Synthesis, Characterization and Application of Norm Encapsulated Zinc Phthalocyanine Nanoparticles as Photo Dynamic Therapeutic Agents

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Abstract

Nanosized organically modified silica (NORM) particles are promising platforms for encapsulating/conjugating active agents for petitions in bioimaging, light activated therapies and drug delivery. Photodynamic therapy (PDT) is an encouraging and significant therapeutic technique in which light is used to activate photosensitizer molecules, that further reacts with molecular oxygen to produce highly reactive and cytotoxic singlet oxygen. Localized PDT can lead to selective killing of malicious cancer cells. Herein, we have synthesized zinc phthalocyanine (ZnPc) encapsulated NORM particles (ZnPc/NORM), in which ZnPc acts as the photosensitizer and NORM particles act as a carrier and also stabilizer of ZnPc. Further characterization of nanoparticles has been done by various techniques to study the morphology, structure and optical properties. ABMDMA dye was used to evaluate the photodynamic property of ZnPc/NORM particles. These nanoparticles have great potential for being a PDT agent as these nanoparticles significantly generate singlet oxygen on irradiation with laser light, along with some hyperthermia (rise in temperature). *In vitro* studies have been carried out using adenocarcinomic human alveolar basal epithelial (A549) cells to study the anticancer PDT efficacy of ZnPc/NORM.

Keywords: NORM; Zinc Phthalocyanine; Photodynamic Therapy; Hyperthermia; Cell Viability Assay

Introduction

In recent years chemotherapy, radiotherapy, surgery and few other methods were used for cancer treatment [1-3]. Although these techniques prove to be effective, one of the main issue encountered in treatment is the destruction of healthy cells along with cancerous cells. To overcome these complications photodynamic therapy (PDT) is actively used in treating several cancers in the clinic, along with dermatological disorders and microbial infections [4-6], etc. PDT is a non-invasive technique in which a photosensitizer drug is activated with light for the transmutation of molecular oxygen into the cytotoxic singlet oxygen [7,8]. Pure

photosensitizer alone is harmless and have no impact on either abnormal or healthy tissues in the absence of light. PDT has many advantages over other therapies such as highly localized, cost effective, specific tumor treatment, and higher cure rate for some tumors, etc. [9-11].

Phthalocyanines belongs to the family of macrocycles which contains extensively delocalized 18- π electrons system. Their structural planarity makes them insoluble in common organic solvents [12-14]. Owing to their excellent singlet oxygen photogeneration, phthalocyanines have been applied in PDT as efficient photosen-

sitizers [15-19]. However, owing to their poor aqueous solubility, they have been formulated in several micro and nano-sized delivery systems for stable aqueous dispersion [20-25]. These delivery systems also ensure sustained release, avoid plasmatic fluctuation, reduce side effects, decrease the frequency of administration and enhance the drug uptake by targeted tissues, thereby improving the treatment potency [26,28]. For example, the hydrophobic zinc phthalocyanine was incorporated in a liposomal formulation for successful delivery [29,30]. Zinc phthalocyanine has powerful absorbance (red region) of spectrum of visible light, and a powerful emission in the range of 600 - 800 nm [31]. Light activated CP-NPs experience singlet (1O_2) to triplet (3O_2) intersystem crossing because of charge transfer and simultaneously nonradiative decay under fixed near infrared light irradiation wavelength. This phenomenon produce singlet oxygen quantum yield and elevated photothermal efficacy [32]. Keeping this in view, we have prepared a nanoparticle-based delivery system in which photosensitizer (ZnPc) was encapsulated inside the nanosized organically modified silica (NORM) particles. Silica-based nanoparticles are efficient carrier of biomolecules due to their high stability, durability, and easily modifiable surface chemistry. NORM particles have a large surface area, along with chemical, colloidal and thermal stability, which makes them suitable for their use as carrier agents [33-35]. NORM can easily penetrate cancer cells without causing any significant cytotoxicity *in vitro* [36-39]. After thorough characterization of the ZnPc-encapsulated NORM (ZnPc/NORM) particles, we have investigated their singlet oxygen photogeneration efficiency and light-activated toxicity in cancer cells *in vitro*.

