Research Paper

Loading *Brucea javanica* Oil into pH-sensitive Chitosan Grafted Mesoporous Silica Nanoparticles by Supercritical Carbon dioxide Impregnation

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The anti-tumor effect of *Brucea javanica* oil is remarkable, but the existing preparations have serious deficiencies in targeting and controlled release. This work developed a pH-sensitive *Brucea javanica* oil mesoporous silica Nano drug delivery system to improve the insufficient controlled release and targeting properties of the preparations. The pH-sensitive mesoporous silica Nano drug delivery system containing *Brucea javanica* oil was prepared using the supercritical solution impregnation technique. The structure was characterized by scanning electron microscope, Fourier transform infrared, X-ray diffractometer, thermal analysis and nitrogen adsorption-desorption analysis, and the *in vitro* pH-responsive release behaviour was evaluated. The supercritical solution impregnation method successfully loaded *Brucea javanica* oil into chitosan-modified mesoporous silica, with an encapsulation rate of over 90 %. Scanning electron microscope, Fourier transform infrared, X-ray diffractometer, thermal analysis and nitrogen adsorption-desorption analysis confirmed the successful preparation of the chitosan-modified mesoporous silica Nano drug delivery system of *Brucea javanica* oil. *In vitro* dissolution tests demonstrated that the cumulative release rate of *Brucea javanica* oil increased significantly as the solution pH dropped from 7.0 to 5.8, at which point the goal of pH-controlled release of *Brucea javanica* oil was achieved. The supercritical solution impregnation method successfully prepared the pH-sensitive *Brucea javanica* oil mesoporous silica Nano drug delivery system, which is expected to enhance the controlled release and targeting of *Brucea javanica* oil preparations.

Key words: *Brucea javanica* oil, supercritical carbon dioxide impregnation, mesoporous silica, nanoparticle

The traditional Chinese medicine *Brucea javanica* contains over 20 % fatty oil, namely *Brucea javanica* Oil (BJO). The anti-tumor research on BJO began in the 1950 s. The use of BJO as a novel broad-spectrum anti-cancer drug has been demonstrated by decades of research to be very effective in inhibiting the growth of tumor cells, inducing apoptosis, inhibiting migration/invasion, causing autophagy, and inhibiting angiogenesis[1,2]. The BJO emulsion prepared from BJO, including oral liquid and injection, has now been widely used in the treatment of digestive tract tumors, lung cancer, lung cancer brain metastasis, and cervical cancer, especially showing good efficacy for lung cancer brain metastasis. It is a rare pure natural anti-cancer drug[3].

The clinical application forms of BJO are relatively limited, mainly including intravenous emulsions, oral emulsions, granules, capsules, etc. However, liquid formulations such as emulsions have poor storage stability and can cause irritation to the

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stomach, making them unsuitable for long-term use. Ordinary granules and capsules still have significant deficiencies in terms of bioavailability, targeting, and controlled release. Therefore, how to improve the controlled release and targeting properties of BJO is an urgent scientific issue to be addressed. The Nano-delivery system is the research area that currently concentrates on the development of BJO; as a result, the system can improve the targeting ability of the BJO by allowing it to have good controlled release performance[4,5]. The mesoporous silica nano delivery system is a very promising drug delivery form. Especially when mesoporous silica is modified and loaded with BJO, BJO can be selectively delivered to the tumor site, increasing the drug concentration in the tumor area. Additionally, the intelligently controlled-release BJO can sustain drug concentration at an effective level for an extended duration, thereby ensuring a prolonged and efficient anti-tumor impact. Simultaneously, it reduces the toxicity of BJO to normal tissues and other organs, minimizing the drug's harmful side effects.

Mesoporous Silica Nanoparticles (MSNs) have emerged as a highly promising approach in the field of drug delivery due to their high surface area (>900 m2/g), adjustable pore size (2-50 nm), and excellent biocompatibility[6]. Their honeycomb-like structure enable high drug loading capacity, while surface functionalization allows for responsive release upon stimulation. For instance, pH sensitivity based on the acidic tumor microenvironment (pH approximately 6.5) or lysosomal compartments (pH approximately 5.0) can trigger drug release, thereby minimizing non-targeted effects[7]. Despite these advantages, unmodified MSNs suffer from premature drug leakage and lack of mucosal adhesion, which limits their retention at the target site[8]. To overcome these drawbacks, biopolymer grafting-particularly using chitosan as the base material-has been employed to enhance stability and introduce stimulus-responsive behaviour.

