INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
SHORT ABSTRACT OF THESIS

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SHORT ABSTRACT

The contents of this thesis have been divided into five chapters according to the results of experimental works that have been performed during the research period. **Chapter I** is the introductory chapter of the thesis that represents an overview of Gd(III) and Mn(II)-based complexes and nanoparticles as alternative MRI contrast agents with enhanced relaxivity and other physicochemical properties to target various endogenous conditions. This includes a brief discussion about the strategies for optimization of multiple factors like hydration number, water exchange rate, rigidity, dissociation kinetics, retention time, *etc.*, while designing novel Gd(III)-/Mn(II)-chelates and nanoparticle-based contrast agents to effectively satisfy the requirements for high relaxivity along with profuse contrast enhancement in MRI.

Considering the hydration, lipophilicity, stability, and rigidity factors, **Chapter II** demonstrates the synthesis of a novel bis-aquated acyclic Mn(II)-complex (**2A**) based on a pentadentate ligand Li$_2$[BenzPic$_2$] comprising of two picolinate moieties and a rigid hydroquinazoline unit. The complex exhibited logK_{cond} = 11.62, at pH ~ 7.4, as well as, impressive relaxometric properties with r_1 = 5.32 mM^{-1}s^{-1} at 37 °C, 1.41 T, which further escalated to 19.09 mM^{-1}s^{-1} in the presence of 0.67 mM BSA at 37 °C. The pseudo-first-order rate constant of the amphiphilic complex **2A** (log P = -0.45) was $k = 2.13 \times 10^{-3}$ s^{-1} at the physiological conditions. *In vivo* MR images of a healthy C57BL/6 mouse were acquired at 7 T, before and after 0.08 mmol/kg intravenous administration of complex **2A** solution. Correspondingly, an intense contrast enhancement in the gallbladder (~160 %) and kidneys (~110 %) as well as a highly vascularized liver region corresponding to the long retention of the contrast material in the blood vessels was realized.

Chapter III illustrates the non-covalent confinement of thermodynamically stable mono-positive, tris(aquated) Gd(III)-complex {Complex **3A**, $[Gd(OH_2)_3(hbda)]^{1+}$} (pGd 18.5) and neutral mono-aquated Mn(II)-complex {Complex **3B**, $[Mn^{II}(PyDPA)(OH_2)]^0$} (pMn = 8.97) within porous silica nanoparticles (PSNs) to improve relaxivity values, thereby protecting the paramagnetic core from scavenger ions (physiologically relevant cations and anions). The geometrical confinement within the nanosphere decreased the motion of complex molecules and resulted in efficient enhancement in r_1 value compared to the untrapped molecules. The efficiency of the complex incorporated PSNs as a T_1- or T_1-T_2 dual-mode MRI contrast agent was examined by recording phantom images. The biocompatibility was further tested on various cell lines to ascertain its bio-applicability and cellular uptake.

Chapter IV describes the syntheses of mono-aquated Mn(II)-complex **4A** (pMn 9.18) and **4A** impregnated within porous silica nanoparticles with a Zn(II)-selective ligand functionalization on the surface (**4A**@SiO_2–Py_2PicNPs). The latter showed r_1 of 13.19 $mM^{-1}s^{-1}$ at 1.41 T, 37 °C, and pH ~ 7.4. A discernible and gradual augmentation in r_1 relaxivity was noticed on the successive elevation in the concentration of Zn(II) ions in HEPES buffer in the case of **4A**@SiO_2–Py_2PicNPs, at pH 7.4, and the r_1 value reached 46.30 $mM^{-1}s^{-1}$ in the presence of BSA and 40 equivalent amounts of the zinc ion, selectively over various other physiological ions. Hereafter, 1-hour post-contrast *in vivo* MR imaging on a batch of mice at 7 T showed ΔCNR ~ 100 % in the pancreas in the presence of **4A**@SiO_2–Py_2PicNP, compared to the pre-injected MR image. However, in the presence of glucose, a substantial contrast enhancement (ΔCNR ~ 138 %) was realized reinforcing the ternary interaction of the contrast agent with the secreted Zn(II) ions in the presence of HSA [**4A**@SiO_2–Py_2PicNPs•HSA•Zn(II)]. In a nutshell, we have reported a non-gadolinium-based Mn(II)-complex entrapped silica nanoparticles that can behave as a "smart" MRI contrast agent in the presence of Zn(II) ions.

Chapter V delineates the mono-aquated, H_2tpada-based Mn(II)-complex, **5A** (pMn 8.80), and thereafter incorporation inside folic acid functionalized porous silica nanoparticles forming **5A**@SiO_2–FA NP. The nanomaterial showed a longitudinal relaxivity value of 21.51 $mM^{-1}s^{-1}$, at pH ~ 7.4, 1.41 T, and 37 °C which improved to 40.97 $mM^{-1}s^{-1}$ in the presence of 4.5% (w/v) BSA (to replicate the plasma model). Alongside, the developed nanoprobe reflected high kinetic inertness towards high equivalents of endogenous ions. Furthermore, cell uptake studies of FITC-labelled **5A**@SiO_2–FA nanoparticles, conducted on the HeLa and HEK293 cell line, demonstrated the rapid internalization of the nanoparticles within an hour utilizing the folate receptor-mediated pathway. This effect was further authenticated by injecting the **5A**@SiO_2–FA suspensions in cancer-infected C57BL/6 mice as a ~100% contrast enhancement was visualized in the region where the cancer cells were accumulated, compared to the control mice (healthy mice, injected with the identical dosage of **5A**@SiO_2–FA NPs).