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Mesopores Silica and Chitosan Coated Nanoparticles for Targeted Controlled Drug Delivery in Pancreatic Cancer Therapy

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ABSTRACT
Pancreatic cancer is a very aggressive and fatal cancer that is often diagnosed late with limited therapeutic choices. Conventional chemotherapy is faced with considerable limitations such as low drug bioavailability, systemic toxicity, and rapid clearance of drugs, leading to less-than-optimal therapeutic effects. Targeted drug delivery systems have now become a promising field to avoid these limitations. Among the other nanocarriers, chitosan-coated nanoparticles and mesoporous silica nanoparticles (MSN) are prospective carriers for targeted and controlled delivery of anticancer drugs in cancer treatment because of their distinguished physicochemical properties, including high surface area, tunable pore size, and biocompatibility.

Keywords: Nanoparticles, Pancreas, Cancer.

1. INTRODUCTION

Cancer is a condition characterised by the unregulated proliferation and maturation of atypical cells. There exist about 200 distinct varieties of cancer. Cancer and its therapies can impact various bodily systems, including the lymphatic, immunological, circulatory, digestive, and endocrine systems. The staging and grading of cancer provide insight into the potential growth rate of the malignancy and the most effective treatment options. However, for certain individuals, cancer may recur. Certain cancers cannot be cured but can be managed with various therapies, medications, and treatments. Among many cancers, pancreatic cancer (PC) is challenging to identify and treat, and there has been little progress in its therapy.

Presently, 97% of the disease burden from prostate cancer is attributed to years of life lost owing to early mortality, with a median survival duration of six to ten months for locally progressed cases and three to six months for metastatic cases. The intrinsic chemo-resistance of pancreatic cancer cells, coupled with compromised drug delivery mechanisms, is a significant obstacle in managing pancreatic cancer. Solid tumour masses are regarded as having insufficient vasculature accompanied by a pronounced desmoplastic response. Consequently, it becomes challenging for chemotherapeutic drugs to penetrate the stroma, thereby accessing the interior of these tumours. Instead, it is posited that this induces additional activation of drug-resistant mechanisms. Even for the widely utilised first-line chemotherapy drug gemcitabine, resistance develops rapidly. The chemo-resistant characteristics of pancreatic cancer cells, whether inherent (de novo) or acquired (therapy-induced), result in a low success rate. Consequently, there has been minimal enhancement in the overall survival rate of pancreatic cancer over the past several decades.

Pancreatic cancer arises when pancreatic cells undergo mutations and proliferate uncontrollably, resulting in tumour formation. "The pancreas is a gland located in the abdominal cavity, situated between the spine and the stomach." It produces hormones that regulate blood glucose levels and enzymesthatfacilitatedigestion. The majority of pancreatic tumours originate in the ducts of the pancreas. The principal pancreatic duct (duct of Wirsung) links the pancreas to the common bile duct. Initial pancreatic neoplasms are not detectable with imaging examinations. Consequently, numerous individuals do not obtain a diagnosis until the cancer has metastasised. Pancreatic cancer exhibits resistance to numerous conventional oncological therapies.

2. MATERIALS AND METHODS

Material

N-cetyltrimethylammonium bromide (CTAB), tetraethylorthosilicate (TEOS), sodium hydroxide (NaOH), dialysis membrane (cut-off 12 kDa) and 3-(4,5-dimethylthiazol-2-yl)-2,5- diphenyl tetrazolium bromide) (MTT reagent) were

purchased from Sigma Aldrich Mumbai, India. Curcumin (95% purity) was obtained from Alfa Aesar, India. Pancreatic cancer cell line (MIA PaCa-2) was obtained from national centre for cell science (NCCS), Pune, India. Dulbecco's modified e□gle medium (DMEM), dulbecco'sphosph□te-buffered saline (DPBS), fetal bovine serum (FBS), trypsin, streptomycin and trypan blue were purchased from HiMedia, India. All chemicals were used as received, without further purification. Deionized water (DW) (Millipore, 18.2 MΩ-cm) was used for all experiments.