Chitosan, cationic polysaccharide, which is extracted from the chitin, gives a special advantage for the delivery of drugs: biodegradability, mucoadhesion, and pH-dependent solubility (pH<6.5)[9]. Grafting chitosan onto MSNs creates a "gatekeeping" mechanism where the polymer swells under acidic conditions, enabling controlled drug release[10,11]. This pH sensitivity aligns with the tumor microenvironment, ensuring selective drug release at cancerous sites while sparing healthy tissues.

Supercritical Fluid (SCF) technology, especially with the use of supercritical Carbon dioxide (scCO2), has revolutionized nanoparticle drug loading. Because SCF have a high diffusion coefficient, low viscosity, and no surface tension, they serve as effective carriers for the intercalation and embedding of small molecules into mesopores. This results in high drug-loading efficiency without the need for organic solvents[12]. This approach helps preserve thermolabile compounds (such as BJO's quassinoids) and ensures an even distribution of the drug throughout the carrier. Compared to traditional methods like solvent evaporation, SCF technology enhances scalability and reduces environmental impact, aligning with green chemistry principles[13].

The preparation of MSNs using SCF technology is a new method that has only emerged in the past decade. There have been some related reports both domestically and abroad[14-19]. In 2024, we prepared a pH-responsive cinnamon oil (volatile oil) mesoporous silica drug delivery system using the supercritical solution impregnation method[20]. However, there has been no report on the research on loading herbal fat oil into a mesoporous silica drug delivery system modified by chitosan through the supercritical solution impregnation method both at home and abroad.

This study aims to develop a gate-controlled permeation method that can directly load the BJO into the mesoporous silica modified with chitosan. The pH-responsive release behaviour of the drug, the morphological and structural features, and the drug loading situation will be studied in order to assess the non-destructiveness and feasibility of this method.

MATERIALS AND METHODS

Materials:

MCM-41 mesoporous silica was acquired from Beike Nano Materials Co., Ltd.; high-viscosity chitosan (>400 mPa.s) and 3-glycidyloxypropyltrimethoxysilane (97 %) were supplied by Macklin Chemical Technology Co., Ltd.; BJO was prepared in our laboratory; methyl oleate (>99.0 %), benzyl benzoate (99.0 %), and boron trifluoride-methanol (50 %) were purchased from Shanghai Aladdin Bio-Chem Technology Co., Ltd.; high-purity CO2 (99.99 %) was provided by Chenzhou Guoneng Gas Co., Ltd. (Hunan Province, China); all other reagents were of analytical grade

and commercially available.

Synthesis of MSNs (MCM-41) grafted with chitosan (CS-MSNs):

The synthesis method of CS-MSNs was as reported *via* Huaping Lei *et al.* etc.,[20]. 10 g chitosan was added to 1000 ml of 5 % acetic acid solution. The solution was agitated for 24 h in order to get a 1 % chitosan solution. 5 g of mesoporous silica MCM-41 was dispersed in 500 ml of anhydrous ethanol and treated by ultrasound for 15 min. Using acetic acid, the pH of the solution was adjusted to about 4. Quickly 5 g of 3-Glycidyl Ether Propyl Trimethoxysilane (GPTMS) was added, stirred for 3 h, added 1000 ml of the 1 % chitosan solution, stirred for 24 h, then performed centrifugation (500 rpm), filtration, obtain the precipitate, centrifuged (7000 rpm) and cleaned it with distilled water and anhydrous ethanol each for 3 times respectively, and dry to obtain MSNs.

Preparation of BJO@CS-MSNs:

The instrument utilized in this study is identical to those referenced in the literature[21]. 1.0 g of CS-MSNs was placed into a stainless steel basket with a dense stainless steel mesh at the bottom. The basket was then placed inside a sealed loading chamber with a capacity of 70.7 ml, having an inner diameter and height of 3 cm and 10 cm, respectively. A high-pressure constant flow pump injected 5 ml of BJO into the loading chamber through the inner wall of a coaxial nozzle with an inner diameter of 120 μm. CS-MSNs were immersed in BJO for a period of time. At the same time, CO2 was sent out through the high-pressure pump, heated by an electric preheater, and sent into the charging chamber through an external nozzle. Before the pressure reached the present value, carbon dioxide was continuously supplied and maintained at a high pressure for a period of time to transport BJO into CS-MSNs. Finally, a certain period of depressurization operation was performed, and then CO2 was slowly discharged. Eventually, the completed product BJO@CS-MSNs was took out.

