Calcium Phosphate Based Theranostics

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Editorial

"Theranostics", a collaborative fusion of therapeutics with diagnostic agents into a single nanoplatform (NP), provide a personalized approach permitting efficient diagnosis, therapeutic delivery and effective monitoring of treatment regimes [1]. These NPs are bestowed with remarkable capabilities that include targeted delivery, efficient pharmacotherapy, image guided therapeutics and precise treatment response monitoring [2]. Towards this end, liposomes, quantum dots, iron oxide and silica nanoparticles have been extensively researched [3-6]. However drawbacks such as stability, toxicity, hypersensitivity and non-biodegradability limit their application potential *in vivo*.

Calcium phosphate (CaP) ceramic nanoparticles present a unique class of delivery systems owing to their wide range of properties including facile functionalisation, biocompatibility, bioactivity and efficient biodegradability *in vivo* [7]. These properties strongly depend on the Ca/P molar ratio and crystallinity which ranges from bioactive hydroxyapatite (HA, Ca/P =1.67) to resorbable tricalcium phosphate (Ca/P =1.5). Ca/P ratios ranging between 1.67 - 1.55 result from the loss of Ca2+ ions from the unit cell possess varying biodegradable characteristics that play an important role in bone remodeling and bone formation [8,9]. Therefore, the dissolution rate of calcium-deficient hydroxyapatites (CDHA) NPs can be controlled by subtle adjustment of Ca/P ratio and crystallinity, potentially varying the release rate of incorporated drug. In this regard, we have previously demonstrated that CDHAs encapsulating doxycycline exhibit both single and two-stage release profiles depending on their Ca/P ratios. An initial burst release attributed to desorption of doxycycline from the CDHA surface is followed by a slow release due to dissolution of the doxycycline-CDHA complex [10]. Particle size, shape, surface charge and aspect ratio play a crucial role in the stability, circulation lifetimes, and cellular internalization of NPs *in vivo* [11]. NPs with sizes between 100−200 nm have been shown to extravasate into tumors through enhanced permeability and retention effect, and escape filtration by liver and spleen prolonging their circulation time *in vivo* [12]. In addition, CaP NPs with average particle sizes <150 nm and possessing rod or needle shaped morphology tend to be internalized more effectively by cells in vitro. This observation could be attributed to the small aspect ratios (L/D) of these NPs which could have led to faster internalization with minimal membrane disruption in cells [13]. Furthermore, it has been extensively reported that close to neutral charged NPs have longer circulation lifetimes and less systemic toxicity *in vivo*[12]. In this regard, we have previously demonstrated that neodymium doped supramolecular HA NPS possessing 20-40 nm size with needle-shaped morphology were prepared for effective cellular internalization *in vitro* [14].

Cyclodextrins (β-CD) and cucurbiturals (CB[7]) are supramolecular systems with unique molecular structures and have been widely recognized as pharmaceutical excipients [15,16]. β-CDs are hollow truncated cones and CB[7] are macrocyclic pumpkin shaped hexamers, both comprising of hydrophobic cores which demonstrate superior complexing capabilities with hydrophobic drugs. From this view point we can assume the presence of β-CD/CB [7] in the engineered NPs might augment drug loading capabilities and enhance therapeutic efficacy. We thus synthesized cucurbituril/HA based NPs with high aspect ratio and needle shaped morphology. These particles with varying sizes, surface charges and tunable degradation profiles manifested the advantages of the presence of cucurbituril with respect to drug loading, encapsulation efficacy and release kinetics. *In vitro* release profiles with two model drugs; hydrophilic Doxorubicin hydrochloride and hydrophobic Nile Red ascertained that hydrophilic Dox was released at a faster rate compared to

hydrophobic NR over similar time periods. The concomitant presence of samarium, conferred theranostic potential with luminescent emission observed at 590 nm [17]. In addition, as described previously CDHA nanoparticles endowed with a strong tendency for ionic substitution can readily replace their Ca^{2+} ions with variant lanthanide (Ln) dopant elements [18].To this end we have also prepared neodymium-doped surface modified CaP NPs, functionalized with alginic acid using APTS and EDC mediated chemistry to confer pH responsiveness to the synthesized systems delivering the model drug 4acetyl salicyclic acid to the colon after oral administration [19]. These NPs possessing 20-40 nm size with negative surface charge thus facilitate simultaneous imaging of colon cancer cells and stimuli responsive drug delivery. In parallel, europium doped CDHA core NPs functionalised with (β-CD) and ($CB^{[7]}$) demonstrated controlled and sustained release profile of drug 5-fluorouracil along with fluorescence imaging capabilities [20]. Moreover the emissive intensities of the NPs in the carrier systems increased with cumulative released amounts of drug suggesting that the release of drug could be monitored by changes in luminescent intensity that can be exploited for theranostic applications.

Our approach in CaP based theranostics has been to engineer lanthanide-based 'theranostic' NPs with optimal physicochemical properties to simultaneously image and treat solid tumors. We believe that careful manipulation of crystallinity, aspect ratio, precise geometry, Ca/P ratios and surface charge will effectively tailor the degradation characteristics of CaP NPs which will in turn fine-tune the release profiles of the encapsulated drug. In addition subtle modification of the crystallinity of these CaPs by heat treatment, pH adjustment and reaction time will improve the atomic arrangement of the apatite structure. This is expected to impart better imaging properties as the dopant ions are rigidly confined in the crystal lattice. We also anticipate that modulating all the above listed parameters will promote emission enhancement with greater fluorescence yield. This approach will potentially advocate the development of safe, efficacious CaP-based theranostic NPs for cancer therapy.

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