Viscous Polyester Terpolymers as a Short-Term Drug Delivery Platform

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Statement of Purpose: Viscous terpolymers prepared from lactide, glycolide, and caprolactone are being developed as an injectable biodegradable polymer drug delivery platform. These materials have been synthesized using various hydroxyl-containing initiators. Polymer properties such as viscosity and degradation can be tuned by varying polymer molecular weight, choice of initiator and monomer composition. The purpose of this work was to investigate the loading and release of hydrophilic and hydrophobic compounds from viscous terpolymers to assess suitability for drug delivery applications.

Methods: Polymerizations were conducted as previously presented[1]. In summary, polymerizations were conducted in the melt using various mole ratios of monomers and a catalyst. Polymers were prepared using various alcoholic initiators. Polymerizations were conducted at elevated temperature under inert atmosphere followed by a vacuum stripping to remove residual (un-reacted) monomers. The reported molecular weight (Mw) is the weight-average molecular weight as determined by GPC against polystyrene standards. Actual monomer composition of the final product is reported based on determination by NMR. Viscosities measurements were performed on a TA Instruments AR-2000 ex rheometer using a parallel-plate geometry fixture and a 1-mm gap. Measurements were performed at room temperature (20-22°C) on the neat polymer. In vitro degradation studies were carried out on samples incubated at 37°C in pH 7.4 phosphate-buffered saline (PBS). Blends were prepared by mixing goserelin acetate (Genzyme Pharmaceuticals, MA) bupivacaine base (BASF Orgamol Pharma Solutions SA, Saint Maurice, Switzerland) or risperidone (Jubilant Organosys, Delhi, India) of known particle size into neat polymer. Detection of drug was determined using established HPLC methods. In vivo pharmacokinetic studies were conducted in Sprague –Dawley rats (375 g, n=3).Goserelin acetate was mixed into the polymer at a 10 wt% loading and administered subcutaneously at a 16 mg/kg drug dose level. Risperidone was mixed into the polymer at a 2% loading level and administered subcutaneously at a 53 mg/kg drug dose level. Doses were injected using either a 19-gauge syringe-needle assembly for goserelin acetate or a 20-gauge syringe-needle assembly for risperidone. Plasma concentrations were determined using established LC-MS methods.

Results: Polymer viscosity can be tuned by changing the molecular weight or monomer ratio (Table 1). Lowering the lactide monomer ratio and reducing molecular weight can substantially affect the viscosity of the polymer. By lowering the viscosity, an injectable polymer is achieved such as example 6. Using an identical polymer, release is directly proportional to the hydrophilicity of the active ingredient (Figure 1). Using one example, in vivo levels of model active ingredients were observed for 7 days (Figure 2).

Table 1: Terpolymer samples used in this investigation

Sample	Mw, kDa	L:G:CL Ratio	Tg, °C	Viscosity, poise
1	9.9	27:19:54	-31.4	1720
2	10	27:21:52	-23.2	6510
3	5.7	16:31:53	-27.5	2639
4	4.5	50:30:30	-35.4	13300
5	4.8	31:20:49	-35.4	655
6	4.8	16:26:58	-43.8	282

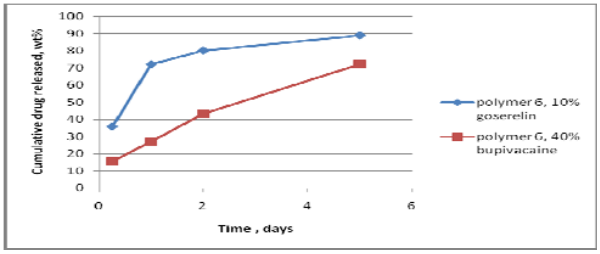

Figure 1: in vitro release of goserelin or bupivacaine from terpolymer.

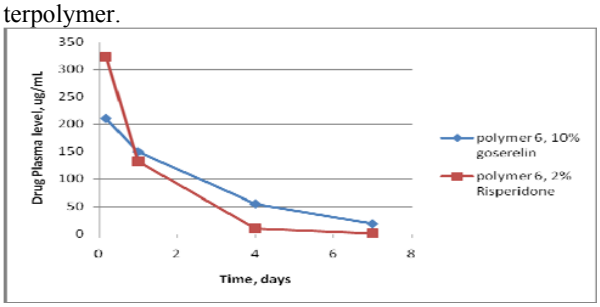

Figure 2: in vivo release of goserelin or risperidone from terpolymer

Conclusions: Investigations have shown that viscous terpolymers of lactide, glycolide, and caprolactone can be produced. Polymerization variables such as the initiator influence viscosity of the resulting polymer. Extended release of hydrophilic or hydrophobic compounds was achieved for approximately 7 days in both in vitro and in vivo test models. These studies demonstrate the suitability as an injectable drug delivery platform.

References: [1](Markland P., Controlled Release Society 36th Annual meeting and exposition, poster #268.)