Determination of Encapsulation rate:

Unwashed test solution: 0.4 g of each sample was weighed separately, and then ultra-sonicated in 5 ml of acidic ethanol (adjusted to a pH of around 4.0 with acetic acid) for 2 h to fully release BJO loaded in the mesoporous silica. Subsequently, the total acid content of the samples was measured.

Washing of test solution: 0.4 g of each sample was weighed separately. Firstly, 10 ml of anhydrous ethanol was used to wash the sample, which was then filtered and dried. Then, the sample was ultra-sonicated in 5 ml of acidic ethanol (adjusted to a pH of approximately 4.0 with acetic acid) for 2 h to completely release BJO loaded in the mesoporous silica, and measured the total acid content.

Determination of total acid content: A 0.4 g sample (with the blank control being CS-MSNs) was accurately weighed and mixed with 20 ml of neutral ethanol. Then, 5 ml of a 0.5 mol/l KOH ethanol solution was added, and the mixture was refluxed for 30 to 40 min. After cooling, the condenser was rinsed with 10 ml of neutral ethanol. One drop of phenolphthalein indicator solution was then added, and the solution was titrated with a 0.1 mol/l hydrochloric acid solution until the red color disappeared, using the blank test as a control. Calculate according to the following formula:

Total acid content=(B-A)×N×282.5/1000/G×100 %

In the formula: A-The amount (in ml) of hydrochloric acid solution that the test sample was used; B-The amount (in ml) of hydrochloric acid solution used in the blank test; G-The grams of the test sample and N-The correction factor for the molar concentration of the hydrochloric acid solution.

Encapsulation rate (%)=Total acid content in the mesoporous silica after washing/Total acid content in the un-washed mesoporous silica×100 %.

Characterization:

A Scanning Electron Microscope (SEM) (Sus 5000, Hitachi Company, Japan) was utilized to observe the morphologies of BJO@CS-MSNs, CS-MSNs, and MSNs. Using BET and a surface area and pore analyser (TriStar, Micromeritics Co., Ltd., United States of America (USA)) to measure the samples for the purpose of drawing the nitrogen-adsorption-desorption isotherms, the internal pore architectures of the samples were implemented. The particle size and Zeta potential of MSNs, CS-MSNs, and BJO@CS-MSNs were measured using a nanoparticle size and Zeta potential analyser (Nano-ZS90, Malvern, UK). The samples were dispersed in ultra-pure water, ultrasonic treated for 5 mins and then determined. The pH value for Zeta potential determination was 7.0.

Fourier Transform Infrared (FT-IR) spectrophotometer

(Cary 630 FTIR, Agilent Corporation, USA) was used for obtaining FT-IR transmission spectra with KBr discs in 4000 to 400 cm-1 region. X-Ray Diffractometer (PXRD) patterns were obtained using the XRD (Ultima IV, Rigaku Company, Japan). The patterns were commonly collected over 2θ at 3°-10°. Simultaneous thermal analysis was implemented with thermogravimetric (DSC-TGA SDT 650, TA Corporation, USA) from 40° to 800° under N2 atmosphere.

