Multifunctional Neodymium Doped Hydroxyapatite Supramolecular Complexes as Luminescent Drug Carriers

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Introduction

Hydroxyapatite (HA) is one of the most extensively employed calcium phosphates owing to its similarity to the main mineral constituent of bone tissue. Cyclodextrins (CD) have a unique molecular structure that makes them ideal candidates for drug delivery and for the stabilisation of proteins [1, 2]. Neodymium (Nd) ions show photoluminescence and can be used in imaging. Doping HA-cyclodextrin complexes with neodymium seems to be an interesting strategy for simultaneous targeted drug delivery and near-infrared fluorescence imaging guidance. The presence of cyclodextrin could impart higher hydrophobicity and augment the encapsulation efficiency of the drug. This higher hydrophobicity is also particularly useful for the preferential adsorption of albumin. Thus the ability to design particles that can preferentially interact with particular protein can obtain desired targeting effects. Furthermore the Neodymium ions being endowed with good photoluminesence capability can be utilized for biological imaging studies.

Materials & Methods

Photoluminescent hydroxyapatite complexes were prepared by co-precipitation technique. Briefly a known amount of calcium chloride was dissolved in 100 ml of distilled water. Neodymium chloride was added and stirring continued for few hours. Then fresh conjugate base prepared with 5.4 wt% tri sodium acetate was added and the reaction stirred for 5 min. To this solution disodium hydrogen phosphate along with cyclodextrin solution was added dropwise from a burette and the stirring maintained for 24 h. The resulting complexes obtained were washed with distilled water, centrifuged and lyophilised. The complexes were analyzed by X-ray diffraction (XRD), transmission electron microscopy (TEM), Fourier transform infrared (FT-IR), Atomic Force Microscopy methods and Dynamic Light Scattering (DLS) methods. The blood compatibility and cytotoxicity of the nanoparticles were evaluated by cell aggregation, haemolytic and MTT Assay studies respectively. Drug delivery was demonstrated using a model drug doxorubicin by UV spectroscopic technique. Photoluminescence (PL) was evaluated using fluorescence spectroscopy.

Results & Discussion

The XRD diffractogram of the complexes showed all reflections of cyclodextrin including the characteristic peaks at 2θ=26.12◦ and 32.13◦ that corresponded well to those expected from the HA structure. The average crystalline size of the doped particles as estimated using Scherrer formula with (0 0 2) diffraction peak has been found to be 30 nm as compared to 40 nm in the undoped HA. The doping led to smaller particle size as the ionic radius and charge of neodymium is different from that of calcium and could affect the growth of the HA crystal. The size of the complexes as analyzed using DLS and AFM was between 150 nm and 250 nm respectively. The bright field TEM images of the HA doped nanoparticles depicted in Figure 1 were thin and long with nano-plate like morphology. Figure 2 shows the

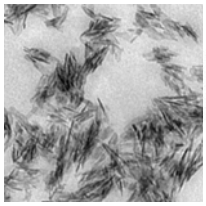

Figure 1

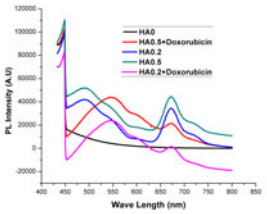

Figure 2

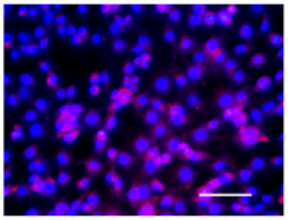

Figure 3a

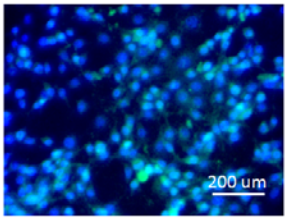

Figure 3b

Figure 1. TEM micrograph of HA doped with Nd. Figure 2. PL of HA complex and PL of Nd doped HA complex with and without drug Figure 3. Intracellular delivery of HA complexes (a) drug (b) Nd

photoluminescent behaviour of HA complexes doped with Nd. Haemolysis, platelet, RBC and WBC aggregation studies reveal no significant haemolysis or aggregation. Similarly the cytotoxicity index of the complexes reveals that more than 80% of the cells were viable in nature. On excitation at 420 nm, the nanoparticle complexes exhibit a strong near-infrared emission at 680nm and the photo luminescent (PL) intensity can be adjusted by varying the concentration of Neodymium. Moreover it exhibits strong PL even after loading of drug molecules and permits the monitoring of PL intensity. Fluorescence microscopy confirmed the uptake of HA complexes by cells for delivery of doxorubicin *in vitro* (Figure 3).

Conclusion

The prepared cyclodextrin capped hydroxyapatite complexes doped with Neodymium exhibit minimal toxicity to the cells in vitro, and show a high drug adsorption capacity and sustained drug release using doxorubicin as a model drug. The nanoparticle complexes obtained in the present study are promising for applications in the biomedical field as multifunctional drug delivery systems for simultaneous targeted drug delivery and near-infrared fluorescence imaging guidance.

References

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