431h A Novel Serum-Stable Micelle System for Controlled Release of Rapamycin

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Rapamycin is a potent anti-tumor agent having efficacy against a broad range of solid tumors (typical $IC_{50} < 10^{-8}M$). However, poor solubility (< 2.6 μg/ml) has made formulation difficult, delaying clinical development over 20 years since its discovery. The purpose of this work was to develop a micelle formulation of rapamycin for high-dose delivery and sustained drug release.

Rapamycin was loaded into peglylated-phospholipid micelles (PEG_{2000}-DSPE) using a solvent extraction technique. Drug incorporation into micelles was verified by SEC and quantified by HPLC. Increasing amounts of α-tocopherol, vitamin E, were co-incoporated with rapamycin and micelles characterized. Drug release kinetics were evaluated *in vitro* utilizing a "perfect sink" release apparatus maintained at 37°C. Micelle stability and drug release kinetics were further evaluated under simulated *in vivo* conditions by the addition of serum albumin to the release medium.

Rapamycin was incorporated at over 20% w/w in PEG-DSPE micelles increasing solubility >1000 fold. Resulting micelles were ca. 20 nm in diameter and able to solubilize at least 5 mg/ml of drug. Release experiments demonstrated sustained release with a release $t_{1/2}$ of 35 h. However, addition of 4% w/w serum albumin to release media destabilized micelles as indicated by SEC, resulting in bulk release of rapamycin ($t_{1/2}$ ca. 2 h). The co-incorporation of 2:1 tocopherol (molar w.r.t. phospholipid) stabilized the PEG-DSPE micelles achieving an 11-h $t_{1/2}$ in the presence of physiological concentrations of serum albumin.

In conclusion, a micelle formulation of rapamycin was developed having sustained release properties and high drug solubilization, and the PEG-phospholipid polymeric micelle carrier was stabilized for intravenous use by the co-incorporation of tocopherol.