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RESEARCH PAPER

Formulation of Silica-Chitosan Hybrid Modified by BSA-Folate as a Drug Nanocarrier

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ABSTRACT

A novel pH-responsive drug delivery platform based on silica-chitosan hybrid containing quercetin drug (67 % entrapment efficiency) modified by folic acid-bovine serum albumin (BSA-FA) was developed in current study. The chemical properties, structure, specific surface area, and morphology of developed nanocarrier were evaluated by FTIR, XRD, BET, and SEM analyses. This nanocarrier was investigated in terms of pH-responsive release behavior in phosphate buffer solutions with pH of 5.6, and 7.4, near to acidic condition of cancer tissue and the normal condition of the body. The in-vitro release indicated an almost rapid release at the first 12 h, which then followed by a slower and gradual release for both media, so that 15 % and 26 of entrapped quercetin were released from nanocarrier at firs 12 h, respectively. In addition, a further cumulative drug release (54 % after 96 h) was observed in acidic medium compared to natural medium (36 % after 96 h), indicating the pH-sensitive behavior of hybrid nanocarrier, which is mainly related to greater swelling of the BSA-FA modification layer in response to changes in the pH of solution. These findings support the pH-responsive and smart function of designed hybrid nanocarrier against acidic medium of cancerous cells.

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INTRODUCTION

Cancer cells are a type of cell that has uncontrolled and abnormal growth so their continuous and uncontrolled proliferation causes them to spread to other tissues and cause interference in the body. These problems can eventually lead to the death of the patient [1, 2]. Until now, many treatment strategies and methods such as chemotherapy and radiation therapy are being implemented. However, many disadvantages of these treatments such as non-selective drug delivery, high drug toxicity and significant side effects in the body, and low effectiveness in inhibiting cell proliferation have limited their use [3, 4]. In this field, the development of pharmaceutical systems based on nanotechnology is at the forefront of drug delivery research as a promising option for cancer treatment [5, 6]. Drug delivery using polymeric nanocarriers has many advantages, such as improving the solubility of anticancer drugs, improving biodistribution, increasing drug circulation time in the bloodstream,

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increasing drug permeability and retention, and more effective drug delivery around tumor cells [7, 8]. However, the effectiveness of these systems is limited due to some disadvantages such as low physical stability, unfavorable chemical strength, high cost, and some problems with drug loading and unproper distribution of drugs within the carrier [9]. In this regard, using inorganic materials such as silica mesopores which have high stability, multifunctionality, good porosity, and high surface area is promising [10, 11]. Therefore, development of organic-inorganic hybrid drug carriers seems to can overcome these issues, and generate the advanced drug platforms higher efficiency.

Silica has the ability to connect with organic materials in the form of Si-C covalent bonds, which leads to the synergistic properties of inorganic and organic components. In addition, mesoporous silica has been recognized as a safe substance by the Food and Drug Administration [12]. However, the efficiency and application of unmodified hybrid carriers can be limited due to their undesirable and uncontrolled properties [11]. The surface of silica-based hybrid carriers can be engineered using stimuli-responsive organic and biocompatible materials, such as pH-sensitive polymers to develop smart drug platforms. Chitosan, as a natural cationic biopolymer, has attracted much attention in the field of designing hybrid carriers with its biocompatibility and biodegradability properties [12, 13]. However, chitosan-based carriers need to be improved due to poor transfection efficiency, and lack of targeting [14]. Thanks to the existence of abundant proper functional groups and pH-responsive properties in Bovine serum albumin (BSA) this biopolymer is recommended for chemical modification in hybrid carriers [15, 16]. Although the BSA has many proper functional groups and can acts as an appropriate pH-responsive biopolymer, this protein has been given less attention for use in pH-responsive nanocarriers. In addition, using specific ligands such as folate receptors to create the local release properties is of immense importance in designing the nanocarrier [17].

In this study, we aimed to design a novel silica-chitosan hybrid modified by folate-decorated BSA layer for the targeted delivery of quercetin anticancer drug. Here, chitosan was used for improvement of the silica matrix, and folate decorated BSA was applied as pH-responsive modification layer.

