SynBiosys microspheres as a platform for local delivery of Sunitinib: Formulation and characterization


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ABSTRACT
Sunitinib malate is a multi-targeted receptor tyrosine kinase (RTK) inhibitor which demonstrates promising responses in the treatment of many angiogenesis related diseases. We developed sunitinib loaded polymeric microspheres that can be used for local antiangiogenic therapy. Sunitinib release from the microspheres can be tailored by controlling the percentage of soft to hard block of SynBiosys multi-block copolymers, resulting in preparations that effectuated sustained release for a period of at least 30 weeks. Sunitinib microspheres showed successful suppression of angiogenesis in a chicken chorioallantoic membrane (CAM) assay.

INTRODUCTION
Vascular endothelial growth factor (VEGF) has been associated with neovascularization of many diseases such as renal cell carcinoma (RCC), lung, breast and colorectal cancers as well as ocular diseases including age-related macular degeneration (AMD), diabetic retinopathy and retinal vein occlusion (1). VEGF signaling pathways represent a validated target for monoclonal antibodies or small molecule drugs to normalize the neovascularization associated with such kinds of diseases. Sunitinib is known to suppress the development of blood vessels by blocking the activity of vascular endothelial growth factor receptors (VEGFRs) (2). Sunitinib, however, is associated with dose dependent adverse effects ranging from mild fatigue and hand-foot syndrome to life-threatening cardiac toxicity (3). The tolerability of sunitinib can be improved by local delivery of the drug, thus ensuring high local concentration at the desired site of action.

We propose to formulate sunitinib in biodegradable polymeric microspheres, with injectable administration and long-term sustained release of sunitinib. Amongst the family of biodegradable polymers, amphiphilic block copolymers hold a great promise for sustained delivery of drugs. In the current investigation we utilized SynBiosys multi-block copolymers (Figure 1), consisting of a hard, semi-crystalline poly(L-lactide) block, and a soft, amorphous block containing poly(DL-lactide), and polyethylene glycol (PEG). Release of small molecules such as sunitinib from SynBiosys microspheres can be tailored by varying the ratio between the amorphous and hydrophilic PEG-poly(DL-lactide) block (‘soft block’) and the semi-crystalline poly(L-lactide) block (‘hard block’). The average particle size of sunitinib loaded microspheres was ~30 µm which can be injected using 25-gauge needles.

EXPERIMENTAL METHODS
Sunitinib was encapsulated into SynBiosys polymeric microspheres by an oil/water emulsification solvent evaporation method. Briefly, sunitinib malate was dissolved in DMSO and added to the solution of polymer in DCM. The organic phase was then emulsified into a water phase containing 1% (w/v) of PVA as emulsifier. In vitro release of sunitinib was
studied under sink conditions by incubating 10 mg aliquots of the microspheres in PBS at 37°C for 30 weeks. Every 10 days the microspheres were centrifuged, the supernatant was analyzed by HPLC/UV and cumulative percent of drug release was calculated. Anti-angiogenic activity of sunitinib released from the microspheres was studied in ovo using fertilized white leghorn eggs by incubating at 37°C and 60–65% relative humidity. To study the effect of the drug on the angiogenesis, nitrocellulose rings were applied on the top of the CAM and free sunitinib (100 ng) or sunitinib microspheres (0.5 mg suspended in 30 µl PBS) were applied inside the ring. Pictures were taken using a digital camera before and 24 hours after applying the drug.

CONCLUSION

We have developed microspheres with high encapsulation efficiency (<80%) and sustained release of the multikinase inhibitor sunitinib for ~30 weeks. The microspheres were found to successfully suppress angiogenesis in ovo. These sunitinib microspheres show promise for long-term suppression of ocular neovascularization by intra-vitreous injection as they can be injected using small needle size (25-gauge, which are used in clinical practice for a minimally invasive intravitreal administration of depot preparations) or for the inhibition of cancer-related angiogenesis.

REFERENCES


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