Loading of curcumin in MSN

Rotary evaporation method was used for loading of curcumin in MSN. 160 mg of MSN was placed in the rotary evaporation flask followed by addition of 40 mg of curcumin to it. 10 mL of methanol was added to the flask, sonicated for 2 min using a bath sonicator and then attached to the rotary evaporator. Methanol was evaporated slowly from the suspension under vacuum and at a temperature of 50 °C for 10 min. These samples were designated as MSNCur. The amount of curcumin loaded in MSN was calculated by thermogravimetric analysis (Diamond TG/DTA, Perkin Elmer, USA).

Synthesis of mesoporous silica nanoparticles

Initially, 0.25 g of CTAB was added to 120 mL of DW, followed by addition of 0.875 mL of 2M NaOH to it. The resulting solution was stirred for 1 h at 300 rpm and 35 °C. Then the temperature was raised to 80 °C, and 1.25 ml of TEOS (silica precursor) was added to the solution. Stirring was continued for 30 min at 80 °C. After that, the solution was cooled down to room temperature. Then silica nanoparticles were collected by centrifugation at 14000 rpm for 10 min. Solid products were filtered and washed several times using water. They were dried-up overnight in the oven. Later, to remove the surfactant, CTAB was removed by calcination of nanoparticles in the furnace at 540 °C for 6 h. MSN was then stored at room temperature.

In vitro drug release

Equal amount of drug loaded nanoparticles were added into separate dialysis bags and kept in falcon tubes containing 35 mL of PBS (1% Tween 80) at pH 7.4 and pH 5.5. The falcon tubes were kept at 37 °C, with constant shaking (100 rpm) in orbital shaker. The samples were taken out at predetermined intervals and replaced with a fresh amount of PBS. Then 2 mL of methanol was added to 1 mL of sample and sonicated for 10 min, followed by centrifugation at 10000 rpm for 10 min. The collected samples were analyzed by UV-Vis spectrophotometer at an absorbance of 428 nm for curcumin, to determine the amount of drug released.

Nanoparticle characterization

The hydrodynamic size of nanoparticle formulations was analysed using zetasizer Nano-ZS (Malvern). The morphology of the nanoparticles was studied using high-resolution transmission electron microscope (JEOL JEM 2100 ultra HRTEM 200 kV). The various functional groups and bonding in the nanoparticles were confirmed by FTIR (3000 Hyperion Microscope, Bruker). The surface area, pore size and pore volume of nanoparticles were calculated using surface area analyzer (QuantachromeAutosorb AS-1Version-1.55).

In vitro cytotoxicity

The sensitivity of human pancreatic Mia PaCa-2 cells to the drug and drug-loaded nanoparticle were determined by MTT colorimetric assay. After cells reached the 90% confluency in 25 cm2 flask, the cells were counted using a hemocytometer. The cells were seeded at a density of 5000 cells per well and then incubated for 24 h at 37 ºC, 5% CO2. After 24 h, the supernatant was removed from each well and washed with PBS once. The biocompatibility study of MSN on Mia PaCa-2 cells was done at a concentration from 100 to 500 µg/mL for 48 h. The drug and drug-loaded nanoparticle added to cells at concentration from 5 to 25 µg/mL for 48 h. The supernatant was removed from each well and given PBS wash once to remove the dead cells. The cells were treated with MTT reagent and then incubated for 4 h. The supernatant was removed, and 100 µL of DMSO added to each well to dissolve the formazan crystals. The optical density was recorded at 565 nm in plate reader. All experiments were done in triplicate.

$$\%\ of\ cell\ viability = \frac{MeanOD_{sample}}{Mean\ OD_{negative\ control}} \times 100$$

Internalization of curcumin using confocal laser scanning microscopy

The internalization of curcumin within cancer cells was analysed using confocal microscopy. $5x10^4$ cells were seeded on the coverslip and then allowed to attach for 24 h. 20 µg/mL of curcumin and equivalent curcumin loaded MSN were added to 12 well plate and kept in an incubator for 12 h. Then 1 mL of PBS was given twice to the cells to remove the excess drug present on the cell membrane. 4% paraformaldehyde solution was added to cells and kept in an incubator for 10 min, to fix the cells. Then the cells were washed twice with PBS. Then the coverslips were mounted on glass slides using VECTASHEILD. The coverslips from the plates were taken out and put on the glass slide inversely. Immediately, a nail polish coating was applied around the coverslips to avoid the formation of bubbles. Later, the slides were taken for imaging, using the green laser.