MATERIALS AND METHODS

Chemicals

Tetraethyl orthosilicate (TEOS, 99 % v/v), chitosan (medium molecular weight), quercetin (Qur, purity > 95 %), folic acid (FA, > 99 %), bovine serum albumin (BSA, 99%), 1-ethyl-3-[3-dimethylaminopropyl] carbodiimide (EDC, 99%), N-Hydroxy succinimide (NHS, 98%), dialysis bag (MWCO: 12 KDa) were supplied by Sigma-Aldrich. Ethanol (C_2H_5OH, 99.9 %), hydrochloric acid (HCl, 37 %), ammonia (NH_3, 30 %), isopropyl alcohol (C_3H_8O, ≥ 99 %), n-hexane (C_6H_{14}, ≥ 99 %), and acetic acid (CH_3COOH, ≥ 99 %) were provided from Merck Chemical Co.

Synthesis of silica-chitosan hybrid

The silica-chitosan organic-inorganic hybrid containing 15 %wt chitosan, signed as SCh, was synthesized using sol-gel method. Briefly, an aqueous solution containing 1mL of TEOS and 4 mL water was prepared and stirred for 1 h. 0.5 mL of 0.01 M HCl was then added to solution to enhance the hydrolysis of TEOS. Then, 4 mL of aqueous solution of chitosan containing 50 mg of chitosan dissolved in acetic acid (2 %v/v) was separately provided and slowly mixed with TEOS solution under stirring condition for 8 h. Here, covalent bonds create among hydrolyzed silica and chitosan in resultant sol. The gel network containing silica-chitosan forms after dropwise addition of ammonia to reaction medium, which leads to enhancing the pH up to 8. The resultant gel was washed tree times with isopropyl alcohol and n-hexane, and dried at 50 ºC for 18 h.

Quercetin encapsulation

Encapsulation of drug into the as-synthesis SCh hybrid was carried out as follows: 20 mg of SCh was mixed with quercetin solution (9 mg of Qur in 5 mL ethanol) for overnight under dark medium at room temperature. The drug-loaded SCh was then separate from the quercetin solution using centrifuge, and washed tree times with ethanol: water mixture (50 % v/v) to remove unloaded drug, and then dried under vacuum at -20 ºC. This drug-loaded SCh was denoted as SCh-Qur. The supernatant containing unloaded quercetin was collected after centrifuge stage, and analyzed by UV-visible spectrum at 374 nm. In addition, a standard curve with specific concentrations was prepared and used to measure the encapsulation efficiency (EE%) as weight of loaded quercetin/

initial quercetin weight.

Folate decorated BSA Preparation

The EDC/NHS coupling method was applied to synthesis folate decorated BSA. Typically, 7 mg of folic acid and 4 mg of NHS was dissolved in 3 mL of phosphate buffer, and the mixed by 5 mL of BSA solution containing 50 mg of BSA and 6 mg of EDC under stirring for 5 h at 4 °C and dark condition. The solution was then poured into a dialysis bag and dialyzed against phosphate buffer for 1 day and then water for another 1 day to remove unreacted reagents. Finally, folate decorated BSA, denoted as BSA-FA was achieved by lyophilization dialyzed BSA solution at -40 °C for 24 h.

BSA-folate modified SCh-Qur preparation

To modify the surface of SCh-Qur carrier by folate decorated BSA, 8 mg of BSA-FA along with 8 mg of EDC and 5 mg of NHS were dissolved in 3 mL of deionized water, and stirred for 2 h at ambient temperature. This solution was then poured in reaction medium containing 20 mg of SCh-Qur, and 2 drop diluted NaOH in 3 mL deionized water. This mixture was stirred for 5 h under dark medium at ambient temperature. Thereafter, the suspension was centrifuged at 4000 rpm for 10 min, and washed tree times with deionized water. Finally, the BSA-folate modified SCh-Qur hybrid nanocarriers, denoted as SCh-Qur@BSA-FA was obtained by lyophilization the resultant solid at -40 °C for 24 h. The efficiency of BSA-FA modification was calculated by analyzing the concentration of remain BSA-FA in the supernatant using UV-visible spectroscopy.

Release studies

The pH-responsive release pattern of the prepared carriers was studied using phosphate-buffered saline (PBS) with two different pHs of 5.6 near to acidic medium of cancer cells, and 7.4 similar to the normal medium of the body, at 37 °C during 96 h. Briefly, 20 mg of SCh-Qur@BSA-FA was dispersed into 2 mL PBS and injected into a dialysis bag, and located in the release medium containing 20 mL of PBS at 37 °C and light-free condition under mild shaking. Then at determined time intervals, 2 mL of release medium is removed and replaced with 2 ml of fresh buffer. The removed solution containing the released drug was analyzed at 374 nm using UV-visible spectroscopy and the related absorbance was recorded. Then using the previously plotted standard curve and the recorded absorbance, the amount of released quercetin was calculated.

