



# Thermoresponsive nanogels for prolonged duration local anesthesia

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## ABSTRACT

Nanogels based on poly(N-isopropylacrylamide) are attractive vehicles for prolonged duration local anesthesia because of their tunable size, number of functional groups, thermoresponsiveness and anionic charge. Nerve block durations of up to 9 h were achieved using acrylic acid-loaded nanogels loaded with bupivacaine. Increasing the anionic charge density of the nanogels or (for more highly acid-functionalized nanogels) decreasing the nanogel size facilitated longer duration of anesthetic release. Small (<300 nm diameter) nanogels formed dense aggregates upon injection in vivo and induced only mild inflammatory responses, while large (>500 nm diameter) nanogels typically remained as liquid-like residues in vivo and induced more severe inflammatory reactions.

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## 1. Introduction

Prolonged duration local anesthesia after surgery is a significant current clinical need. To meet this goal, bioerodible polymer implants [1,2], liposomes [3–5], degradable microparticles [6–11], hydrogels [12–15], viscous polymer formulations [16], drug-grafted polymer solutions [17], or combinations thereof [18,19] have all been applied as drug delivery vehicles for local anesthetics. In most cases, injectable systems for local anesthetic delivery are successful in prolonging local anesthesia over the course of several hours relative to injections of the anesthetic solution alone, although the use of synergistic drug combinations may extend this time period to several days [5].

Nanogels, sub-micron hydrogel particles with colloidal properties, are interesting candidates as drug delivery vehicles because the hydrogel nanostructure of nanogels can be engineered to achieve controlled pore structures, chemical topologies and swelling responses to environmental stimuli [20], while the colloidal nanoparticle macrostructure of nanogels offers the advantages of high specific surface areas and ready injectability. Thermosensitive nanogels based on poly(N-isopropylacrylamide) (PNIPAM) offer the further potential advantage of undergoing a volume phase transition as they are heated above a critical temperature, resulting in significant gel deswelling and (in some cases) thermally triggered aggregation of the

nanogel particles to form aggregates and/or physically cross-linked hydrogels [21]. Since thermosensitive nanogels can exhibit triggerable changes in pore size and colloidal stability, they have been widely investigated for the “on-demand” delivery of drugs or model drugs, including acetylsalicylic acid [22], fluorescein-labelled dextran [23], insulin [24] and bovine serum albumin [25], among others. In vitro drug release has also been demonstrated from macroscopic assemblies of nanogels, including polyelectrolyte-assembled nanogel thin films [26,27], surface-grafted nanogel monolayers [28] and bulk hydrogels comprising cross-linked nanogel particles [29].

Functionalized thermoresponsive nanogels could be particularly effective for controlling the release of local anesthetics, which are generally cationic, given the ease of functionalizing nanogels with high concentrations of anionic groups (enhancing the affinity between the drug and the nanogel phase) and the potential application of the thermal phase transition to induce nanogel aggregation to localize nanogels at a desired site. The ability of anionically functionalized PNIPAM nanogels to bind and release cationic drugs (such as commercially available anesthetics) has been demonstrated [30,31]. We have also previously shown the potential of PNIPAM-based nanogels as highly effective binding agents and/or scavengers for bupivacaine, a common local anesthetic [32]. Here, we investigate the capacity of nanogels to facilitate controlled release of bupivacaine to provide long-term local anesthesia, using a rat sciatic nerve animal model to assay the in vivo performance of nanogel drug delivery formulations.

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