431m Hydrolysable Prodrugs of Geldanamycin for Efficient Nanoencapsulation and Sustained Release

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Geldanamycin, a potent heat shock protein 90 (Hsp90) inhibitor and potential chemotherapeutic, is relatively large (MW 560) and amphiphilic ($\log P_{oil/water}$ 1.3) making formulation difficult. The purpose of this work was to develop prodrugs of geldanamycin that are solubilized by polymeric micelle formulations.

Geldanamycin was poorly encapsulated by peglylated poly-ε-caprolactone (PEG-PCL), < 1% w/w, and PEG-phospholipid micelles, < 4% w/w. We hypothesized the amphiphilic nature of geldanamycin hinders drug incorporation into the hydrophobic micelle core and postulated reversible conjugation of fatty chains would increase lipophilicity and improve micelle loading. Geldanamycin was derivatized at the C17 position to introduce an unhindered hydroxyl group via a short acyl chain for facile esterification. A series of fatty acid derivatives was then synthesized, and drug loading into PEG-PCL 5000:10000 Da micelles was evaluated.

Increased drug loading was observed for the fatty acid derivatives (6 to 16 carbons). Hexadecanoate derivatives of geldanamycin were encapsulated at over 15% w/w. Drug release kinetics were evaluated *in vitro*, and micelle formulations demonstrated sustained drug release ($t_{50\%}$ > 60 h) at physiological conditions (pH 7.4, 37°C).

In conclusion, a series of geldanamycin prodrugs was developed capable of high loading in polymeric block-copolymer micelles and sustained release at physiological conditions.