthermore, the average transition temperatures for the two components were found to shift with a change in the relative ratio of ePC to chitosan. The change in the T_m values for the lipids may be attributed to an interaction between the chitosan and lipid components of the blends. X-ray diffraction analysis demonstrated that domains of lipid and lipid-lipid interactions are present within the chitosan-ePC films. In addition, it appears that components of the lipid are organized into lamellar like structures within the blend. The thermal and X-ray diffraction analyses provided an understanding of the microdomain morphology that was visualized by confocal microscopy. For the 1 : 0.2 (wt/wt) chitosan-ePC film, the lipid was present in irregularly shaped domains that were dispersed throughout the film. At higher lipid concentrations, the lipid was aggregated and assembled in circular or spiral shaped domains that were also dispersed throughout the film. The size of the microdomains varied from 1 to 30 µm depending on the amount of lipid within the blend. The composition of the film was also related to the mechanical properties of the blend. For example, the storage modulus decreased as the amount of ePC was increased over the temperature range examined. Therefore, the addition of ePC to chitosan was used to decrease the modulus of chitosan in order to produce a softer and more flexible film. The Young's modulus of the dry chitosan-ePC films are in agreement with those observed by DMA analysis. For the chitosan-ePC films that were immersed in phosphate buffer solution, the average Young's modulus was three orders of magnitude lower than that obtained for the dry films. The decrease in the modulus is mainly attributed to the plasticizing effect of water. The modulus of the blends was also found to increase as the amount of ePC increased within the blend. This trend was also related to the stability of the films. Indeed, the stability of the chitosan-ePC films in a physiological solution increased as the amount of ePC increased within the films. The stability of the film with high lipid content was likely attributed to the overall increase in hydrophobicity of the film and the specific interactions between chitosan and ePC.

Conclusions: Chitosan and ePC are compatible, partially miscible biomaterials that form films with unique properties. The ratio of chitosan to ePC was found to be related to the film's properties. Specifically, as the amount of ePC increased within the blend, the size of the lipid microdomains increased and the modulus of the dry chitosan-ePC films decreased. It was also found that the Young's modulus and the stability of the films increased as the amount of ePC increased within the film. Therefore, as the extent of phase separation increased, the mechanical properties and the stability of the films were enhanced. The relationships established between composition and properties will be used as a guide in the design of the chitosan-ePC system for use in drug delivery. Overall, this study demonstrates the potential usefulness of partially miscible chitosan-based blends for biomedical purposes.

Acknowlegements: The authors are grateful to NSERC for an operating grant and OCRN for a translational research grant to C. Allen.

References:

[1] Grant J, Blicker M, Piquette-Miller M, Allen CJ. J Pharm Sci 2005; 94: 1512-27.
[2] Ho EA, Vassileva V, Allen C and Piquette-Miller M. J Control Release 2005; 104: 181-91.