Characterization

The X-ray diffraction analysis (XRD, PANalytical X'Pert-Pro, Netherland) in the range of 10 °C to 80 °C was used to determine the structure and phase identification of SCh-Qur and SCh-Qur@BSA-FA nanocarriers. Fourier transform infrared spectroscopy (FTIR, Magna-IR 550 spectrometer presented by Nicolet Co.) from 400 cm^{-1} to 4000 cm^{-1} was used to evaluate the functional groups and chemical properties of SCh-Qur and SCh-

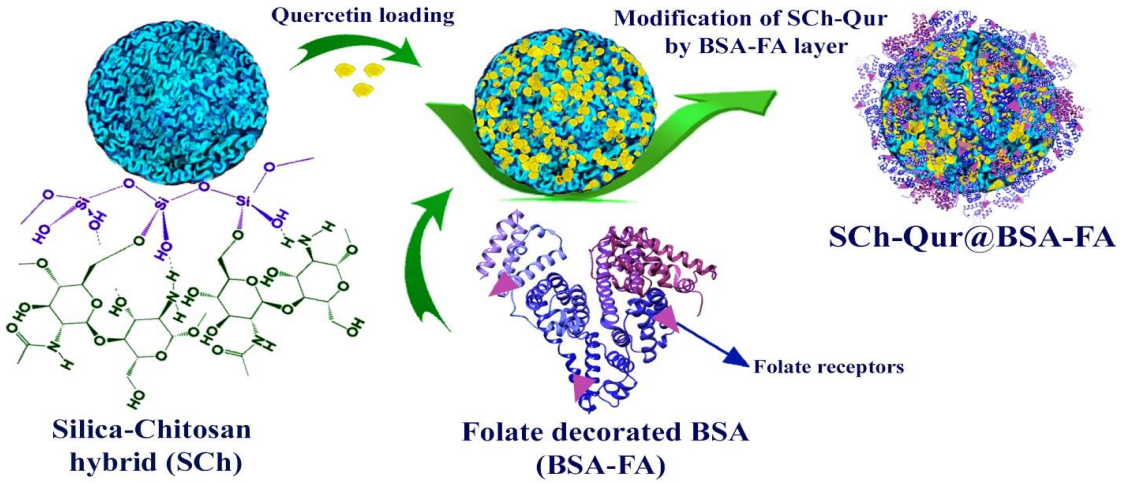

Fig. 1. overall steps of the preparation and structure of the SCh-Qur@BSA-FA nanocarrier.

Qur@BSA-FA nanocarriers. Brunauer–Emmet–Teller (BET) and Barrett-Joyner-Halenda (BJH) techniques using N_2 adsorption-desorption isotherm were used to measure surface area, pore volume, and pore size. Here, degassing of sample before the test was done at 150 °C under vacuum for 3 h. The morphology of the prepared SCh-Qur@BSA-FA nanocarriers were investigated using scanning electron microscopy (SEM, EM-3200, KYKY Co. China) technique.

RESULTS AND DISCUSSION

Fig. 1 represents a scheme of the overall steps of the preparation and structure of the SCh-Qur@BSA-FA nanocarrier. Here, the SCh hybrid was first prepared based on sol-gel method from silica and chitosan. Then quercetin was encapsulated into SCh, and then drug-loaded carrier was modified by BSA-FA layer to increase the sensitivity of carrier to acidic medium of cancerous cells. Here, the swelling of the BSA-FA layer in the acidic condition and the diffusion of the drug from the porous structure of the SCh hybrid controls the drug release from the prepared nanocarrier.

Materials characterization

In surface modification processes by semi-crystalline polymers, decisive information about the structure and crystallinity regions can be obtained from X-ray analysis [18]. Fig. 2.a shows the x-Ray diffraction pattern of prepared SCh-Qur and SCh-Qur@BSA-FA hybrid nanocarriers. As is clear, the crystallographic patterns of both samples show a characteristic broad peak in the range of 15-30°. The appeared peak is thought to be mainly related to amorphous phase of silica, in accordance with JCPDS PDF data (29-0085) [19], as well as due to amorphous nature of semi-crystalline BSA protein [20]. In addition, semi-crystalline biopolymer of chitosan shows an approximately sharp peak around 20°. However, this peak did not appear in the XRD profiles, which could be due to the overlap with silica and chitosan peaks in this area, and also the low amount of chitosan in the structure [21]. Considering the decrease in peak intensity of SCh-Qur@BSA-FA compared to SCh-Qur and more appearance of an amorphous halo in modified carrier, it is concluded that drug-loaded SCh was modified by BSA. Obtained XRD patterns clearly confirm the formation of amorphous structure in SCh-Qur and SCh-Qur@BSA-FA carrier.

