Absorbable Microparticle Surface Modification and Examination of Resultant Charge Density

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Statement of Purpose: Microparticles are widely used in the field of biomaterials and especially related drug delivery matrices. The purpose of this study is to modify the surface of polymer microparticles. The microparticles, examined in this study, are comprised of a linear hydroxy/carboxyl terminated polyetherglycolide and dihydroxy-terminated polyetherglycolide particles of sizes between 7.2µm and 12µm. In this communication, the charged microparticles are used as additives in drug delivery systems consisting of polyether-ester-urethanes gel matrices. After modification, we examined the resultant product for the extent of acylation reaction and resultant effects on a typical drug delivery system gel.

Methods: To begin the process of particulate succinylation, a 1% (w/v) solution of succinic anhydride in xylene was prepared as the active reagent. The solution was heated and stirred mechanically to dissolve the anhydride. Once the anhydride was dissolved a 20% (w/v) amount of microparticles was added to the flask. The temperature was increased to 100°C and the reaction stirred for approximately eight hours. After cooling to room temperature, the contents were poured into 50 mL centrifuge tubes and the flask was rinsed with xylene to collect all of the microparticles. The product was centrifuged and xylene decanted. Acetone was added to the tubes then sonicated to break up the centrifuged pellet. This step was repeated multiple times to ensure the complete removal of unreacted anhydride. Next, the microparticulates were placed under a hood for air drying before being placed in a vacuum oven overnight to completely dry the material. To test for acidity, approximately 100 mg of particles were weighed into 1.5 mL centrifuge tubes. An excess of crystal violet solution (5% w/v) in water was placed in the centrifuge tube. The tube was then vortexed and sonicated to suspend the particles in the dye solution. This allowed for the positive charged dye to bind with the negative charge placed on the particles. The product is then centrifuged and excess dye solution decanted. The particles were then rinsed with acetone until the decanted acetone no longer had color from the dye. The particles were then dried in a vacuum oven overnight. Once dry, the particles were weighed, dissolved in hexafluoroisopropanol and examined by spectroscopy to determine the absorbance that results only from bound dye that is released upon dissolution. The acid value was determined from the weight of the microparticles and the amount of bound dye. Two types of microparticulate were chosen for modification, Type A has no initial carboxylate groups and Type B was polymerized with a carboxylate containing initiator.

Results: As shown in Table 1, there is a significant change to the acid value of the particles after the succinylation procedure. The dyeing process quantitates the acid groups bound to the exposed polymeric chain terminals on the surface of the micro particles. The dye procedure was performed using a saturated solution to ensure there were no sites left unbound on the surface of the particles. When incorporated into drug delivery systems using polyether-ester-urethanes, the succinlyated microparticles are generally shown to slow the release of the drugs from the urethanes. Depending on the therapeutic agent, the composition of the microparticles, and other factors, succinylation of the particles can have varying effects on the release. Figure 1 shows the effect of succinylating the microparticles in a representative hydrophilic drug (doxycycline) delivery system.

Table 1. Comparison of microparticles after modification

Microparticulate		Acid Value (g/eq)
A	Unmodified	2,835,117
	Succinylated Lot 1	153,319
	Succinylated Lot 2	262,049
B	Unmodified	406,560
	Succinylated Lot 1	171,672
	Succinylated Lot 2	102,829

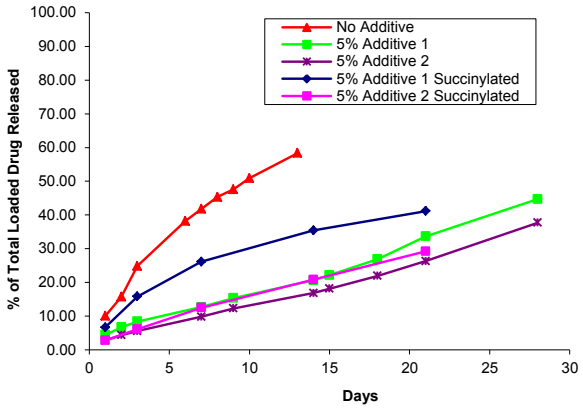

Figure 1. Release of doxycycline from polyether-ester-urethanes with microparticle additives

Conclusions: We report the surface modification of absorbable microparticles by means of succinylation and the associated quantitation of the carboxyl loading placed on the particle surface. Based on drug delivery results, the succinylation of microparticles can serve as another means to modulate the release profiles of drug delivery matrices. This allows biomaterial systems that incorporate absorbable microspheres another degree of freedom to be modulated based on imparted charge density and related characteristics.

References:

1. Shalaby, S.W. et al., U.S. Pat app. 12/454,774 (2009).
2. Shalaby, S.W. et al., U.S. Pat app. 12/385,030 (2006).