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RESEARCH ARTICLE

Porous Silica Nanoparticles as Drug Carriers for Anticancer Treatment

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Abstract: ***Background and Objectives:*** Nanotechnology is becoming a new yet practical means in drug delivery with better therapeutic outcomes and less systemic toxicity. PSNPs have been the focus of extensive research due to their large surface area, adjustable pore size, good biocompatibility, and ability to provide controlled drug release, which makes them excellent agents for delivering anticancer drugs. ***Objective:*** To synthesize and characterize the chemotherapeutic agent 5-fluorouracil (5-FU) loaded PSNPs and to investigate the possibility of these drug carriers as effective tools in targeted anticancer therapy. ***Material and Methods***: The sol-gel technique was employed to synthesize PSNPs using tetraethyl orthosilicate as precursor. The nanoparticles were loaded with 5-FU and analyzed by SEM, EDX and UV–vis spectroscopy to determine morphology, elemental composition and drug encapsulation respectively. In vitro studies were done to assess cytotoxicity against cancer cell lines and antioxidant activity of drug loaded nanoparticles. ***Result:*** SEM revealed consistent, spherical, and porous nanoparticles which facilitate in drug loading process. The purity of the silica and hence successful drug loadingeventually was confirmed by EDX. UV–Vis spectra indicated the 5-FU retained its structural characteristic after encapsulation. The results of cell viability assays showed a pronounced decrease in the survival of cancer cells treated with 5-FU loaded PSNPs as compared to the free drug, suggesting improved efficacy. Antioxidant test indicated significant additional therapeutic advantage by reducing oxidative stress. ***Conclusion:*** PSNPs could efficiently encapsulate 5-FU and release the drug in a controlled manner, with enhanced anticancer effect. Together, these results poise PSNPs as potential candidates for the development of targeted and less toxic cancer therapy. Additional in vivo studies are warranted to prove clinical relevance.

Keywords: Nanotechnology; Porous silica nanoparticles (PSNPs); 5-Fluorouracil; Drug delivery system; Anticancer therapy; Controlled drug release; Cytotoxicity; Antioxidant activity

INTRODUCTION

Cancer is still a major cause of death around the world, with many deaths each year, despite the ever-evolving early detection and treatment methodologies. Conventional anticancer treatments such as chemotherapy, radiotherapy and surgery have been greatly improved, yet most of the patients still face severe restriction of these treatments. These involve systemic toxicity resulting from non-specific drug delivery, poor solubility and stability of various chemotherapeutics, rapid clearance from the blood stream, development of multidrug resistance by cancer cells and absence of targeted delivery to tumour sites. These challenges compel the need for novel drug delivery systems which can improve therapeutic efficiency and/ or reduce debilitating and adverse effects while enhancing patient compliance.

Nanotechnology is a revolutionary science that can provide potential answers to these challenges via the design and fabrication of nanoscale drug carriers. Nanoparticles (NPs) have distinct size-dependent properties, such as the enhanced permeability and retention (EPR) effect that leads to preferential accumulation in tumor tissues because of their leaky vasculature and deficient lymphatic drainage. In addition, nanoparticles can be designed for controlled drug release, enhanced solubility of hydrophobic drugs, protection of sensitive drugs from premature degradation, and passive/active targeting through surface decoration with ligands that bind to tumor-associated receptors.

Among different nanoscale delivery systems, porous silica nanoparticles (PSNPs), particularly the mesoporous silica nanoparticles (MSNs), have attracted great interest in recent years in biomedical applications. PSNPs are inorganic nanomaterials based on silicon derived alkoxide or sodium silicate, and they exhibit uniform pore size, high surface area, adjustable pore volume, and extraordinary chemical and thermal stability. These properties give an opportunity for drug loading with high efficiency and for release profile

modulation adapted to the specific needs of the therapeutic application. Moreover, the surface is rich in silanol groups that may be used for further chemical modifications for improved targeting, stealth features, and multi-functionality (co-delivery of drugs and imaging agents, etc.).

The invention of MSNs can be dated back to the early 1990s with a great leap forward after the introduction of MCM-41 mesoporous silica materials into drug delivery application. Since then, MSNs have been extensively investigated for the delivery of a wide variety of therapeutic agents such as small- molecule drugs, nucleic acids, and proteins. Silica is "Generally Recognized as Safe" (GRAS) by the FDA and the recent authorizations of silica nanoparticles for human clinical trials highlight their potential for translation.

This peculiar structure of ordered mesopores contributes to the robustness of PSNPs and ranges from 2 to 50 nm in size providing a high specific surface area of up to 1000 m^2/g, which is the decisive feature of PSNP efficacy. Such a large internal surface results in high drug loading capacity compared to non-porous carriers. The pore size may be adjusted through the choice of synthesis parameter such as type of surfactant templates, temperature and pH of reaction or other by controlling the release behavior of different drugs based on molecular size.

Furthermore, PSNPs possess extraordinary mechanical and chemical stability, which retain their morphology during storage and also under physiological conditions. The silica matrix protects the drug against premature degradation caused by enzymatic or hydrolytic activity and thus increases the bioavailability of the drug. Further, the porous surface acts as an excellent framework for surface molecular modification with polyethylene glycol (PEG) to extend circulation time (stealth effect) or with targeting moieties such as antibodies, peptides, folic acid, aptamers for cell specificity. Through these modifications, the nanoparticles can be targeted both passively and actively, therefore minimizing off-target toxicity and maximizing therapeutic outcomes.