FTIR analysis was used to address the functional groups and chemical properties of SCh-Qur and SCh-Qur@BSA-FA nanocarrier, as indicated in Fig. 2.b. The observed broadband at about 3400 cm^{-1} in the both spectra shows the O−H and N−H stretching vibrations [22]. Successfully formation of silica network in both samples confirms by observing main bands of silica at about 470, 870, and 1100 cm^{-1} related to Si−O stretching, Si−O bending

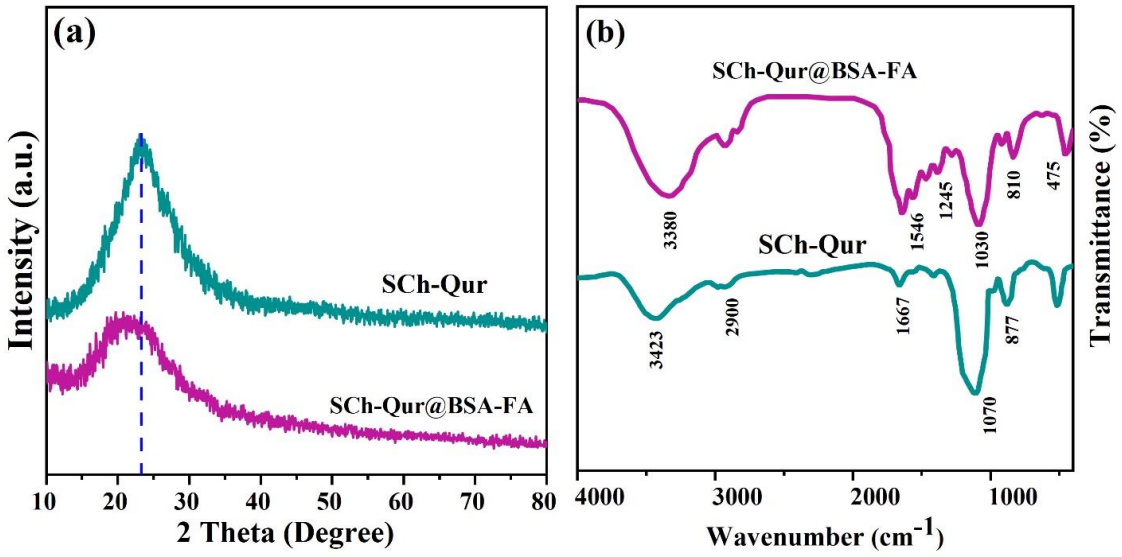

Fig. 2. (a) XRD pattern and (b) FTIR spectra of SCh-Qur and SCh-Qur@BSA-FA hybrid nanocarriers.

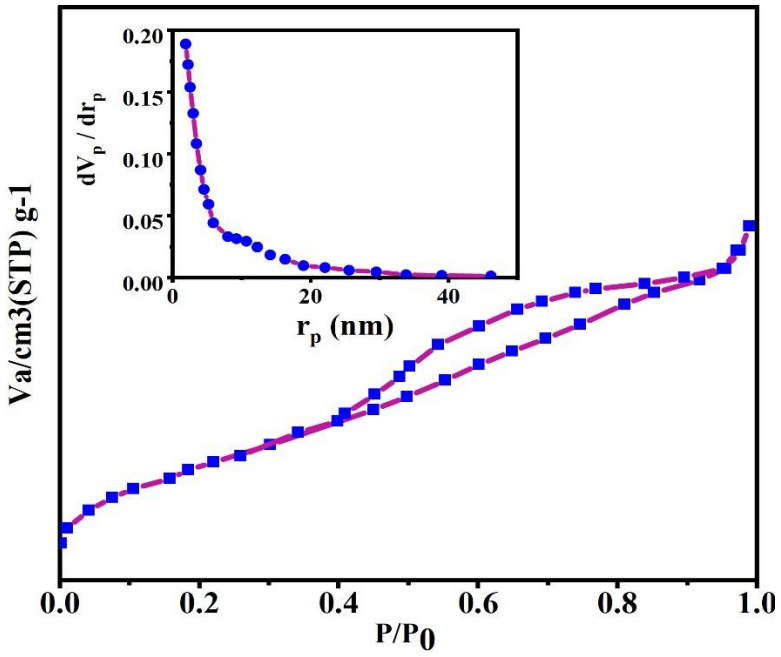

Fig. 3. Nitrogen adsorption-desorption isotherm of SCh-Qur@BSA-FA hybrid nanocarrier.