Experimental Procedure

Materials

9,10-anthracenediyl-bis(methylene)dimalonic acid (ABMDMA), vinyltriethoxysilane (VTES), aminopropyl tetraethoxysilane (APTES), and n-butanol were purchased from Sigma-Aldrich Co. India. Dioctyl sulfosuccinate sodium salt (AOT), Dimethyl sulfoxide (DMSO), phthalonitrile, zinc chloride ($ZnCl_2$), lithium pentoxide (Li_2O_5), acetone, methanol, ammonia, and concentrated H_2SO_4 were purchased Merck Darmstadt (Germany). Fetal Bovine Serum (FBS), antibiotics (streptomycin and penicillin), Dulbecco's Modified Eagle Medium (DMEM), and MTT reagent [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide] were acquired from Genetix (India). A-549 cell lines were obtained from National Centre for

Cell Science (NCCS), Pune, India. Double distilled water was used during the experiment.

Synthesis of ZnPc

A mixture of $ZnCl_2$ (0.25mmol) and phthalonitrile (1mmol) was refluxed under the purged nitrogen atmosphere in the solution of Li_2O_5 (10 ml) with constant stirring for 8 hours at 70 °C. The product was cooled to RT and after that methanol (20 ml) was added [30]. The prepared zinc-phthalocyanine was separated and filtered to obtain a solid product. The solid product was washed with DMSO and acetonitrile for removing unreacted and side products. The synthesized ZnPc (PS) was further dried in an oven at ambient atmosphere for 24 h at 150°C and used for further characterization and applications.

Synthesis of ZnPc/NORM

A, oil-in-water microemulsion was ready by mixing 0.22g of the surfactant (AOT) in 10 ml of H_2O , along with 400 μL of co-surfactant (n-butanol) [33]. To this 50 μL of PS (1 mg/ml) in DMSO was added and the solution was vigorous stirring for 1 hour. Later, 100 μL of VTES was added and the resulting solution was vigorously stirred for 1 hour. Finally, 10 μL of APTES was added to the solution and left overnight under stirring for nanoparticle formation. At the end of the synthetic process a bluish translucent solution was seen indicating the formation of nanoparticles. The surfactant, co-surfactant, and extra unreacted molecule present in the solution were eliminated by dialysis against double distilled water for nearly 48 h, employing a cellulose dialysis membrane with a cut off size of 12-14 kDa. At the edge of dialysis, the nanoparticles were sterile filtered utilizing a 0.45 μm syringe filter and stored below at 4°C for future use.

Characterization

The ZnPc/NORM particles were characterized using different techniques to confirm the morphological, structural, and optical properties. The shape, size and morphology of the synthesized nanoparticles were confirmed by Scanning (SEM-JEOL JSM-6610LV) electron microscope and transmission (TEM-TECNAI G2-30 U TWIN) electron microscope. The size range of the formed nanoparticle was confirmed by the dynamic light scattering technique (DLS-NANO-JS series Malvern Zetasizer). The structural characterization was done by x-ray diffractometer (XRD: Bruker D8 Discover), Fourier transform infrared spectrometer (FTIR: Per-

kin Elmer RXI spectrometer), nuclear (NMR- ECX-400PNMR at 400 MHz and 100MHz) magnetic resonance, and mass (MS: MALDI-TOF spectrometer: Agilent Technology-650) spectrometer. The optical spectra of the nanoparticles were observed by UV-Vis (SHIMADZU UV-1601, JAPAN) and fluorescence (Varian Palo Alto, CA) spectrophotometer.

Photobleaching of ABMDMA dye

In this experiment for singlet oxygen detection ($^1\text{O}_2$), 1mg/ml of the stock solution of Na salt of ABMDMA (16 μM) in H_2O was prepared and sonicated with pure ZnPc or ZnPc/NORM (100 $\mu\text{g}/\text{mL}$) nanoparticles. The final concentration of ZnPc was 8.0 μM . The prepared solutions were continuously stirred and irradiated in a quartz cuvette using a power tunable diode laser of 635 nm wavelength and power of 38 mW/cm^2 for different periods of 5, 10, and 15 mins. Finally, the optical density was measured for all the samples using the UV-Vis spectrophotometer. Reduction in the optical density of ABMDMA peaks (around 400 nm) directly correlated with the $^1\text{O}_2$ production.