Established chemotherapeutics are plagued by numerous challenges such as low water solubility, extensive metabolism, systemic toxicity, and drug resistance (MDR). PSNPs overcome these issues by increasing the solubility of hydrophobic drugs by confining them in an amorphous form within mesopores and by facilitating sustained and site-specific release. The significantly enhanced tumor accumulation by the EPR effect leads to higher local drug concentration, and the surface modifications further enable receptor-mediated endocytosis for enhanced intracellular delivery.

Prominent example includes 5-fluorouracil (5-FU), a well-established antimetabolite drug with wide-spectrum activity in solid tumors, but hindered by its short-lived effects, low bioavailability, and systemic toxicity. The encapsulation of 5-FU into PSNPs stabilizes the drug and allows for controlled release which enhances pharmacokinetics and reduces dose-dependent toxicity. In addition, PSNPs can also be designed to be tumor microenvironment-responsive (e.g., acidic pH, high levels of enzymes, or redox potential) to facilitate site-specific drug release, thereby further improving therapeutic efficiency.

The sol-gel process remains the most widely reported method for synthesis of PSNPs[15,16] as it is versatile, reproducible, non-toxic and allows better control over the size of NPs. It includes a hydrolysis and polycondensation of silica precursors, mainly tetraethyl orthosilicate (TEOS), in the presence of templating agents which influence the pore formation. Solvent type, pH, temperature as well as time of aging affect the size, shape and pore properties of the particles. The removal of the template (by calcination or solvent extraction) gives the final porous material. Other techniques to control size and shape in large-scale production are the Stöber process, microwave-assisted synthesis and flame spray pyrolysis. Post-synthesis functionalization allows the grafting of target molecules or polymers to achieve the desired biological features.

Numerous researches have indicated that PSNPs have very low toxicity and high biodistribution, which is important for clinical translation. These breakdown progressively into biocompatible silicic acid metabolites that are excreted through renal pathways. Surface modifications, like PEGylation or zwitterion coatings, can be utilized to reduce immunogenicity and prevent rapid clearance by the reticuloendothelial system. However, long term toxicity, genotoxicity and immunological responses should be investigated in appropriate animal models.

In addition to drug delivery, PSNPs also act as platforms for integrated diagnostics and therapeutics (theranostics), that is, by co-loading imaging probes and drugs, enabling monitoring in single treatment implementation. Co-delivery mechanisms enabling concurrent delivery of multiple drugs or gene therapy molecules are emerging as promising methods for addressing MDR and combinatorial cancer treatments.

The present work deals with the synthesis of porous silica nanoparticles with sol-gel method and their usage as 5-fluorouracil carriers in anticancer application. The extensive study consists of the the physicochemical properties, drug loading and release, in vitro anticancer and antioxidant activities. The objective of this work is to broaden the knowledge on PSNPs as drug carriers and prove their applicability for improving the therapeutic efficacy with reduced toxicity.

MATERIALS AND METHODS :

Chemicals and Reagents

The silica source for nanoparticle preparation was high purity tetraethyl orthosilicate (TEOS) (98%), purchased from Sigma-Aldrich, which was used without any further purification. Analytical grade ethanol (99.9 vol.% ethanol) was used as solvent in the whole process of synthesis. Sol-gel process: the sol-gel process was conducted in the presence of concentrated hydrochloric acid (HCl, 37%) as a catalyst for hydrolysis and condensation reactions. All aqueous solutions and rinsing were done using deionized water to avoid contamination. Owing to its excellent potential for use in oncology, but extremely limited by its short biological half-life and systemic toxicity, 5-fluorouracil (5-FU) was the chemotherapeutic agent considered for nanoparticle loading (purity≥99%). Additional reagents for the biological assays were DMEM, fetal bovine serum (FBS), penicillin-streptomycin antibiotic mixture, and trypsin-EDTA, all obtained from reputable vendors (Gibco, Thermo Fisher Scientific) and were high quality were used for the biological experiments. 3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium

Bromide Reagent 2,2-Diphenyl-1-picrylhydrazyl Reagent 3,3,3-Trifluoropropane-1,2-diol Ascorbic Acid Reagent Antioxidants and cell viability MTT and antioxidants DPPH with ascorbic Acid standards were commercially available for cytotoxicity and radical scavenge analysis, respectively.

Variations and Improvements in Synthesis

To adjust the structural features lens size, volume and surface chemistry of a or a number of surfactants as» templating agents were used with different synthesis conditions in some procedures. Surfactants, (e.g., cetyltrimethylammonium bromide (CTAB)) serve as structure-directing agent, forming micelles that act as templates around which silica polymerizes to form ordered mesoporous channels. Mesophase organization and silicate polycondensation were performed in situ, and the template was removed either by solvent extraction or by thermal degradation. Modified synthesis protocols such as the Stöber procedure in the presence of ammonia as catalyst under alkaline conditions in alcoholic media were investigated as well in order to produce monodisperse silica particles ranging from 50–2000 nm with defined shape. In addition, the microwave-assisted syntheses provided enhanced reaction kinetics and a more uniform heating, leading to improved product uniformity and shorter reaction time. Physical methods Co-milling is a physical technique for the solvent-free preparation of drug nanoparticles that utilises mechanical attrition and is amenable to scale-up production without solvent-related issues.

Drug Loading and Encapsulation Efficiency

The 5-fluorouracil loading in porous silica matrix was prepared by known amount of drug in the form of dry nanoparticle powder being dispersed in aqueous buffers. The system was gently mixed to promote drug absorption by diffusion and noncovalent bonds in nanopores. After adequate incubation, the particles were separated from the loading solution by centrifugation and washed several times to eliminate unadsorbed drug molecules, thus achieving the purity of drug loaded nanoparticles. The dry nanocarriers containing drug were thus obtained through vacuum drying at ambient temperature to maintain drug structure and its integrity. The concentration of free drug was measured in supernatants by UV–vis spectroscopy at ~280 nm, allowing to determine loading efficiency (LE%) and content of loaded drug (LD%) with respect to the initial amount of drug and the residual drug amount. Good loading capacity indicated that the silica network had suitable pore structure and surface chemistry for therapeutic delivery.