mode, and Si−O−Si stretching, respectively [23]. Existence of chitosan was proved by characteristic band of C=O stretching at about 1667 cm^{-1} in the SCh-Qur sample and 1640 cm^{-1} in the SCh-Qur@BSA-FA nanocarrier [24]. The successfully loading of quercetin into the SCh hybrid, was confirmed by observing the band around 1160−1270 cm^{-1} corresponded to ketone, phenol, and aryl ether ring in the quercetin structure [25]. In addition, the weak bands at about 1400 cm^{-1} can show the

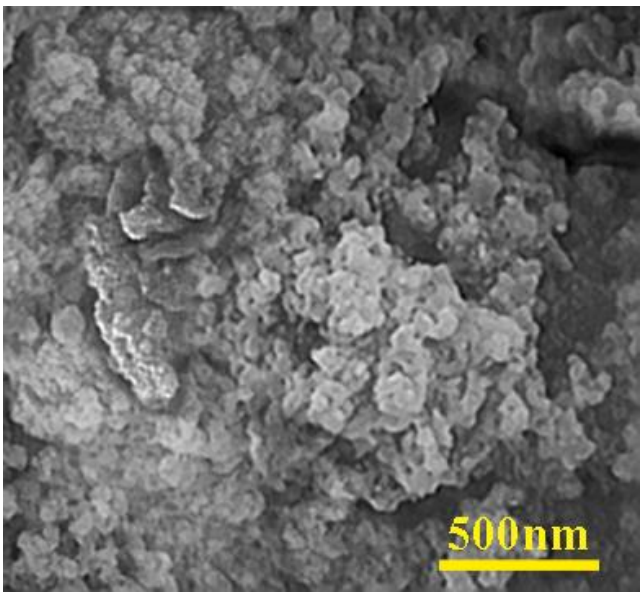

Fig. 4. FESEM micrograph of SCh-Qur@BSA-FA carrier.

absorption band of the C=N and phenyl rings in the folic acid [26]. Furthermore, the bands around 1245 cm^{-1} (amide-III), 1546 cm^{-1} (amide-II), and 1671 cm^{-1} (C=O stretching or amide-I) in the SCh-Qur@BSA-FA sample illustrate the characteristic bonds BSA [15].

In the design of hybrid nanocarriers, the shape, pore size, and surface area can have a direct effect on the drug-loading properties as well as the drug-release behavior [27]. Therefore, it is important to know these physical properties. Here, nitrogen adsorption-desorption isotherm was performed to address the physical properties of the SCh-Qur@BSA-FA hybrid nanocarrier. Here, the surface area, mean pore size and total pore volume, measured using BET, and BJH techniques, were obtained at about 284 m^2/g, 5.1 nm, and 0.66 cm^3/g, respectively. Fig. 3 shows the nitrogen adsorption-desorption isotherm of SCh-Qur@BSA-FA nanocarrier. According to the IUPAC classification, it seems that the adsorption isotherm follows the adsorption behavior of type-IV, indicating formation of mesoporous structure in the SCh-Qur@BSA-FA sample [19, 28]. In addition, the appeared hysteresis loop seems to be in line with type H-2, which mainly observe in the mesoporous structures [21, 29]. The pore size distribution in Fig. 3. inset indicated a narrow distribution in the range of 2-35 nm, confirming formation of mesopores structure.

The size, shape and porosity of nanocarriers is one of the most important features in the design of drug delivery systems, which can greatly affect the biodistribution, and removal of the particles from bloodstream by the immune system [30]. FESEM micrograph of SCh-Qur@BSA-FA in Fig. 4 shows formation of a porous structure along with approximately spherical particles in the range of 50–250 nm, which is proper for biomedical applications.