***In vitro* pH-responsive release behaviour of BJO@ CS-MSNs:**

500 mg of BJO@CS-MSNs were precisely weighed, and respectively added 900 ml of pH 7.0 and pH 5.8 phosphate buffer solution (containing 1 % Tween 80) into them. The sample was slowly stirred them in a 37.5° water bath at a rotation speed of 50 r/min. The paddle method was employed for determination as outlined in Part IV General Rules 0931 of the 2020 Edition of the Chinese Pharmacopoeia. 1 portion of 5 ml was took out at regular intervals. After taking the 5 ml solution it was placed in a 50 ml evaporating dish and then it was evaporated in a 60° water bath. The sample was extracted 4 times with 1 ml of hexane each time, and each extraction was ultra-sonicated for 1 min. The extract was transferred to a 10 ml beaker with a stopper, evaporated in a 60° water bath, added 2 ml of 0.5 mol/l KOH methanol solution, and then saponified for 25 min at 60° in a water bath until all oil droplets evaporate. The sample was cooled, followed by the addition of 2 ml of a 15 % trifluoroborane ethyl ether solution. It was then placed in a 60° water bath for 2 min to undergo methylation. After cooling, 2 ml of n-hexane was added and vortex mixed, followed by 1 ml of saturated sodium chloride solution. The mixture was vortex mixed again and allowed to stand. The upper layer solution was took out, which is the final product. The samples undergo GC analysis. The regression equation of the standard curve was utilized to calculate the amount of oleic acid released from BJO@CS-MSNs and create the release curve.

Establishment of the standard curve for oleic acid:

Internal standard solution: Approximately 0.5000 g of benzoic benzoate was weighed precisely, and added n-hexane to make the volume up to 100 ml.

Reference solution: 100 mg of oleic acid was precisely weighed separately, added n-hexane to make up to 25 ml. 250 µl, 1 ml, 2 ml, 5 ml, and 10 ml of the above solutions were exactly taken from each, and placed them in 25 ml volumetric flasks. 1 ml of internal standard solution was added to each volumetric flask, added n-hexane to the mark, and shook well. A volume of 1.0 µl of the solution was injected for GC analysis. Utilizing the ratio R of the peak areas of oleic acid and the internal standard as the independent variable, with concentration as the dependent variable, the linear regression was conducted and the standard working curve was created.

The GC analysis was investigated using a GC-2010 pro gas chromatograph with FID detector and a Wonda Cap5 chromatographic column (30 m×0.25 mm×0.25µm) (Shimadzu Company, Japan). The column temperature was programmed: initial temperature 100° was adjusted to 200°, by 20°/min, then to 230° by a rate of 2.5°/min, and finally to 270° at a rate of 10°/min; the injection port temperature: 200°, the detector temperature: 220°; split injection, split ratio 100:1; carrier gas flow rate of nitrogen with a flow rate of 2.0 l min; injection volume of 2.0 µl.

RESULTS AND DISCUSSION

Our initial experiments indicate that the compact internal structure of Chitosan-Modified Mesoporous Silica (CS-MSNs) under neutral conditions makes it quite challenging for BJO to penetrate the MSNs through ordinary impregnation, even after being gently stirred for 24 h. Therefore, how to efficiently load BJO into CS-MSNs without the "opening" operation and to fabricate a pH-sensitive nanodeivery system is a scientific problem that this research needs to solve. We has been engaged in the research of SCF for many years. Could the supercritical CO2 fluid, with its large diffusion coefficient, low viscosity and no surface tension, efficiently load BJO into CS-MSNs? Our experiments have proved that, without the "opening" operation, through the assistance of the green and surface tension-free supercritical CO2, BJO can be successfully loaded into CS-MSNs.

In the supercritical state, CO2 displays solvent characteristics akin to those of a liquid, rendering it an effective solvent for non-polar or weakly polar compounds like BJO. Then, the BJO/CO2 complex passes through the pores formed by chitosan and enters the internal channels of CS-MSNs. Two special features of supercritical CO2 are responsible for this: on the one hand, supercritical CO2 has

the same small interfacial tension as a gas, which gives supercritical CO2 a strong permeability and the capacity to penetrate the chitosan branches, in contrast to ordinary liquid solvents; on the other hand, when supercritical CO2 inserts into the gaps between chitosan branches, it weakens the intermolecular forces, making the "door" through which BJO enters relatively loose. Previous material investigations have also shown that this effect of the intermolecular forces is weakened by supercritical CO2, as is the preparation of graphene[22].

As shown in Table 1, with the increase in pressure, the encapsulation rate increasingly increased. The fact that the density of the supercritical CO2 fluid is positively connected with its solubility may be the reason for this[23]. Therefore, as the pressure increases, the density of the supercritical CO2 fluid becomes larger, its solubility increases, and the encapsulation rate also rises.