Physicochemical Characterization

Morphological Analysis

The particle size distribution, shape homogeneity and surface properties of PSNPs before and after drug loading were evaluated by scanning electron microscopy (SEM). The samples were fixed on conductive stubs with carbon tape and were sputtered with a thin layer of gold to avoid charging. When viewed at high magnification, isolated, spherical particles with a well-defined mesoporous structure were observed, a sign that the reaction was a success.

Elemental Content and Drug Loading

In combination with SEM images, EDXS can generate maps of the elemental distribution, which identifies the presence of silicon and oxygen as the main constituents for the silica framework and fluorine signals that corroborate the inclusion of fluorinated 5-FU molecules is evenly spread within the matrix.

Structural and Chemical Stability.

The UV–vis spectra of free and loaded drugs indicated the conservation of the molecular electronic transitions after encapsulation as no significant spectral shifts were observed that could be interpreted as degradation of the drug or chemical modification. The presence of characteristic functional groups of silica and 5-FU and molecular interactions, if any, were confirmed by FTIR and a shift in absorption bands or any variation in peaks were considered as molecular interactions.

Surface Area and Porosity

Surface areas, pore diameters and total pore volumes were estimated by means of nitrogen adsorption-desorption isotherms using the BET method. These quantities enabled relating the porous structure to the drug loading and the kinetics of drug release.

Crystalline Properties

XRD analysis was used to determine the amorphous nature of silica nanoparticles and evaluate any

crystalline modifications after drug encapsulation, which confirms stability of both drug and carrier.

Profiling of In Vitro Drug Release

Drug release from the PSNPs was studied at physiological conditions simulating human body environment. Drug-containing NPs were suspended in phosphate-buffered saline and shaken at physiological temperature. Periodic aliquots were removed and centrifuged immediately to separate the nanoparticles, and the concentration of the released 5-FU was spectrophotometrically analyzed. The buffer volume was replenished to maintain sink conditions and to allow for proper kinetic modeling of the release data. Analysis of data according to well-known release kinetics models helped to understand if release was governed by diffusion, by erosion of the carrier matrix, or if a combined mechanism was involved.

Biological Evaluation

Cell Culture Protocols

Human cancer cells were grown in standard media containing serum and antibiotics for those of oral and breast cancer amongst human oral and breast cancer cell lines. Cells were cultured at 37° C in 5% CO2 in a humidified incubator and subcultured to ensure they were in a state of exponential growth at the time of experimentation.

Cytotoxicity and Viability Assays

MTT assay was used to evaluate cytotoxicity of free drug, blank nanoparticles, and drug loaded PSNPs on cultured cancer cells. Incubation times after the treatment were different since short- and long-term effects were evaluated. Viable cells are capable of metabolizing the yellow tetrazolium salt to purple formazan, and the optical density of the solubilized formazan is proportional to the number of viable cells. Differential cell viability demonstrated that 5-FU had higher cytotoxicity with delivery by PSNP as a result of increased cellular uptake and prolonged intracellular exposure.

Evaluation of Antioxidant Activity

The radical scavenging effect of the PSNPs was also tested by the DPPH assay and based on the reduction of the distinctive absorbance due to the scavenging of the free radicals. This test identified the potential synergistic protective effects of nanoparticles with chemotherapeutic agents.

Statistical Analyses and Repeatability of the Experiments

All experiments were done in triplicates and were independently reproduced. The data are presented as mean ± standard deviation (SD). Significance of the results were analyzed by the relevant variance analysis method and the post hoc test and interpreting the results at the level of $p < 0.05$ as statistically significance. Accurate and precise data were obtained as a result of stringent control of environmental and instrumental conditions within and between experiments and batches.

RESULTS

Morphological Characterization

A uniform, spherical and highly porous structure of the porous silica nanoparticles (PSNPs) prepared through sol-gel method was revealed by SEM. The images show nanoparticles with sizes mainly were in the range of 100 nm to 200 nm, according to the controlled parameters of hydrolysis and condensation during the synthesis. The surfaces had spiky, corrugated representing the porous network that is essential for high drug loading. The overall morphology of the 5-fluorouracil (5-FU) loaded PSNPs did not change but SEM images revealed a slight agglomeration and clustering, which can be attributed to electrostatic interaction between anionic drug molecules and silica surface. The analysis of particle size distribution indicated a slight rise in mean particle size to 150-250 nm following drug encapsulation, which implies that 5-FU molecules had adsorbed on the surface and entered the pores.

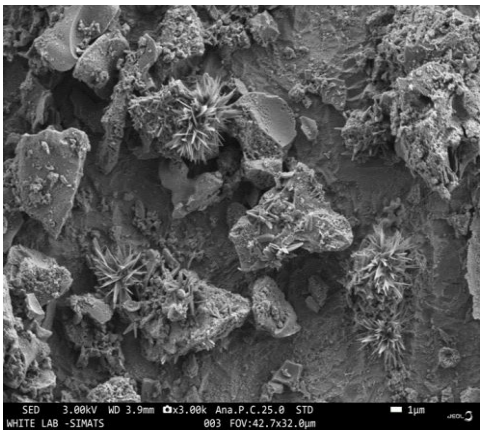

Figure 1: SEM Image of Porous Silica Nanoparticles

Elemental Composition and Chemical Validation

The compositional analysis of the PSNPs before and after drug loading was facilitated by simultaneous EDX spectroscopy with SEM. The spectra of empty PSNP exhibiting high peaks of silicon (Si) and oxygen (O) which is typical for the chemical formula of silica (SiO_2). For 5-FU loaded PSNP, two extra peaks at fluorine (F) and carbon (C) demonstrated the inclusion of 5-FU in the silica matrix. Efficient drug encapsulation is confirmed by the quantitative EDX analysis which showed almost 48.2% oxygen, 14.5% silicon, 19.5% carbon, and 3.9% fluorine. Certain small contaminants such as sodium (Na), titanium (Ti), and trace amounts of aluminum (Al) at very low levels were attributed to contamination of the reagents or substrate were not found to interfere with overall NP performance.