Encapsulation efficiency and release studies

The prepared SCh-Qur@BSA-FA carrier was used to evaluate the encapsulation property and release behavior of quercetin. Here, the entrapment efficiency measure using UV spectroscopy method were obtained at about 67 %, which shows a good loading. In a similar work by Gaware et al [31] which developed chitosan-silica nanocomposite as drug carrier, the entrapment efficiency of curcumin was obtained at about 60 %. El-Shahawy et al [32] in another similar work based on chitosan @silica coated carbon nanotubes composite reported entrapment efficiency of doxorubicin at about 64 %. The high quercetin encapsulation efficiency is mainly due to proper surface area and appropriate

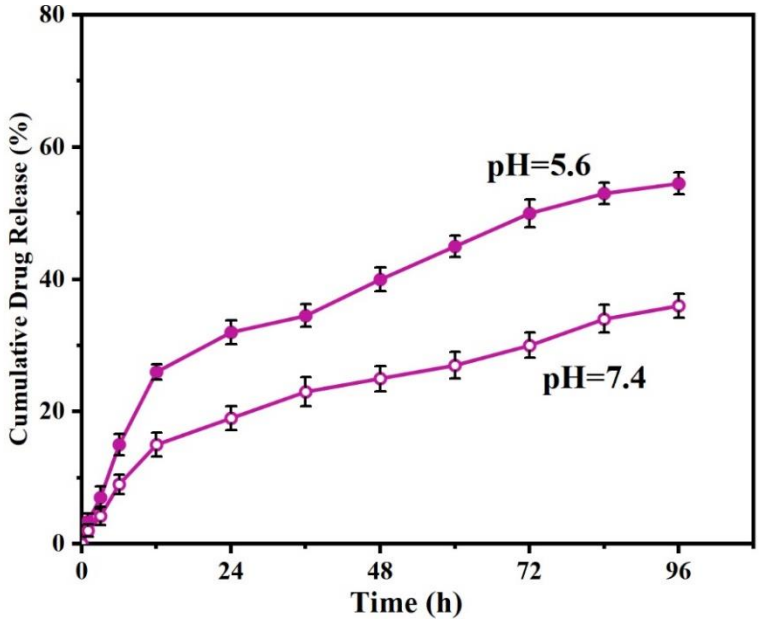

Fig. 5. In-vitro release pattern of quercetin from SCh-Qur@BSA-FA carrier at acidic and natural media.

interactions between drug and functional groups in SCh hybrid [33].

The release behavior of quercetin from SCh-Qur@BSA-FA nanocarrier was evaluated using two different PBS media of natural (pH=7.4) and acidic (pH= 5.6) during 96 h at the physiological temperature of the body, as indicated in Fig. 5. The release profiles showed an approximately rapid release at the first 12 h, and then a slower and mild release until 96 h, for both media, so that 15 % and 26 of loaded quercetin were released from nanocarrier at firs 12 h, respectively. It should be attended that the surface area of SCh-Qur@BSA-FA was obtained at about 284 m^2/g, which can creates a fast release rate at early time for drug molecules that located at surface layers and large pores and have not a proper chemical interaction with main matrix [34]. However, after 24 h, a slow and gradual release, especially for natural medium was observed, which is mainly due to using BSA-FA modification layer in nano carrier which prevents the easy movement of drug molecules from the carrier to the release medium. However, this modification layer slowly swells during 96 exposures in the buffer solution and causes a gradual release of the drug over time.

In addition, a further cumulative drug release was observed in acidic PBS solution compared to natural medium, confirming the pH-responsive behavior of designed SCh-Qur@BSA-FA hybrid nanocarrier. This behavior is due to the greater swelling of the BSA-FA layer in response to changes in the acidity of the environment and subsequently easier movement of the drug molecules entrapped into SCh toward the release solution. Here, the cumulative release of quercetin from the SCh-Qur@BSA-FA was achieved at about 36 % at natural medium and 54 % at acidic medium after 96 h, respectively. A similar result for was also indicated by Maheswari et al [15] which developed a folic acid functionalized BSA-CaFe2O4 nanohybrid carrier as controlled delivery. They reported that using folic acid functionalized BSA layer was led to significant increase of pH-responsive release behavior, so that higher release was observed under acidic pH conditions compared to normal pH.

