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Enhancing the anti-gastric cancer activity of curcumin with biocompatible and pH sensitive PMMA-AA/ZnO nanoparticles

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ABSTRACT

Curcumin loaded ZnO nanoparticles were successfully synthesised and encapsulated with co-polymer PMMA-AA (Cur/PMMA-AA/ZnO NPs). The ZnO nanoparticles have been converted as good cargo materials to carry the well-known hydrophobic drug curcumin by surface functionalization. Physical characteristics of these novel nanomaterials have been studied with transmission electron microscopy (TEM) and powder X-ray diffraction (XRD) in conjunction with spectral techniques. A narrow particle size distribution with an average value of 42 nm was found via TEM. Most importantly, the pH-responsive release of curcumin from the nano-vehicle ensures safer, more controlled delivery of the drug at physiological pH. The drug entrapment efficiency and loading was evaluated and the in vitro efficacy as anticancer drug delivery vehicle was analyzed. The potential toxicity of Cur/PMMA-AA/ZnO NPs was studied by using AGS gastric cancer cell lines via MTT assay. These results revealed that the proposed nanomaterials induce a remarkable cell death in in-vitro models. The multifunctional properties of Cur/PMMA-AA/ZnO NPs may open up new avenues in cancer therapy through overcoming the limitations of conventional cancer therapy.

1. INTRODUCTION

Chemotherapy is the most widely used frontline strategy for cancer therapy in clinics [1]. One of the most crucial obstacles for modern cancer chemotherapy is the limited availability of effective delivery systems for hydrophobic anticancer drugs. Drugs that are poorly solvable in the physiological environment require a complicated treatment to achieve intravenous administration. Over 40% of small-molecule anticancer drugs produced by pharmaceutical companies have poor water solubility [2,3]. Therefore; it is of great importance to build-up drug delivery systems with enhanced drug solubility. It may lead to improve their bioavailability and efficacy. Leveraging nanotechnology is a promising route to achieve this goal. The use of nanotechnology in cancer treatment offers some exciting possibilities, including the possibility of destroying cancer tumours with minimal damage to healthy tissue and organs, as well as the detection and elimination of cancer cells before they form tumours. The combination of biotechnology and nanotechnology has led to the development of new technologies that display potential in targeted therapy, molecular diagnosis, etc. [4–6]

Nanoparticles comprising biodegradable polymers may also play crucial role in providing a route to sustained, controlled, and targeted chemotherapy. Nanoparticle-based drug delivery systems provide exciting opportunities for safer and more effective targeted drug delivery using nanocarriers, particularly in cancer treatment [7,8] where the limiting factor is traditionally a lack of selectivity towards cancer cells and tissues [9]. Since, the nanocarriers with optimized physical, chemical, and biological properties are uptaken by cells more easily than larger drug molecules, so they can be successfully used as delivery tools for currently available bioactive compounds. Liposomes, [10] solid lipids nanoparticles, [11] dendrimers, [12] polymers, [13] and magnetic [14] nanoparticles are some of nanocarriers that have been tested so far. Hybrid materials [15–17] and inorganic materials [18–20] are upcoming materials for delivery [21,22] therapy [23,24] sensors [25,26] etc. The following references should be included into the introduction to show what they are currently used for and also some additional to show what they can be used in the future

Gastric cancer is a globally prevalent cancer with high incidence and mortality rates; it is notoriously difficult to treat [27]. In 2012, gastric cancer accounted for 8.5% of all cancer diagnoses in human [28] which high-risk populations typically residing in Japan, China, Eastern Europe, and Latin America. Interestingly, many south Asian countries, particularly India, have been found in reduced rates of gastric cancer

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because of their regular consumption of turmeric. Curcumin, a vibrant yellow spice, is a major constituent of the perennial herb (turmeric), and it is one of the widely studied chemopreventive agents, is a natural compound extracted from *Curcuma longa* L. It can induce cell apoptosis, especially in malignant cells, by causing DNA damage. Extensive research over the last half century has revealed that curcumin may inhibit the proliferation of numerous tumour cells in culture, prevent carcinogen induced cancers in rodents and inhibit the growth of tumours in xenotransplant or orthotransplant animal models [29].

ZnO nanoparticles with tunable size and shape exhibit unique physical and chemical properties compared to the bulk material [30]. In the drug delivery systems the ZnO has many advantages due to their less toxicity, stable towards environment and it has shown promising performance in biological applications [31]. The surface sites in the ZnO are the origin of charge trapping states that can be passivated by inorganic shells or by adsorption of organic molecules on the surface of ZnO nanoparticles [32]. Drugs incorporated with ZnO nanoparticles may promote the penetration into cancer cells by intracellular delivery through hydrophobic and coulombic interactions [33,34]. ZnO nanoparticles are stable around pH 7, but rapidly dissolve at pH < 6, and it can efficiently deliver the drugs at the specific target, since the tumour cells might stable at pH 6. Fortunately, ZnO itself is nontoxic, but after decomposition Zn^{2+} ions are cytotoxic. Since, the target was at lower pH ($\sim$5.4), it may triggered the intracellular and open-up the polymer links in nanocomposite and releases the respective drug/drugs, at this stage the non-toxic Zn^{2+} also separated out from the ZnO nanocomposites due to its dissolution. These subsequent processes in the drug delivery system, causes mitochondrial dysfunction which in turn produces reactive oxygen species (ROS), lipid peroxidation and DNA damage [35].