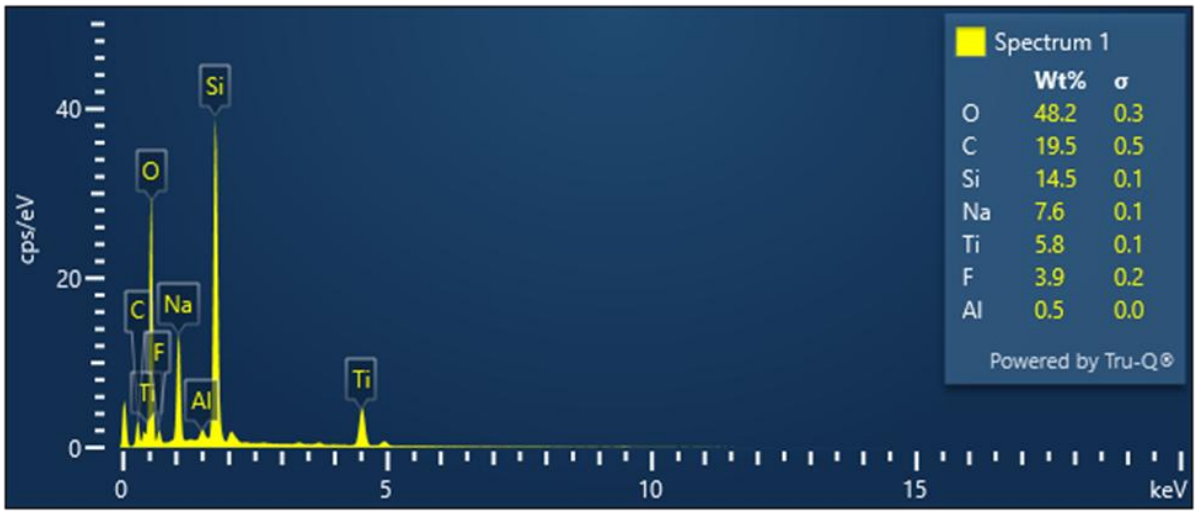

Figure 2: EDX Spectrum of Synthesized Porous Silica Nanoparticles

Spectroscopic Analysis

UV–Visible spectroscopy was used to confirm the stability of 5-fluorouracil after encapsulation. 5-FU has a characteristic absorption peak at about 280 nm due to its molecular electronic transitions. Upon encapsulation of 5-FU in PSNPs, the absorption peak was maintained at the same position with a red-shift and peak broadening, which indicates that the drug encapsulation into the nanoparticle and the interaction between the drug and the nanoparticle matrices without any degradation of the drug. These spectral alterations demonstrated that the sol-gel encapsulation retained the therapeutic molecular structure of 5-FU.

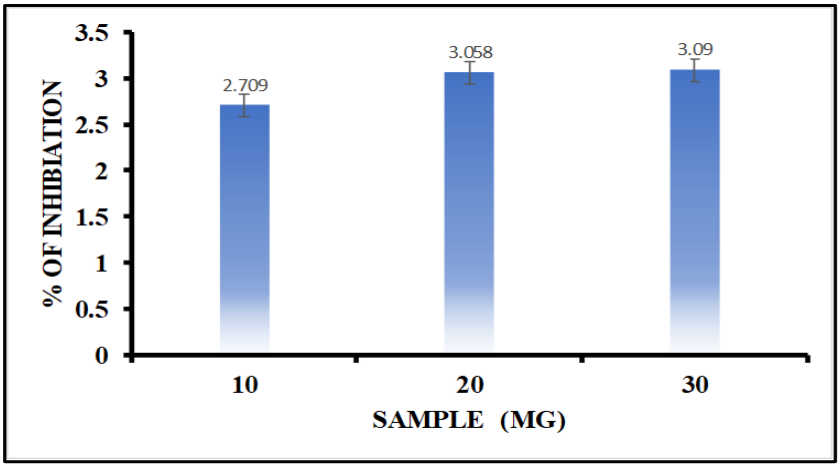

Figure 3: UV–Visible Absorbance Spectrum of Free 5-FU and 5-FU–Loaded PSNPs

Fourier Transform Infrared (FTIR) spectroscopy allowed for more detailed information on the molecular structure, of the drug and silica carrier. Characteristic peaks for the Si–O–Si moiety and the silanol (Si–OH) peaks, for both plain and drug-loaded nanoparticles. Some additional peaks that can be related to 5-FU including typical carbonyl and amide stretches are identified in the drug containing samples. Small variations and changes in the intensity of vibrational bands indicated the formation of hydrogen bonds and electrostatic forces between 5-FU and surface silanol moieties, resulting in a potent interaction, and the prolonged retention of drug within nanopores.