CONCLUSION

Here, a silica-chitosan nanohybrid was fabricated and loaded with quercetin as an anticancer drug. This drug carrier was modified by a pH-sensitive layer of folate-decorated BSA, and investigated in terms of pH-responsive release behavior against acidic and natural media. The high surface area of silica-chitosan and proper chemical interactions between quercetin and carrier led to a high drug loading. The in-vitro release profile from the BSA-FA modified drug-loaded carrier indicated an approximately rapid release at the earlier times, which was followed by a slower and mild release, for both media. In addition, a more cumulative release from the carrier was observed in acidic conditions than in neutral conditions, indicating the pH-responsive behavior of the designed carrier. This is due to more swelling of the BSA modification layer that can create easier movement of the drug toward the PBS solution. These outcomes confirmed the smart function of the designed drug platform related to more release of drugs in an acidic medium of cancerous cells.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

REFERENCES

1. Ibrahim RAA-Z, Suhail FSA, Al-Hakeim HK. Stability of Anticancer Drug 5-Fluorouracil in Aqueous Solution: An Assessment of Kinetic Behavior. Nano Biomed Eng. 2018;10(3).
2. Tian B, Hua S, Liu J. Multi-functional chitosan-based nanoparticles for drug delivery: Recent advanced insight into cancer therapy. Carbohydr Polym. 2023;315:120972.
3. Behranvand N, Nasri F, Zolfaghari Emameh R, Khani P, Hosseini A, Garssen J, et al. Chemotherapy: a double-edged sword in cancer treatment. Cancer Immunology, Immunotherapy. 2021;71(3):507-526.
4. Wagner AD, Syn NLX, Moehler M, Grothe W, Yong WP, Tai B-C, et al. Chemotherapy for advanced gastric cancer. Cochrane Database Syst Rev. 2017;2017(8).
5. Jahangirian H, Ghasemian lemraski E, Webster TJ, Rafiee-Moghaddam R, Abdollahi Y. A review of drug delivery systems based on nanotechnology and green chemistry: green nanomedicine. International Journal of Nanomedicine. 2017;Volume 12:2957-2978.
6. Chatterjee P, Kumar S. Current developments in nanotechnology for cancer treatment. Materials Today: Proceedings. 2022;48:1754-1758.