In vitro studies

The A-549 (Adenocarcinomic human alveolar basal epithelial) cells, cultured under optimum growth conditions, were used for *in vitro* studies. At a cell confluence of about 75 - 80% (102 cells/ mL media), the cell cytotoxicity assay was performed. A sterile 24-well cell culture plate was taken in which four different concentrations of NPs (20, 50, 100, 150, 200, 250, 300 $\mu\text{g}/\text{mL}$) were added in separate wells, mixed gently, and incubated for 48 h in dark. Irradiation in desired wells was done just after the 2 h of incubation by a 635 nm wavelength red laser light (power density 40 mW/cm^2) and further incubated for 48 h. After incubation, each well was thoroughly washed with sterile PBS and 100 μL of MTT reagent (5 mg/mL in PBS) was added and leave for 2h. The formed blue color formazan crystal was mixed in 1 ml of DMSO and record the optical density of this solution spectrophotometrically at a particular wavelength ($\lambda = 540 \text{ nm}$). Untreated cells with assigned 100% cell viability were taken as the positive control.

Results and Discussion

Figure 1a indicates the powder x-ray diffraction (XRD) pattern of as-prepared ZnPc, NORM and ZnPc/NORM. The ZnPc showed sharp diffraction peaks in the XRD spectrum and the peaks match well with the standard monoclinic phase (JCPDS card #39-1882)

[24]. Similarly, the XRD of NORM and ZnPc/NORM were measured and seen that the diffraction patterns were almost similar, matching the standard spectrum of ZnPc. No peak shift was observed in NORM after ZnPc encapsulation; on the other hand, we observed a decline in the peak's intensity. No ZnPc peaks was observed in ZnPc/NORM owing to its encapsulation.

The FTIR spectra for ZnPc, NORM, and ZnPc/NORM are exhibited in figure 1b. The ZnPc FTIR spectra shows strong peaks around 1112, 1056, and 1083 cm^{-1} which are characteristic peaks of phthalocyanine ring in accordance with the literature [22]. The NORM FTIR spectrum shows the presence of Si-O-Si at 1110 cm^{-1} and several other bands due to silanol groups e.g. 1604 cm^{-1} (Si-O-H bending), and 1274 cm^{-1} (Si-O stretching) bonds and the unhydrolysable amino-groups introduced due to the APTES precursor. For ZnPc/NORM spectrum the absorption bands around 2956 cm^{-1} indicated the presence of $-\text{C}-\text{NH}_2$ stretching vibrations which establish amino group incorporation in the synthesized of ZnPc/NORM.

Figure 1: (a) XRD, (b) FTIR spectra of ZnPc, NORM and ZnPc/NORM.

Furthermore, the NMR spectrum was also taken for ZnPc/NORM, which is as shown in figure S2 (ESI). In ^1H -NMR all the sixteen hydrogens can be seen. The peak for the eight protons of four rings of the benzene group appeared at 7.55 ppm, whereas the rest of eight protons appeared separately at 8.10 and 9.39 ppm for four hydrogens. HRMS spectra $[\text{M}+\text{H}]^+$ peak was found at m/z 578.1047 (calculated value: 577.0862) which is in agreement with the molecular formula $\text{C}_{32}\text{H}_{16}\text{N}_8\text{Zn}$ of the compound in figure S3 (ESI). Based on the ^1H -NMR [16] and HRMS spectra the structure of the compound was confirmed. The compound appeared to be blue in color. The absorption spectra of different samples were also taken

as represent in figure S3 (ESI). The absorption spectrum of NORM does not exhibit any peak while the PS sample show two characteristic peaks centered at 650 and 775 nm. The ZnPc/NORM sample also show same peaks as ZnPc but with less intensity due to the low concentration of ZnPc in NORM/ZnPc.