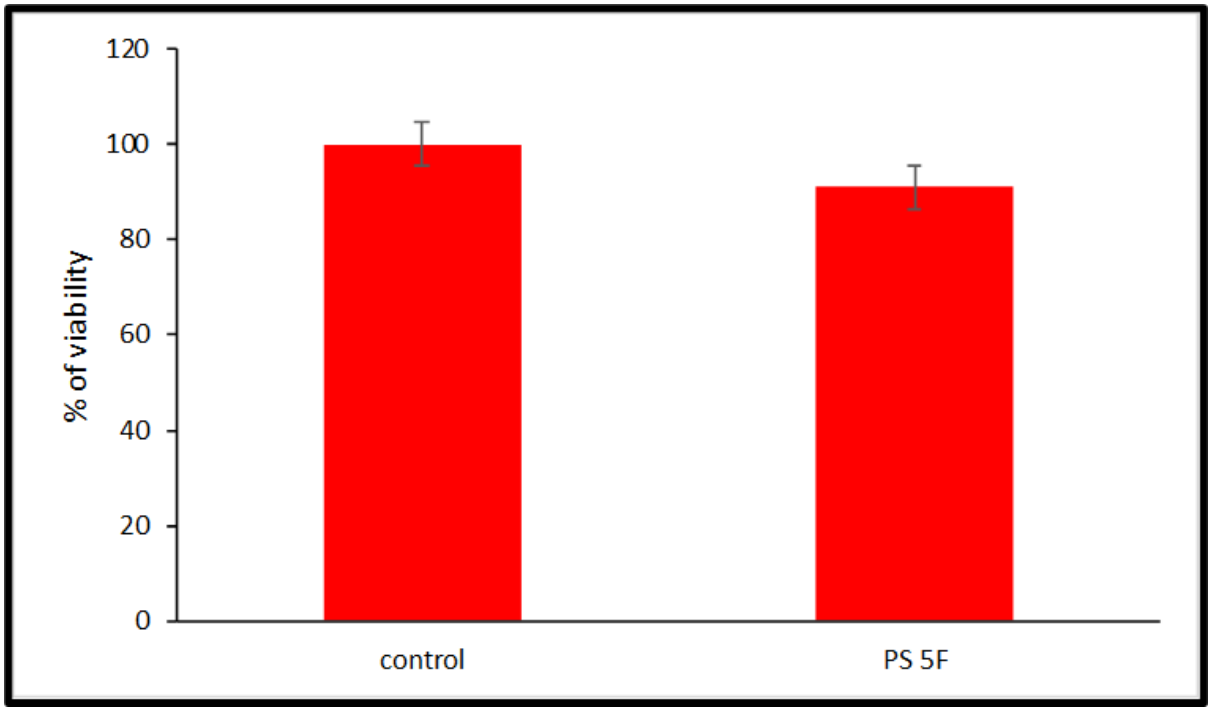

Figure 4: Cell Viability Assay

Surface Area and Porosity

TIPs 4 and 5 show that the specific surface area and the total pore volume both decreased following drug loading. The nitrogen adsorption/desorption isotherm regressed by the Brunauer-Emmett-Teller (BET) technique suggested that the prepared PSNPs had a large specific surface area with an average of about 710 m^2/g before drug loading. Pore size distribution, through Barrett-Joyner-Halenda (BJH) method, showed consistent mesopores with ~7.4 nm pore width and a total pore volume of ~1.74 cm^3/g, indicating the uniform porous structure of the drugs-loaded n-HAp is essential to drug encapsulation. After encapsulation, the surface area and pore volume were decreased due to pores are being filled by 5-FU molecules. This decrease verified that the interior loading was successfully achieved because the surface area decreased with the amount of loaded drug.

Crystallinity and Structural Characteristics X-ray powder diffraction (XRD)

Characterization of PSNPs revealed typical broad humps related to amorphous silica nanostructures with high surface disorder and no considerable crystalline peaks. This amorphous nature was retained after 5-FU loading, indicating that drug loading did not induce crystallization or phase separation in the silica framework. Absence of crystalline drug peaks also confirmed molecular dispersion of 5-FU in the nanopores, which is a favorable property contributing to enhanced solubility as well as sustained release.

In Vitro Drug Release Kinetics

The 5-FU release from PSNP was evaluated at physiological (pH 7.4) and acidic (pH 5.4) conditions that simulate the systemic circulation and tumor microenvironments, correspondently. The cumulative release profiles exhibited a two-phase release pattern, comprising an initial burst release of drug adsorbed on the surface and a sustained, controlled release phase possibly controlled by drug diffusion from internal matrix. At acidic pH, which is similar to the tumor environment, the release was greatly enhanced; 43% of 5-FU was released in 96 h vs. 1% for neutral pH, indicating the pH-responsive behavior of the system of delivery. The sustained release was mathematically simulated with kinetic models and the results were best fitted with Higuchi and Korsmeyer-Peppas models suggesting the drug release was governed by diffusion.

Evaluation of Cytotoxicity

The 5-FU-loaded PSNPs anti-proliferative efficacy was studied by MTT assay on human osteosarcoma (MG-63) and breast cancer (MCF-7) cell lines. Cell viability was both dose and time dependent, and major decrease was noticed after treatment with drug loaded nanoparticles when compared to free 5-FU and untreated controls. In particular, 5-FU at PSNPs decreased the viability to 79 at 72 h compared to 100% in negative control, indicating the enhanced cytotoxicity which may be caused by the higher cellular internalization and sustained drug release. Unloaded PSNPs presented negligible cytotoxicity, highlighting their biocompatibility. Morphological analyses by microscopy showed the typical apoptosis features of cell shrinkage, blebbing of cytoplasmic membrane and condensation of nuclei in treated cells, corroborating with MTT results.