7. Xia W, Tao Z, Zhu B, Zhang W, Liu C, Chen S, et al. Targeted Delivery of Drugs and Genes Using Polymer Nanocarriers for Cancer Therapy. Int J Mol Sci. 2021;22(17):9118.
8. AHUJA R, Panwar N, Meena J, Singh M, Sarkar DP, Panda AK. Natural products and polymeric nanocarriers for cancer treatment: a review. Environ Chem Lett. 2020;18(6):2021-2030.
9. Ghasemiyeh P, Mohammadi-Samani S. <p>Potential of Nanoparticles as Permeation Enhancers and Targeted Delivery Options for Skin: Advantages and Disadvantages</p&gt. Drug Des Devel Ther. 2020;Volume 14:3271-3289.
10. Lim WQ, Phua SZF, Xu HV, Sreejith S, Zhao Y. Recent advances in multifunctional silica-based hybrid nanocarriers for bioimaging and cancer therapy. Nanoscale. 2016;8(25):12510-12519.
11. Corma A, Botella P, Rivero-Buceta E. Silica-Based Stimuli-Responsive Systems for Antitumor Drug Delivery and Controlled Release. Pharmaceutics. 2022;14(1):110.
12. Kumari R, Narvi SS, Dutta PK. Thiol modified chitosan-silica nanohybrid for antibacterial, antioxidant and drug delivery application. J Indian Chem Soc. 2021;98(8):100108.
13. Qamar SA, Ashiq M, Jahangeer M, Riasat A, Bilal M. Chitosan-based hybrid materials as adsorbents for textile dyes–A review. Case Studies in Chemical and Environmental Engineering. 2020;2:100021.
14. Mehrizi TZ, Ardestani MS. The Introduction of Dendrimers as a New Approach to Improve the Performance and Quality of Various Blood Products (Platelets, Plasma and Erythrocytes): A 2010-2022 Review Study. Current Nanoscience. 2023;19(1):103-122.
15. Uma Maheswari P, Muthappa R, Bindhya KP, Meera Sheriffa Begum KM. Evaluation of folic acid functionalized BSA-CaFe2O4 nanohybrid carrier for the controlled delivery of natural cytotoxic drugs hesperidin and eugenol. J Drug Deliv Sci Technol. 2021;61:102105.
16. Kushwah V, Katiyar SS, Dora CP, Kumar Agrawal A, Lamprou DA, Gupta RC, et al. Co-delivery of docetaxel and gemcitabine by anacardic acid modified self-assembled albumin nanoparticles for effective breast cancer management. Acta Biomater. 2018;73:424-436.
17. Hao B-b, Deng X-z, Yang J-k, Jia Y-d, Shang X-j, Shi Y-l, et al. Preparation of Folic Conjugated Magnetic Silica Mesoporous Nanoparticles and Their Encapsulated 10-HCPT Anticancer Behavior. Journal of Inorganic and Organometallic Polymers and Materials. 2022;32(8):2986-2993.
18. Onaș AM, Bîru IE, Gârea SA, Iovu H. Novel Bovine Serum Albumin Protein Backbone Reassembly Study: Strongly Twisted β-Sheet Structure Promotion upon Interaction with GO-PAMAM. Polymers. 2020;12(11):2603.
19. Niazi Z, Ashjari M, Janqamsari Y. Ultrasound-promoted synthesis of high-porosity silica aerogels using embedded recycled PET fibers. Microporous Mesoporous Mater. 2022;332:111682.
20. Yadav P, Yadav AB. Preparation and characterization of BSA as a model protein loaded chitosan nanoparticles for the development of protein-/peptide-based drug delivery system. Future Journal of Pharmaceutical Sciences. 2021;7(1).
21. Aramideh A, Ashjari M, Niazi Z. Effects of natural polymers for enhanced silica-based mesoporous drug carrier. J Drug Deliv Sci Technol. 2023;81:104189.
22. Wang Y, Pitto-Barry A, Habtemariam A, Romero-Canelon I, Sadler PJ, Barry NPE. Nanoparticles of chitosan conjugated to organo-ruthenium complexes. Inorganic Chemistry Frontiers. 2016;3(8):1058-1064.
23. Bananifard H, Ashjari M, Niazi Z, Etemadi M. Efficient reinforcement of wet gel by embedded polymer as newly approach for silica aerogel. Polym Adv Technol. 2020;31(12):3174-3181.
24. Khatami F, Matin MM, Danesh NM, Bahrami AR, Abnous K, Taghdisi SM. Targeted delivery system using silica nanoparticles coated with chitosan and AS1411 for combination therapy of doxorubicin and antimiR-21. Carbohydr Polym. 2021;266:118111.
25. Catauro M, Papale F, Bollino F, Piccolella S, Marciano S, Nocera P, et al. Silica/quercetin sol–gel hybrids as antioxidant dental implant materials. Science and Technology of Advanced Materials. 2015;16(3):035001.
26. Wang Y, Ren J, Liu Y, Liu R, Wang L, Yuan Q, et al. Preparation and evaluation of folic acid modified succinylated gelatin micelles for targeted delivery of doxorubicin. J Drug Deliv Sci Technol. 2018;46:400-407.
27. Che E, Gao Y, Wan L, Zhang Y, Han N, Bai J, et al. Paclitaxel/gelatin coated magnetic mesoporous silica nanoparticles: Preparation and antitumor efficacy in vivo. Microporous Mesoporous Mater. 2015;204:226-234.
28. Kumar KV, Gadipelli S, Wood B, Ramisetty KA, Stewart AA, Howard CA, et al. Characterization of the adsorption site energies and heterogeneous surfaces of porous materials. Journal of Materials Chemistry A. 2019;7(17):10104-10137.
29. Sangwichien C, Aranovich GL, Donohue MD. Density functional theory predictions of adsorption isotherms with hysteresis loops. Colloids Surf Physicochem Eng Aspects. 2002;206(1-3):313-320.
30. Yu T, HUBBARD D, Ray A, Ghandehari H. In vivo biodistribution and pharmacokinetics of silica nanoparticles as a function of geometry, porosity and surface characteristics. Journal of Controlled Release. 2012;163(1):46-54.
31. Gaware SA, Rokade KA, Kale SN. Silica-chitosan nanocomposite mediated pH-sensitive drug delivery. J Drug Deliv Sci Technol. 2019;49:345-351.
32. El-Shahawy AAG, Elnagar N, Zohery M, Abd Elhafeez MS, El-Dek SI. Smart nanocarrier-based chitosan @silica coated carbon nanotubes composite for breast cancer treatment approach. International Journal of Polymeric Materials and Polymeric Biomaterials. 2021;71(12):910-922.
33. Rosenholm JM, Lindén M. Towards establishing structure–activity relationships for mesoporous silica in drug delivery applications. Journal of Controlled Release. 2008;128(2):157-164.
34. Aw MS, Simovic S, Yu Y, Addai-Mensah J, Losic D. Porous silica microshells from diatoms as biocarrier for drug delivery applications. Powder Technol. 2012;223:52-58.