The morphology of the NORM encapsulated ZnPc particles was observed with ESEM, as shown in figure S1a (ESI). The figure shows the low magnification FESEM image of the sample which confirms the formation of NPs. When a small part of it is magnified, as seen in figure 2a, it was seen that the NPs were in spherical shape with size below 100 nm. Furthermore, TEM images of the NPs were taken to study the morphology in precise. Figure S2b and figure 2b shows the low and high magnification TEM images of the samples, respectively, which additionally portray that the synthesized particles are spherical in shape with a size range of nearly 50 nm. The high magnification TEM image shows some dark spots inside the spherical particles illustrating the presence of ZnPc inside the NORM, which was also confirmed from the XRD results. In addition, to know the hydrodynamic size distribution of the prepared NPs, DLS spectrum was taken, which shows that the NPs formed were mostly in the size range of 53 ± 15 nm (Figure 2c). The result are in well accordance with the TEM images.

Figure 2: (a) FE-SEM and (b) TEM images, and (c) DLS of ZnPc/NORM.

The porosity of the synthesized ZnPc/NORM NPs was studied using the isothermal adsorption and desorption techniques, as represented in figure 3a. The surface area and porosity of synthesized NPs were studied using BET (nitrogen adsorption isotherm). The specific surface area per unit mass for ZnPc/NORM sample is $177 \text{ m}^2/\text{g}$ and Barrett-Joyner-Halenda (BJH) pore diameter of mesoporous silica nanoparticle is 2.17 nm (inset of figure 3a). Moreover, the BET for synthesized nanoparticle shows type IV mesoporous nature with reference to the IUPAC data and shows a pronounce hysteresis loop for partial pressure (under nitrogen gas) $P/P_0 > 0.3$, which confirms the mesoporous structure of the spherical nanoparticle. The mesoporous nanoparticle with high surface area characteristics will have high loading of encapsulated ZnPc (PS) that is favorable to study release kinetics. Time-dependent release of ZnPc is shown in the figure 3b. ZnPc/NORM was kept in acceptor solution for 80 h and the release of ZnPc was observed. The residual content of the PS in the NPs confirms the release data and shows a slow and sustained release at pH- 7.4 [39]. There is no fast or burst release behavior which describes the release of PS from ZnPc/NORM NPs is diffusion controlled.

Figure 3: (a) BET (inset shows the pore diameter distribution curve) and (b) Release profile at pH7.4 of ZnPc/NORM.

ABMDMA dye is used as a chemical probe for the photo-induced detection of singlet oxygen ($^1\text{O}_2$). The ABMDMA is a water soluble and was photobleached by singlet oxygen ($^1\text{O}_2$) to its non-fluorescent derivative endoperoxide. Thus, the formation of endoperoxide clearly display the generation of singlet oxygen ($^1\text{O}_2$) and it was

seen spectrophotometrically by recording the decline in optical density at 400 nm (corresponding to the absorption λ_{max} of ABMDMA), as given in figure 4. First, only ABMDMA dye was irradiated and observed that there is no significant change in absorption with irradiation time (Figure 4a). On the other hand, a slight decrease in absorption was perceived for free ZnPc and AMBDMA solution (Figure 4b). But when we irradiated ZnPc/NORM and AMBDMA solution, a significant amount of decrease in absorption was observed (Figure 4c). The photobleaching data is summarized in figure 4d. It can be concluded that significant production of singlet oxygen ($^1\text{O}_2$) occurs due to light irradiation on ZnPc/NORM NPs, which thus is a promising platform for PDT [36-39].

Figure 4: Absorbance versus wavelength plots for the decay of ABMDMA with (a) just ABMDMA, (b) ZnPc with ABMDMA, and (c) ZnPc/NORM with ABMDMA. (d) $\ln(A/A_0)$ versus time plots of all the samples showing the decrease in optical density of ABMDMA at 380 nm.

