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Nanogel scavengers for drugs: Local anesthetic uptake by thermoresponsive nanogels

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ABSTRACT

The use of functional nanogels based on poly(*N*-isopropylacrylamide) for effectively scavenging compounds (here, the model drug bupivacaine) is demonstrated using an in vitro cell-based assay. Nanogels containing higher loadings of acidic functional groups or more core-localized functional group distributions bound more bupivacaine, while nanogel size had no significant effect on drug binding. Increasing the dose of nanogel applied also facilitated more bupivacaine binding for all nanogel compositions tested. Binding was driven predominantly by acid–base interactions between the nanogels (anionic) and bupivacaine (cationic) at physiological pH, although both non-specific absorption and hydrophobic partitioning also contributed to drug scavenging. Nanogels exhibited minimal cytotoxicity to multiple cell types and were well tolerated in vivo via peritoneal injections, although larger nanogels caused limited splenic toxicity at higher concentrations. The cell-based assay described herein is found to facilitate more robust drug uptake measurements for nanogels than conventional centrifugation-based assays, in which nanogels can be compressed (and thus drug released) during the measurement.

1. Introduction

Drug overdose remains a common clinical problem across the globe, occurring both inadvertently and intentionally. Ideally, an antidote is provided, but specific antidotes are frequently not available. Consequently, a broad range of non-specific therapies have been developed to approach this problem, ranging from cathartics to more invasive and sophisticated approaches such as plasmapheresis [1], hemoperfusion [2], hemodialysis [3] or a combination thereof [4,5].

Recently, several nanoparticle-based strategies have been investigated to achieve effective drug scavenging in vivo. Nanoparticles are attractive vehicles for this purpose because of their easy injectability, large surface area-to-volume ratios, and low probability of embolic phenomena. Lipid microemulsions or nanoemulsions [6–8], liposomes [9–11], vesicles [12], nanocapsules [13] and polymer conjugates [14,15] have been developed for scavenging various drugs; indeed, lipid microemulsions have been demonstrated to provide superior performance compared to drug-based therapies for treating anesthetic overdoses [7,16].

Nanogels, sub-micron hydrogel nanoparticles, have highly desirable properties that may make them particularly suitable for such applications. Like hydrogels, nanogels have a three-dimensional, internally crosslinked microstructure, swell in aqueous solvents to provide free volume for non-specific sorption, and can shrink and swell according to changes in the gel environment. Like nanoparticles, nanogels are injectable, have extremely high specific surface areas available for interaction with chemicals in the gel environment, and respond much faster to environmental stimuli. Based on these properties, nanogels have already attracted significant interest as sensors, rheological modifiers, optical devices, mechanical actuators, diagnostics supports, and drug-delivery vehicles, among other applications [17]. Included among these applications is the use of nanogels as a peptide scavenger synthesized by molecular imprintation [18], although few other examples of nanogel drug scavengers have been reported in the literature.

To investigate the capacity of nanogels to scavenge drugs, we have used nanogels based on poly(*N*-isopropylacrylamide) (PNIPAM). Aside from their useful thermosensitive properties, the size, morphology and chemical composition of PNIPAM particles can easily be tuned, making them ideal model systems for investigating the design of nanoparticle-based drug scavengers. Here, we study the effect of altering nanogel size, charge and chemistry on the scavenging of a model drug (bupivacaine, an amphiphilic local anesthetic that is cationic at physiological pH). The capacity of nanogels to absorb and significantly reduce the toxicity of

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