When the temperature rose from 35° to 45°, the encapsulation rate increased. Nevertheless, as the temperature increased to 55°, the encapsulation rate declined. From here, it can be seen that the encapsulation rate increased firstly and then decreased. The reason for this is because the density of the SCF drops with increasing temperature. On the other hand, as the temperature rises, the diffusion coefficient of the BJO increases, which is helpful to the BJO entering the interior of the mesoporous silica. Therefore, the influence of temperature on the encapsulation rate of the drug-loaded system mainly depends on which of the above two factors dominates[24].

In most situation, the rate of encapsulation raised with the impregnation time. More BJO was discharged as a result of the increase in impregnation time. As the depressurization time prolonged, the pressure in the autoclave decreased more slowly, which was beneficial for BJO to remain inside the mesoporous silica.

Fig. 1 illustrates that MSNs were regular adherent particles with a rough surface (fig. 1A). After chitosan modification, the particles significantly increased in size and become irregular adherent particles (fig. 1B). After loading BJO, the morphology of chitosan-modified mesoporous silica became blurred, and the oil on the surface can be seen (fig. 1C).

As shown in Table 2, after chitosan modification, the particle size of mesoporous silica changed from 212.23±4.00 nm to 314.33±14.53 nm. After loading BJO, the particle size further increased to 356.45±17.76 nm. This proved that chitosan successfully modified mesoporous silica and increased the particle size of mesoporous silica. After loading BJO, the particle size further increased to 356.45±17.76 nm, indicating that the BJO was successfully loaded.

TABLE 1: ENTRAPMENT RATE AND WEIGHT FOR *BRUCEA JAVANICA* OIL LOADED CHITOSAN GRAFTED MSNs (BJO@CS-MSNs) UNDER VARIOUS OPERATIONAL CONDITIONS (n=3)

Sample no.	T (℃)	P (MPa)	Impregnation time (min)	Depressure time (min)	Weight (g)	Encapsulation rate (%)
1	45	20	30	10	4.7±0.5	84.6±3.7
2	45	25	30	10	4.9±0.4	91.4±2.6
3	45	30	30	10	5.4±0.3	94.4±1.7
4	35	30	30	10	5.2±0.4	89.5±3.1
5	55	30	30	10	5.3±0.5	90.8±2.9
6	45	30	15	10	5.0±0.3	94.2±1.8
7	45	30	45	10	5.2±0.2	95.5±1.6
8	45	30	30	5	5.1±0.1	90.8±2.9
9	45	30	30	15	5.4±0.2	96.2±1.9
10	45	30	45	15	5.5±0.1	96.7±1.8

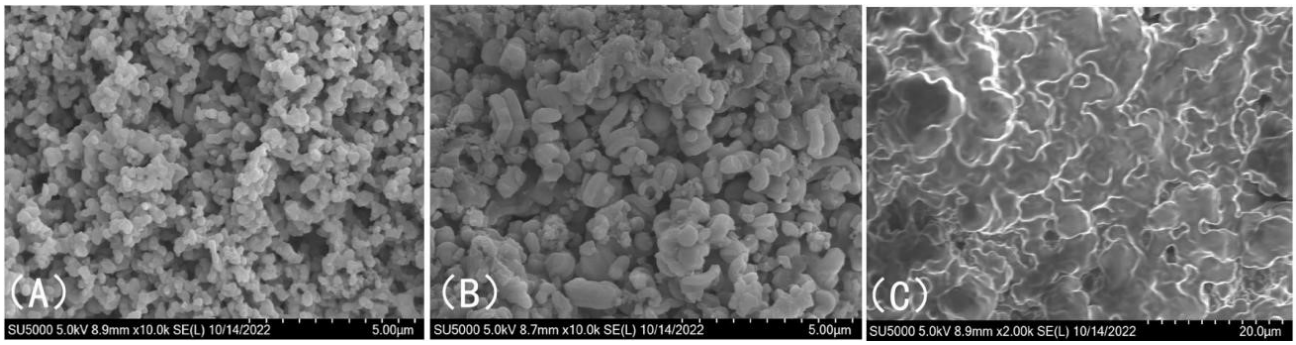

Fig. 1: SEM images (A): MSNs; (B): Chitosan grafted MSNs (CS-MSNs) and (C): BJO loaded CS-MSNs (BJO@CS-MSNs)