Photoactivated ROS generation is often accompanied by increase in temperature of the system (photothermal effect) [32]. In order to examine the photothermal effect of ZnPc/NORM, we investigated temperature rise of the system as a part of time of laser light irradiation. Figure 5 shows that comparative temperature rises of aqueous solution of NORM and ZnPc/NORM continuously irradiated with a diode laser light (power density 40 mW/cm^2) having wavelength of 635 nm. A pen type digital multi thermometer was utilized to correctly measure the change in temperature of the prepared solution after the light irradiation. From the data it can be observed that a temperature rises of only 0.7°C is observed after irradiating NORM sample for a total of 25 minutes. The same exposure conditions on ZnPc/NORM led to a temperature rise of 18.9°C . The result indicates that ZnPc/NORM particles also act as good

photothermal agents, in addition to their PDT effect. However, the rise in temperature is due to the associated singlet oxygen production or not is unknown at this moment.

Figure 5: Temperature versus time plots of different samples.

To examine the Cell viability after PDT *in vitro*, A549 cells were treated with seven different concentration of ZnPc/NORM particles (20, 50, 100, 150, 200, 250, 300 $\mu\text{g/ml}$) and studied the result by MTT assay [37,38]. As shown in figure 6, the ZnPc/NORM particles are non-toxic at all the concentrations tested in the dark (Non-radiated). However, upon light irradiation (Radiated), significant toxicity (about 76% cell death) is observed at the treatment concentration of 300 $\mu\text{g/ml}$. Cells treated with the pure (free) ZnPc equivalent (7.8 $\mu\text{g/ml}$ to that of dosage 300 $\mu\text{g/ml}$ for NORM) did not show much cytotoxicity (about 21% cell death) after light exposure. The result are in agreement with the $^1\text{O}_2$ (singlet oxygen) photogeneration data, where the ZnPc/NORM shows the maximum PDT efficiency.

Figure 6: MTT assay studies in A-549 cells treated with ZnPc/NORM at various concentrations and pure ZnPc, without (Dark) and with (Light) 635 nm diode laser for 10 min.

Figure 7: Low magnification (a) FE-SEM and (b) TEM images of ZnPc/NORM.

Figure 8: NMR data of Zinc Phthalocyanine (ZnPc).

Figure 9: The MALDI-TOF Mass spectra of Zinc phthalocyanine (ZnPc).

Figure 10: The UV-Visible absorbance Spectra of ZnPc encapsulated NORM.

Conclusion

In this report, we have synthesized zinc phthalocyanine (ZnPc) nanoparticles embedded in NORM by a simple microemulsion technique. The FESEM and TEM images confirmed the successful encapsulation of ZnPc within the NORM particles with small hydrodynamic size, and good biocompatibility. The XRD and FTIR results of the NORM/PS sample also reinforce the fact that the ZnPc particles are embedded inside the NORM particles. The photobleaching of ABMDMA dye with ZnPc encapsulated NORM shows a greater yield of singlet oxygen species than the pure ZnPc under laser irradiation. Thus, it can be confirmed that the ZnPc/NORM sample shows good PDT effect than the pure ZnPc. Furthermore, cell viability assays result also showed that the cytotoxicity effect of ZnPc/NORM is high and it improves with the enhancement in the concentration of the nanoparticles. However, pure ZnPc showed low cytotoxicity because of less generation of ROS. Encapsulation of ZnPc in the NORM enhanced its stability in an aqueous medium and improved phototoxicity. The ZnPc/NORM sample also showed a good PTT effect with a temperature rise up to 42.8 °C for 25 min laser irradiation. The data shows that these ZnPc/NORM can be used in sustained drug release applications, and can avoid faster and burst-release behavior witnessed with other drug nanocarriers, including some MOF formulations.

Supplementary Information

This manuscript contains Electronic Supplementary Information (ESI), which contain data of ¹H-NMR data of Zinc Phthalocyanine (ZnPc), The MALDI-TOF Mass spectra of Zinc phthalocyanine (ZnPc) and the UV-Vis absorbance color spectra of ZnPc encapsulated NORM.

Conflicts of Interest

There are no confrontations of attention.

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