According to the NCI Alliance for Nanotechnology in Cancer (https://nano.cancer.gov/learn/now/), the first nanotechnology-based cancer drugs (Doxil and Abraxane) are already on the market and some others are in clinical trials. These inspiriting observations and applications of nanoscale drugs are motivated us to develop a co-polymer encapsulated ZnO nanoparticles for loading natural hydrophobic drug, curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione). Curcumin is highly safe even at high doses but it has some notable limitations due to its poor aqueous solubility, as a consequence it has poor oral bioavailability and multidrug resistance [36]. In order to overcome this limitation and improve its therapeutic efficacy we developed a copolymer encapsulated nanoparticles using shell cross linking technique. In this connection, PMMA was linked with AA, consequently we developed a PMMA-AA copolymer using free radical polymerisation. The PMMA is hydrophobic and AA is hydrophilic polymers, therefore the obtained copolymer (PMMA-AA) will be amphiphilic in nature. PMMA and AA polymer are linked by thiol click method. The thiol which hydrophobically functionalizes the surface of the nanoparticles and direct them to the hydrophobic interior of a shell. PMMA is biocompatible polymer [37]. Therefore, here we report the delivering ability of PMMA-AA encapsulated curcumin in ZnO nanocomposite hydrophobic core as extensive carrier. Moreover, we also have demonstrated here the ZnO is the safe nanoscale level carrier to carry the proposed hydrophobic drug (curcumin) with high potential advantage at highly sensitive pH.

2. Experimental sections

2.1. Materials and methods

Zinc(II) acetate dihydrate with purity 99.5%, ethidium bromide, dimethyl sulfoxide (DMSO) were purchased from Sigma-Aldrich. Sodium hydroxide, curcumin, NaCl, disodium dihydrogen phosphate dehydrate and potassium dihydrogen phosphate were purchased from Merck and used for the preparation of phosphate-buffered saline (PBS). Methyl methacrylate (MMA) and acrylic acid were purchased from S.D.Fine-Chem Limited. All the chemicals used were of analytical grade and used without any further purification. Antibiotics for cell culture (penicillin at 10,000 units mL^{-1} and streptomycin at 10 g L^{-1}) were purchased from Sigma Aldrich. AGS human gastric cancer cell lines derived from human stomach adenocarcinoma was procured from the National Centre for Cell Science, India. DMEM-F12 Ham, Fetal Bovine Serum (FBS), and other growth supplements were purchased from Himedia Chemicals, India. Reagent grade 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was obtained from Calbiochem. Hoechst 33342 and propidium iodide (PI) stains were purchased from Invitrogen.

2.2. Preparation of citrate capped ZnO nanoparticles

Citrate capped ZnO nanoparticles were synthesised by using Zinc (II) acetate (2 g), trisodium citrate (1 g) and sodium acetate (1 g) in H_2O and the reaction solution heated at 70 °C for 5 h with vigorous stirring. The reaction temperature was slowly reduced to room temperature and allows it to stir for another 24 h. Finally, the solution was filtered, centrifuged and dried at hot plate for 100 °C, provided white precipitate as product.

2.3. Preparation of nanocurcumin

Nanoscale curcumin was synthesised as per our earlier reports [38] with slight modifications. Commercial curcumin (1 mg) in chloroform (25 mL) was added dropwise to hot distilled water maintained at 70 °C and stirred vigorously for 1 h. 1% w/w of PVA in distilled water was added in to the above reaction solution, and the temperature was gradually reduced to < 50 °C. Stirring was continued for another 2 h. This final solution was set aside for one day to settle down all the solids at − 8 °C. The settled solid particles were further separated by means of a REMI R-24 centrifuge at 4000 rpm, washed several times with distilled water to completely remove the PVA, and dried at 60 °C yielded a fine powder of nanocurcumin.

2.4. Synthesis of co-polymer

The PMMA-AA copolymers were synthesised via free radical polymerisation of appropriate mixtures of MMA with AA. For the copolymer synthesis, we employed the mixture in a dried flask fitted with a condenser which was purged with inert nitrogen gas in presence of DMF glutaronitrile (0.05 μL) is added. The mixture was refluxed under a temperature of 80 °C for 15 mins. MMA (1 g) and AA (0.83 g) was added to the above DMF mixture by dissolving MMA and AA in DMF (50 mL) the reflux process was continued for 3 h. After completion of the reaction the reaction solution was bring in to room temperature. The co-polymer mixture was poured into the sodium hydroxide (10 M) and potassium dihydrogen phosphate (0.2 M) mixture in distilled water and made up to volume of 20 mL in ice cold condition. The co-polymer solution was stirred for 30 mins, and the white colour precipitate was changed to pale pink colour. The final solution was filtered and washed with DD water and ethanol mixture to remove the excessive glutaronitrile.

2.5. Preparation of co-polymer particles

The non-cross linked PMMA-AA was prepared by double emulsion method. In brief, initially the co-polymer is dissolved in CH_2C_{l2}. 1 g of Polyvinyl pyrrolidinone in DD water (100 mL) was stirred in ice bath under 10,000 rpm. To the above primary solution, the above prepared co-polymer was gradually added at a uniform rate. Emulsification process continued for further 30 mins. For the secondary emulsification the primary emulsion was mixed with the 0.001 M of sodium chloride solution and mild stirring was continued for overnight in order to remove the excess DMF, yielded fine powder as co-polymer particles. The

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