TABLE 2: AVERAGE PARTICLE SEZE AND ZETA POTENTIAL MEASUREMENTS FOR MSNs, CS-MSNs AND BJO@CS-MSNs

Sample	Average particle size (nm)	Zeta potential (mV)
MSNs	212.23±4.00	-21.77±0.74
CS-MSNs	314.33±14.53	-5.64±1.15
BJO@CS-MSNs	356.45±17.76	-29.13±4.80

Due to the large amount of Si-OH on the surface, MSNs presented a negative potential (-21.77±0.74 mV), and after chitosan modification, the potential became -5.64±1.15 mV. This is because chitosan contains a positively charged amino group, which neutralizes part of the negative charge of MSNs, resulting in an increase in Zeta potential. These findings show that MSNs was successfully modified by chitosan. After loading BJO, the Zeta potential of the particles dropped again. This is because the triglycerides in BJO contain many negatively charged carboxyl groups.

The BET structure parameters of BJO@CS-MSNs, CS-MSNs together with MSNs were showed in Table 3. CS-MSNs revealed a lager BET surface area in comparison with that of BJO@CS-MSNs and MSNs, attributing to grafted chitosan branches. After loading BJO, the pore volume decreased markedly. The pore sizes became a little small after grafting chitosan branches and loading BJO. Fig. 2 illustrates that there are no appreciable changes in the amount of nitrogen adsorption by mesoporous silica both before and after chitosan modification. However, after loading the BJO, the nitrogen adsorption amount of mesoporous silica dropped sharply, which is consistent with the results obtained from scanning electron microscopy.

By comparing the infrared spectra of the three samples in fig. 3, compared with MSNs, CS-MSNs have C-H stretching vibration peaks at 2925 cm-1 and 2981 cm-1, indicating that chitosan has successfully been modified onto the mesoporous silica. The peak near 1750 cm-1 in BJO@CS-MSNs shows the signal of carbonyl groups, and many characteristic peaks appear near 1500 cm-1 and 1200 cm-1, which are significantly different from those in fig. 3A and fig. 3B, proving the introduction of a new functional group structure. The outcome shows that the BJO was loaded into CS-MSNs with success.

As can be seen from fig. 4A, the powder X-ray diffraction pattern of MSNs shows a series of peaks, indicating that it has crystalline properties. By comparison, it can be found that the addition of chitosan modification and the loading of BJO into mesoporous silica significantly reduced the height of its diffraction peaks. This is due to that the introduction of the organic functional groups decreased the crystallinity of the sample and after organic groups loading the crystal lattice structure and arrangement of the sample has changed.

Fig. 5 illustrates that thermogravimetric and differential scanning calorimetry analyses were performed in a nitrogen atmosphere to examine the composition ratio of the samples. The weight loss rates of MSNs, CS-MSNs, and BJO@CS-MSNs were 18.0 %, 28.5 %, and 65.0 % respectively, showing

the effective modification with chitosan and loading with BJO.

It has been reported in the literature that after chitosan modified onto mesoporous silica, a pH-sensitive mesoporous silica drug delivery system can be fabricated, achieving the purpose of controlled release[10,11]. The principle is as follows: In neutral or alkaline environments, chitosan has a significant number of hydrogen bonds, which leads to the contraction of the system and a more compact internal structure of the particles. This results in a slower drug release rate, creating a "closed" state. Conversely, in acidic conditions, the amino and hydroxyl groups in chitosan become protonated. Due to the repulsion of same charges, the structure of the nanoparticles becomes loose, allowing the drug molecules to freely diffuse and release, presenting a "open" state. Therefore, it has pH-responsive characteristics and can be used as an intelligent material for controlled drug release[25,26].

In fig. 6, the cumulative release curve of oleic acid in BJO clearly showed the release behaviour of BJO@CS-MSNs in response to pH stimulation. As the pH dropped from 7.0 to 5.8, the cumulative release rate of BJO increased significantly, demonstrating that the chitosan-modified mesoporous silica designed for this purpose successfully facilitated pH-controlled release of BJO.