Loading of doxorubicin in MSN-NH_2

25 mg of MSN-NH2 were dispersed in 5 mL of dox solution (4 mg/mL) in DW and then stirred magnetically at 200 rpm for 12 h. The drug loaded MSN-NH2 were then collected for lyophilization, after centrifugation at 14000 rpm for 10 min. Then to quantify the drug loading amount, the supernatant was analyzed using UV-Vis spectroscopy at the wavelength of 480 nm. The samples were designated as MSN-NH2-Dox.

Drug loading % = [(Minitial – Msupernatant)/(Minitial + MMSN)] x 100

Drug entapment efficiency = [(Minitial – Msupernatant)/Minitial] x 100

Where Minitial = initial amount of drug

Msupernatant = amount of drug present in supernatant

MMSN = amount of nanoparticle

3. ANALYSIS AND INTERPRETATIONS

Mesoporous silica nanoparticles improve the therapeutic effect of curcumin in pancreatic cancer cells

Surgery, radiation, hormone therapy, and chemotherapy are employed in the treatment of pancreatic cancer patients. Conventional chemotherapy indiscriminately attacks cells in the human body, so impacting both malignant and healthy cells. Consequently, numerous detrimental side effects are noted. Traditional chemotherapy induces detrimental side effects in normal cells due to its nonspecific nature, inefficacy, inadequate targeting, and insufficient dosage in cancer treatment. Curcumin, a natural di-phenolic molecule derived from turmeric, is renowned for its numerous therapeutic characteristics, particularly its anticancer effects. This natural polyphenolic substance exerts its anticancer effects on pancreatic cancer by regulating many molecular processes, primarily through the reduction of NFκB and STAT3 activation, inhibition of PI3K/AKT signalling, and overexpression of FOXO1. Nonetheless, the primary issue with curcumin is its inadequate solubility, which constrains its actual anticancer efficacy. Clinical investigations in humans demonstrated that a minimum oral intake of 8 to 12 grammes of curcumin is required to detect nanogramme levels of curcumin in the bloodstream. A clinical research of curcumin involving 25 prostate cancer patients indicated that one patient experienced stable disease for over 18 months, while another exhibited a favourable response with a 73% reduction in tumour size.

A multitude of drug delivery vehicles has been developed, utilising calcium ferrite, naturally generated diatom biosilica, cyclodextrin, rod and core-cone shaped mesoporous silica, diatomaceous earth, iron oxide, liposomes, and polymers to enhance the efficiency of drug or protein administration. MSN possesses advantages such as facile production, homogeneous pore structure, elevated surface area, substantial pore volume, and enhanced stability. "Furthermore, the presence of silanol groups on the surface of MSN facilitates the functionalisation with various functional groups, enabling the attachment of diverse polymers, ligands, and fluorescent molecules to the nanoparticle." The objectives of this chapter are to develop mesoporous silica nanoparticles for curcumin delivery in the treatment of pancreatic cancer cells: (i) synthesis of mesoporous silica nanoparticles with a size of less than 200 nm, (ii) maximisation of curcumin release from the nanoparticles at an acidic pH of 5.5 compared to a normal pH of 7.4, and (iii) enhancement of the anticancer efficacy of curcumin utilising mesoporous silica nanoparticles.

4. RESULTS AND DISCUSSION

FTIR

Figure 1 shows the FTIR peaks of MSN, curcumin and MSN-Cur. The peaks at 1093 cm^{-1} and 3446 cm^{-1} are observed due to presence of Si-O-Si and -OH respectively. The peaks at 3508 cm^{-1}(-OH), 1629 cm^{-1} (C=O), 1600 and 1509 cm^{-1} (enol) (C=C), 1000-1300 cm^{-1} (CO-C) belong to curcumin. The peaks of C=O and C=C can be seen in the spectrum of MSNCur. The spectrum of MSN-Cur reveals the signature of both MSN and curcumin.

