Nano-Structured Bioresorbable Films Loaded with Bioactive Agents for Biomedical Applications

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Introduction: Controlled drug delivery offers numerous advantages compared to conventional dosage forms given as a systemic treatment, in particular: improved efficacy, reduced toxicity and improved patient compliance and convenience. Releasing a drug in a controlled manner occurs when a polymer, whether natural or synthetic, is judiciously combined with a drug or other bioactive agent in such a way that the active agent is released from the material in a pre-designed manner. Several of the most investigated biodegradable systems have been based on emulsions. The use of emulsions for such systems is attractive since parameters such as polymer content, organic to aqueous phase ratio and homogenization rate can be varied to design and tailor the release profiles.

In the present study we developed and studied highly porous nano-structured drug eluting systems loaded with various drugs. The porous films were prepared using the inverted emulsion freeze drying technique. This method is unique not only in enabling to achieve a continuous structure (as opposed to microsphere powders which are obtained using a double emulsion) but also in having the ability to preserve the emulsion's original microstructure. The main goal of this study was to determine the effect of nano-structuring, whether by addition of effective surfactants or by altering kinetic parameters, on the release profiles of hydrophilic and hydrophobic drugs from the nano-structured films.

Methods: 50/50 poly(DL-lactic-co-glycolic acid) was used as the host polymer of the continuous phase. Paclitaxel and Farnesylthiosalicylate (FTS) served as the hydrophobic drugs and were incorporated into the emulsion's organic phase, whereas mafenide acetate and ceftazidime hydrate served as the hydrophilic drugs and were incorporated into the emulsion's aqueous phase. Several surface active agents (surfactants) were incorporated into the emulsion in order to achieve a fine and delicate nano-structure. The microstructure of the emulsion was examined using scanning electron microscopy (SEM) and the drug release profiles were evaluated using HPLC for measuring the drug concentrations in the release medium at pre-specified time points throughout the release period.

Results: All specimens obtained were highly porous (70%-90%) and included partially interconnected pores. The parameters which had the most significant effect in reducing pore size were the copolymer ratio and the homogenization rate. Bovine serum albumin (BSA) and horseradish peroxidase (HRP) were found to be the most effective surface active agents which, together with a high homogenization rate, yielded homogeneously distributed nano-sized pores (440-600 nm and 730-775nm for systems loaded with hydrophobic and hydrophilic drugs, respectively).

Most drug release profiles exhibited an initial burst release, accompanied by a decrease in release rate with time, as typical for diffusion-controlled systems. Nano-structuring had a significant effect on the release profiles of hydrophobic drugs from the bioresorbable films. In this case smaller pore sizes resulted in higher burst effects and higher release rates, due to an increase in the surface area for diffusion. Systems containing hydrophilic drugs were less affected by nanostructuring, most likely due to the fact that these drugs have very high release kinetics in an aqueous medium.

Conclusions: In order to obtain a fine and stable inverted nanoemulsion, a delicate balance of the various formulation parameters is required, the two most critical being high homogenization rate and the incorporation of an appropriate surfactant. Understanding the relationships between processing, microstructure and the resulting controlled release behavior will enable to engineer new implants and to adapt them to a wide variety of biomedical applications.

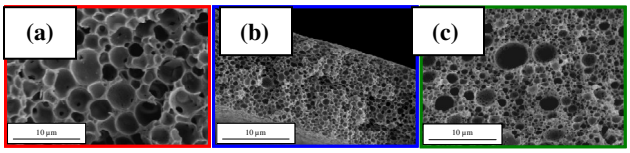

Figure 1: The effect of surfactants on the nanostructure of the highly porous drug- eluting scaffolds: (a) no surfactant, (b) 5%w/v BSA, (c) 5% w/v HRP.

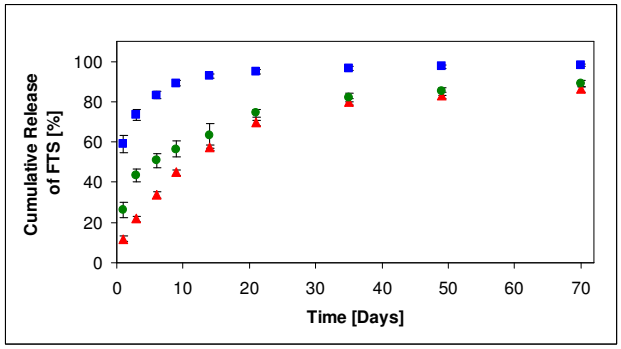

Figure 2: The surfactant's effect on the FTS release profile. ▲ - no surfactant, ■ - 5% w/v BSA, ● - 5% w/v HRP.