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Effect of Poly(allylamine) Molecular Weight on Drug Loading and Release Abilities of Nano-Aggregates for Potential in Cancer Nanomedicine

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ABSTRACT

Poly(allylamine) graft polymers have been shown to hold potential as drug delivery vehicles and complexation agents for biological molecules such as insulin. The nanoparticles formed upon aggregation or complexation allow for enhanced cellular trafficking resulting in enhanced efficacy. Multiple reports have shown the ease of synthesis and reliability of these graft polymers, however, little investigation into the effect of the molecular weight of the homopolymer poly(allylamine) has been carried out. In this work we synthesized a range of oxadiazole grafted poly(allylamine) derivatives of varied molecular weight (15, 17.5, 120 & 900 kDa) set at a 5% polymer:oxadiazole mole grafting. The effect of molecular weight on the size, critical aggregation concentration and drug loading/release was evaluated in model drugs before loading the optimal formulation with doxorubicin and carrying out a preliminary cytotoxicity study. In line with other cationic polymers, the larger poly(allylamine) amphiphilic derivatives resulted in greater drug loading, however, the particle size increased whilst drug loading dramatically decreased, which for cancer nanomedicine could be a barrier for pharmaceutical use.

Introduction

Amphiphilic polymers have played a key role in the development of advanced drug delivery technologies by controlling solubility, release, permeability and stability of active ingredients. Polymeric nano-aggregates can be created from a diverse range of architectures and form a plethora of structures in the aqueous environment including vesicles, polymeric micelles, and nanoparticles.[1] Graft polymers are composed of a water soluble homopolymer backbone with hydrophobic groups randomly grafted on.[2,3] The resulting amphiphilic comb-shaped molecules aggregate through weak non-covalent hydrophobic-hydrophobic interactions in aqueous environments, where the hydrophilic moiety will remain in association with the aqueous phase whilst the hydrophobic moieties will 'shield' themselves, thereby forming a micellar core-shell system.

Amphiphilic polymers possess the ability to encapsulate hydrophobic drug molecules inside their hydrophobic core, hence increasing the aqueous solubility of the drug. *In vivo* a hydrophilic protein corona forms surrounding the aqueous shell of the self-assembly. This is believed to be a contributing factor to the increased stability experienced by these nano-aggregates in blood plasma resulting in increased circulation times and reduced opsonisation and capture by the reticulo-endothelial system. Polymeric aggregates are well-known to possess a lower critical micelle concentration (CAC) compared with surfactant micelles. These properties make polymeric nano-aggregates excellent candidates for drug solubilisation and delivery, particularly for bulky anticancer drugs.[4] However, studies have shown, that in order for nanoparticles to effectively permeate cancer microenvironments, the particle size must be preferentially within the nano-size range.[5]

Poly(allylamine) (PAA) is a positively charged long chain polymer which has previously been investigated for its use as an

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