DLS, TEM and BET analysis

The hydrodynamic size of MSN increased from 97 nm to 103 nm after loading of curcumin in MSN. TEM image of MSN shows the presence of well-ordered porous structure with the hexagonal array, pore size of around 2-3 nm and mean diameter of 95 nm (Figure 4.2a). The curcumin is loaded in the pores of MSN, as it can be observed from Figure 4.2b and mean diameter of MSN-Cur was 99 nm. BET analysis shows that surface area reduced from 592 $m^2 g^{-1}$ to 207 $m^2 g^{-1}$, pore volume from 0.51 $cm^3 g^{-1}$ to 0.33 $cm^3 g^{-1}$, pore diameter from 2.3 nm to 2.25 nm, as one goes from MSN to MSN-Cur. These results confirm the presence of curcumin in MSN.

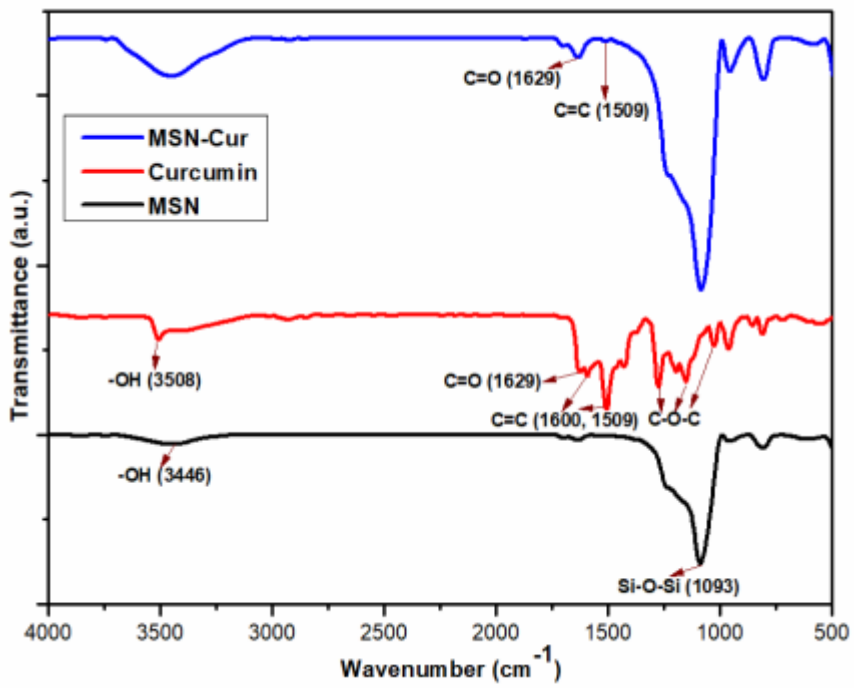

Figure 1: FTIR spectra of MSN, curcumin and MSN-Cur

DLS, zeta potential and BET analysis

The hydrodynamic diameter of MSN was 99 nm which increased to 160 nm for MSNNH_2-Dox-Chitosan after chitosan coating (Table 1). However, as expected hydrodynamic diameter for all samples were bigger than diameters obtained from TEM, because of the hydrate layer present around the nanoparticle. Surface zeta potential gives evidence for the potential stability of nanoparticles colloidal system. If all the particles in the suspension had highnegative or positive zeta potential value, then the particles will have the tendency to repel each other, resulting in no aggregation or accumulation due to weak interaction. Due to replacement of -OH by NH_2 due to functionalization by APTES, the zeta potential of MSN showed an increment from -18 mV to +5 mV. The zeta potential further increased from +5 mV to +26 mV in the case of MSN-NH_2-Dox-Chitosan (Table 1). This was observed because of chitosan coating over MSN-NH_2-Dox. BET analysis showed that surface area reduced from 617 to 126 $m^2\ g^{-1}$, pore volume from 0.54 to 0.19 $cm^3\ g^{-1}$, pore diameter from 2.32 to 2.27 nm, as one goes from MSN to MSN-NH2-Dox-Chitosan.

Table 1: DLS, Zeta potential and BET analysis of nanoparticle formulations

	Average size of nanoparticle obtained from DLS (nm)	Zeta potential (mV)	Surface area ($m^2\ g^{-1}$)	Pore volume ($cm^3\ g^{-1}$)	Pore diameter (nm)
MSN	99	-18	617	0.54	2.32
MSN-NH_2-Dox-Chitosan	160	+26	126	0.26	2.27
MSN-NH_2-Dox	110		187	0.31	2.28
MSN-NH_2		+5			

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