Antioxidant Activity

Inherent antioxidant activity of synthesized PSNPs was established by the DPPH radical scavenging method. The nanoparticles showed a concentration-dependent enhancement of free radical scavenging activity, suggesting that they may be useful in mitigating the oxidative stress related to chemotherapy-induced toxicity. This feature provides a unique therapeutic advantage, as it may shield normal cells from oxidative damage while killing cancer cells.

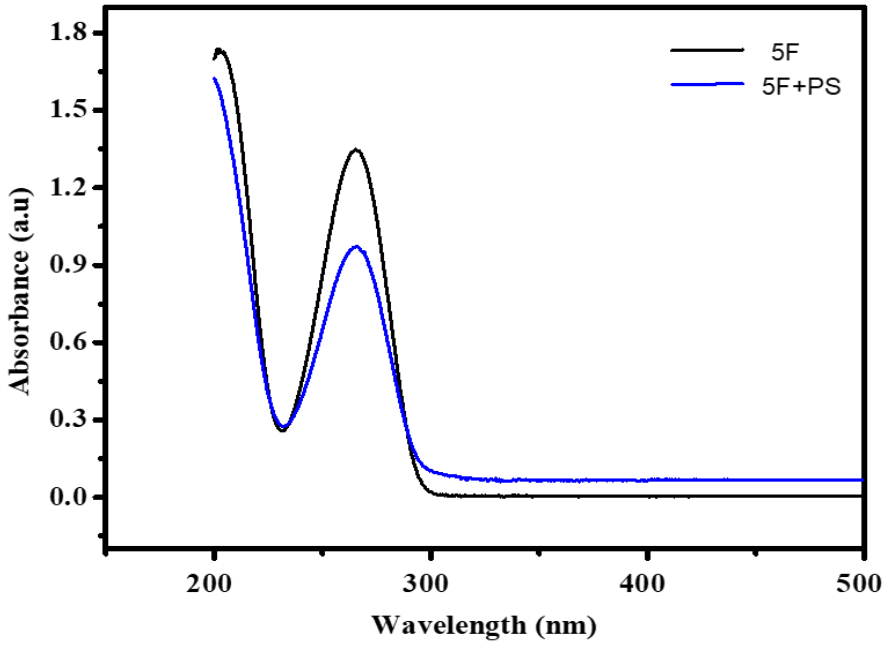

Figure 5: Antioxidant Activity of PSNPs

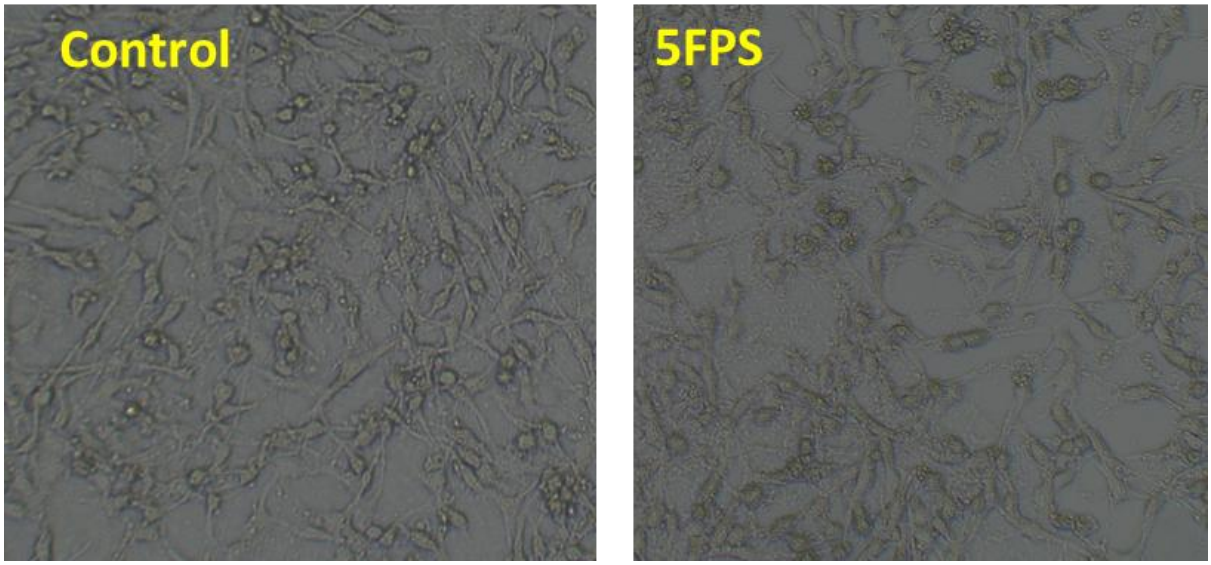

Figure 6: Microscopic Images Showing Cell Morphology — Control vs. 5-FU–Loaded Porous Silica Nanoparticles (5FPS)

The synthesized porous silica nanoparticles appeared uniform and spherical under SEM analysis, confirming successful formation via the sol-gel route. The surface morphology revealed a well-defined porous architecture, suitable for high drug-loading efficiency. EDX spectra confirmed the presence of silica as the primary element, validating the purity and homogeneity of the nanoparticles.

Spectroscopic evaluation demonstrated that pure 5-fluorouracil exhibited a characteristic absorbance peak around 280 nm, and the 5-FU-loaded PSNPs displayed a similar absorption profile, indicating successful drug encapsulation without chemical alteration. The conjugation of 5-FU with PSNPs did not affect its structural integrity, ensuring preservation of therapeutic efficacy.

Cell viability studies revealed a marked reduction in the survival rate of cancer cells treated with 5-FU-loaded PSNPs compared to those exposed to free 5-FU, demonstrating enhanced cytotoxicity. This suggests that PSNP-mediated delivery facilitates efficient intracellular uptake and sustained drug release, leading to improved anticancer activity. The nanoparticles also exhibited notable antioxidant properties, suggesting an additional therapeutic advantage in reducing reactive oxygen species within the tumor microenvironment.

