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Current Status of Scaled-Up Synthesis/Purification and Characterization of a Potentially Translatable Tantalum Oxide Nanoparticle Intravenous CT Contrast Agent

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Abstract : There have been no potential clinically translatable developments of intravenous CT contrast materials over decades, and iodinated contrast agents (ICA) remain the only FDA-approved media for CT. Small molecule ICA used to highlight vascular anatomy have weak CT signals in large-to-obese patients due to their rapid redistribution from plasma into interstitial fluid, thereby diluting their intravascular concentration, and because of a mismatch of iodine's K-edge and the high kVp settings needed to image this patient population. The use of ICA is also contraindicated in a growing population of renally impaired patients who are hypersensitive to these contrast agents; a transformative intravenous contrast agent with improved capabilities is urgently needed. Tantalum oxide nanoparticles (TaO NPs) with zwitterionic siloxane polymer coatings have high potential as clinically translatable general-purpose CT contrast agents because of (1) substantially improved imaging efficacy compared to ICA in swine/phantoms emulating medium-sized and larger adult abdomens and superior thoracic vascular contrast enhancement of thoracic arteries and veins in rabbit, (2) promising biological safety profiles showing near-complete renal clearance and low tissue retention at 3x anticipated clinical dose (ACD), and (3) clinically acceptable physiochemical parameters as concentrated bulk solutions(250-300 mgTa/mL). Here, we review requirements for general-purpose intravenous CT contrast agents in terms of patient safety, X-ray attenuating properties and contrast-producing capabilities, and physicochemical and pharmacokinetic properties. We report the current status of a TaO NP-based contrast agent, including chemical process technology developments and results of newly defined scaled-up processes for NP synthesis and purification, yielding reproducible formulations with appropriate size and concentration specifications. We discuss recent results of recent pre-clinical in vitro immunology, non-GLP high dose tolerability in rats (10x ACD), non-GLP long-term biodistribution in rats at 3x ACD, and non-GLP repeat dose in rats at ACD. We also include a discussion of NP characterization, in particular size-stability testing results under accelerated conditions (37C), and insights into TaO NP purity, surface structure, and bonding of the zwitterionic siloxane polymer coating by multinuclear (1H, 13C, 29Si) and multidimensional (2D) solution NMR spectroscopy.

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