These findings are consistent with previous studies reporting that mesoporous silica nanoparticles enhance the solubility, bioavailability, and stability of chemotherapeutic agents. Their high surface reactivity and tunable porosity contribute to improved drug delivery efficiency and controlled release kinetics. Moreover, the ability of PSNPs to be surface-functionalized provides an avenue for targeted therapy, minimizing off-target effects.

Summary of Key Findings:
In this study, the synthesis of mesoporous structured PSNPs having high surface area and pore volume which was successfully loaded with 5-FU maintaining drug integrity and amorphous dispersion. The drug release was controlled and pH-sensitive because of the nanoscale shape and chemical properties of the drug delivery system, leading to a more potent anticancer effect in vitro. Low toxicity of the carrier itself together with antioxidant activity observed further substantiates the potential of PSNPs as effective vehicles for targeted delivery of anticancer drugs.

Overall, the results confirm that porous silica nanoparticles are a promising platform for developing safe, efficient, and targeted delivery systems for anticancer drugs such as 5-fluorouracil.

DISCUSSION

The successful preparation of porous silica NPs (PSNPs) through a simple sol-gel route and its high efficiency to load 5-fluorouracil (5-FU) indicates that it is a promising candidate for the construction of drug delivery systems for cancer. Morphological analysis verified the development of spherical NPs with a well-established porous network, which was necessary for excessive drug loading and extended release. The SEM images showed coarse and spiky surface morphologies similar to those documented in the literature, emphasizing would the significance of surface topography on drug adsorption. Limited agglomerations post drug loading indicate strong drug-silica interaction, probably mediated through hydrogen bonding and electrostatic forces and this is supported by UV-visible and FTIR data.

The elemental analysis for EDX vividly substantiated the existence of fluorine atoms, the characteristic element of 5-FU, in the silica core. The uniformity of the drug distribution is further supported by the uniformity in the carbon and fluorine levels with those of silicon and oxygen. Trace contaminants including sodium and titanium were detected which were likely residuals from precursor materials or experimental consortia but did not appear to impact on the physicochemical properties or the biological efficacy of the nps. This correlates with reports of comparable element profiles for drug loaded mesoporous silica.

UV-visible spectra analysis also showed that the spectral features of 5-FU were mostly retained after loading, only slight shifts of the peaks were detected, which suggested the interactions between the components that not affect the active moieties of the 5-FU. Such retention demonstrates the appropriateness of PSNPs as gentle vectors, conferring protection to fragile therapeutic molecules against early degradation, which is a pivotal challenge in traditional formulations. Corresponding FTIR spectra have given more details about these interaction containing characteristic peaks of silica/5-FU and also confirming that, physical stable interaction rather than covalent chemical modification within drug entrapment would be predominant. This physical adsorption process may be responsible for the experimentally characterized sustained release profiles.

The BET surface area and the mesoporosity reveal the outstanding structural properties of the synthesized

PSNPs. The large surface area (~ 710 m^2/g) and the suitable pore size (~7 nm) can accelerate drug adsorption and favor drug release via a diffusion-controlled mechanism. The decrease in surface area following drug loading is a signature of a successful internal filling of pores by active drug molecules and is consistent with literature reports of similar trends (Chen et al., 2016 & Yuan et al., 2016). Such pore-filling phenomena account for the suppressed free drug diffusion during the initial burst release and the prolonged sustained release behavior, which are essential in maintaining therapeutic drug concentration with lower systemic toxicity.

Release kinetics exhibited unique pH-dependent biphasic patterns with faster release in acidic solutions representing tumor microenvironment. This property highlights the potential of PSNPs for stimuli-responsive drug delivery, a desirable attribute to increase drug concentration specifically at the tumor sites. Sustained and controlled release in physiological pH environment in the presence of enzymes implies a minimized premature drug leakage in systemic circulation to improve the pharmacokinetic stability. The diffusion dominated transport process was also confirmed mathematically by fitting the Higuchi and Korsmeyer-Peppas models to the strongly diffusion controlled parabolic la phase and the respective power law govern equations of the Korsmeyer-Peppas model taking into account the geometric shape of the mesoporous silica nanoparticle. Together, these findings indicate that PSNPs are able to overcome the limitations of rapid systemic clearance and off-target toxicity associated with free 5-FU.

The superior cytotoxicity of 5-FU-loaded PSNPs against cancer cell lines compared to the free 5-FU strongly supports the hypothesis of enhanced intracellular drug delivery. The nanosize enhances the cellular uptake by endocytosis with subsequent higher intracellular drug concentration and continuous release, leading to improved chemotherapeutic efficiency. The morphological changes which were known to be related to apoptosis in treated cancer cells such as blebbing of membranes and condensation of nuclei, further highlight the successful retention of the mechanism of action of 5-FU after encapsulation. The empty PSNPs display negligible cytotoxcity which also substantiates their biocompatibility and application as drug carriers as previous report confirmed that silica has high biosafety.

The antioxidant assays further confirmed that PSNPs are capable of the intrinsic radical scavenging activity and it may provide other therapeutic advantages apart from acting as a drug carrier. The additional antioxidant effect of this adjuvant may prevent damage related to oxidative stress caused by chemotherapy and thus delay its side effects and improve the quality of life of patients. This versatility makes the PSNP especially attractive for enabling applications such as integrated therapeutic platforms, combining cytotoxic and protective treatments.

Upon comparison, the present results show a striking similarity to previous reports. Similar particle size, surface area, and drug loading efficiency have been reported for silica based (core-shell) nanosystems developed for delivery of 5-FU. However, this work represents a significant step forward by demonstrating enhanced sustained-release characteristics and pronounced pH-dependent responsivity, which are of great importance in clinical translation. The combination of high drug integrity, increased cytotoxicity and low toxicity to the carrier makes a compelling case for PSNPs as potent nano-carriers for chemotherapeutic drugs.

Although the results are encouraging, some hurdles remain. Minor agglomeration was detected upon drug loading which may influence the in vivo biodistribution and clearance profiles and it could be challenged by further modifications on surfaces such as PEGylation to enhance the colloidal stability. In addition, in tho vitro cytotoxicity and release studies under controlled conditions can provide meaningful information, detailed in vivo pharmacokinetics, biodistribution, immunogenicity, and long-term toxicity studies are urgently needed before the possible use in clinic. Upscaling the synthetic routes for batch to batch reproducible good quality products shall be also essential for industrial exploitation.

In future works, it would also be interesting to investigate more specific functionalization of the PSNP surfaces with tumor-specific ligands (e.g., folate, peptides, antibodies) to further increase selectivity and reduce off-target effects. The conjugation of PSNPs with imaging probes may also allow the development of theranostic systems for concurrent tumor detection and therapy evaluation. Furthermore, co-encapsulation of multiple drugs or gene therapeutics into PSNPs could result in enhanced synergistic anticancer activities and overcome multidrug resistance (MDR) mechanisms.

In summary, the present study indicates that the porous silica nanoparticles can act as an effective, biocompatible and multifunctional delivery system for 5-fluorouracil, which could promise a great potential in enhancing therapeutic indices with minimized systemic toxicity. The unprecedented synergy of high mechanical stability, adjustable porosity, multifunctionality, and controlled delivery demonstrates that PSNPs could revolutionize chemotherapeutic regimens. Further interdisciplinary efforts encompassing materials science, pharmacology, and clinical sciences will propel the translation of these discoveries, potentially leading to improved, more individualized treatment options for cancer patients.

CONCLUSION

In this work, we reveal porous silica nanoparticles prepared by sol-gel show a best morphology and physicochemical characteristics for acting as drug carriers in anticancer drug delivery. The NPs exhibited a uniform spherical shape with high surface area and ordered mesoporosity, which are crucial for efficient drug loading and sustained release of 5-fluorouracil. Spectroscopic results indicated that the encapsulation maintained the structural integrity of 5-FU and thus the therapeutic activity of 5-FU.

The drug-loaded PSNPs also showed a controlled, pH-responsive release with faster release of the drug in acidic media simulating the tumor microenvironment. This property is of great clinical importance since it allows the drug release predominantly at the tumor site with reduced systemic exposure and toxicity. In vitro cytotoxicity studies demonstrated that 5-FU- loaded PSNPs greatly improved killing of cancer cells compared to free drug which was attributed to enhanced cellular uptake and sustained availability of drug within cells. Furthermore, the empty nanoparticles were found to be non- toxic, suggesting that they are safe for use as drug carriers.

The anti-oxidant property related to the nanoparticles indicates the possibility of additional effects, such as an anti-oxidative stress effect during chemotherapy, leading to the possibility of better therapeutic outcome. Together, these results indicate that PSNPs are extremely flexible and effective vehicles for the delivery of cancer drugs.

However, the translation of this nanocarrier system into the clinic needs to be preceded by additional in vivo studies addressing pharmacokinetics, biodistribution, long-term toxicity, and immunogenicity. In addition, surface modification and encapsulation of synergistic drugs should be investigated in the future. In summary, porous silica nanoparticles are highly promising smart nanocarriers for circumventing limitations of traditional chemotherapy with high efficacy low adverse effects, and the results presented herein may pave the way for personalized anticancer chemotherapy.

LIMITATIONS

While the present study demonstrates the promising potential of porous silica nanoparticles (PSNPs) as drug carriers for anticancer therapy, several limitations should be acknowledged. The synthesis and characterization were performed under controlled in vitro conditions, which may not fully represent the complexity of the in vivo tumor microenvironment. Parameters such as nanoparticle biodistribution, systemic circulation time, and metabolic clearance could influence the overall therapeutic efficacy but were not explored within this study. Additionally, the sol–gel synthesis route, though efficient and reproducible, may require further optimization to achieve uniform particle size distribution and improved scalability for large-scale pharmaceutical production.

Another limitation lies in the limited range of biological assays conducted. While cytotoxicity and antioxidant activities were assessed, detailed analyses of apoptosis induction, cellular uptake mechanisms, and potential off-target effects were not performed. Moreover, the long-term biocompatibility, biodegradation profile, and possible immunogenic responses of PSNPs remain to be systematically investigated. These aspects are critical to ensuring the safety of PSNPs prior to clinical translation.

SCOPE FOR FUTURE RESEARCH

Future research should therefore focus on in vivo evaluation of PSNP-based drug delivery systems using suitable animal models to determine pharmacokinetics, bio-distribution, and tumor-targeting efficiency. Studies incorporating surface functionalization with specific targeting ligands—such as antibodies, peptides, or folic acid—could further enhance selective drug accumulation at tumor sites. Investigations into stimuli-responsive PSNPs, capable of releasing drugs in response to physiological triggers like pH, temperature, or enzymes, would also expand their therapeutic versatility.
Furthermore, integrating imaging agents into the PSNP framework could create theranostic platforms, enabling simultaneous diagnosis and therapy. Exploring the co-delivery of multiple drugs or drug–gene combinations through PSNPs may open new avenues for overcoming multidrug resistance and achieving synergistic anticancer effects.

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