TABLE 3: THE BRUNAUER-EMMETT-TELLER (BET) STRUCTURE PARAMETERS OF MSNs, CS-MSNs AND BJO@CS-MSNs

Iterms	MSNs	CS-MSNs	BJO@CS-MSNs
BET surface area (m^2/g)	876.824	1031.77	0.0177
Pore volume (cm^3/g)	0.7296	0.68581	0.00038
Average pore size (nm)	3.3284	2.6587	2.1305

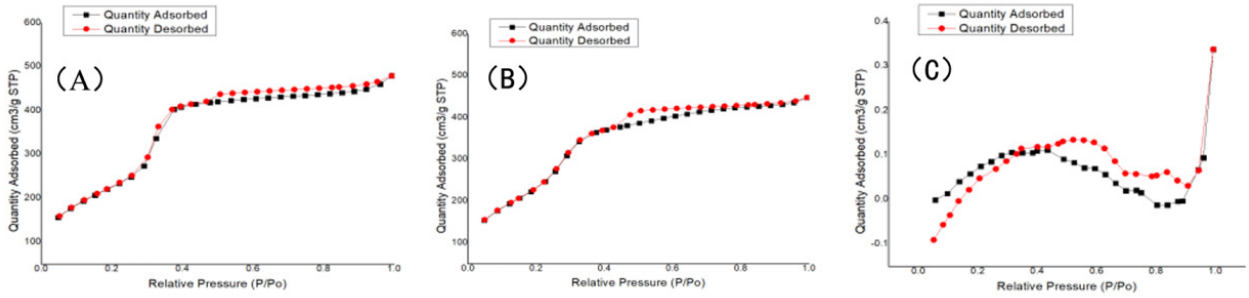

Fig. 2: Nitrogen-adsorption–desorption isotherms (A): MSNs; (B): Chitosan grafted MSNs (CS-MSNs) and (C): BJO loaded CS-MSNs (BJO@CS-MSNs)
Note: ( ): Quality absorbed and ( ): Quality desorbed

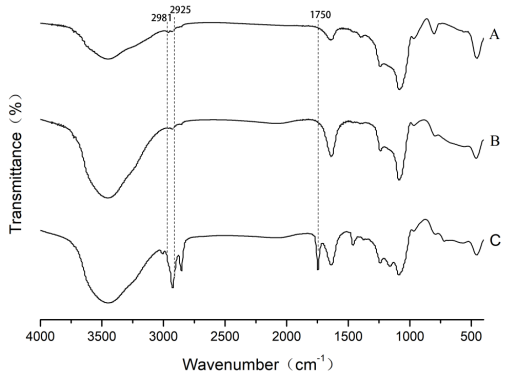

Fig. 3: Fourier transformed infrared (FT-IR) spectra of (A): MSNs; (B): Chitosan grafted MSNs (CS-MSNs) and (C): bjo loaded CS-MSNs (BJO@CS-MSNs)

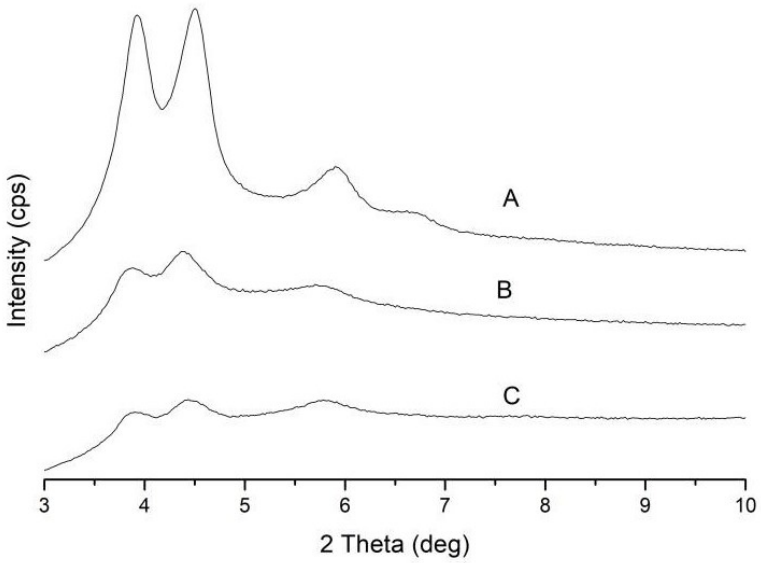

Fig. 4: XRD patterns (A): MSNs; (B): Chitosan grafted MSNs (CS-MSNs) and (C): BJO loaded CS-MSNs (BJO@CS-MSNs)

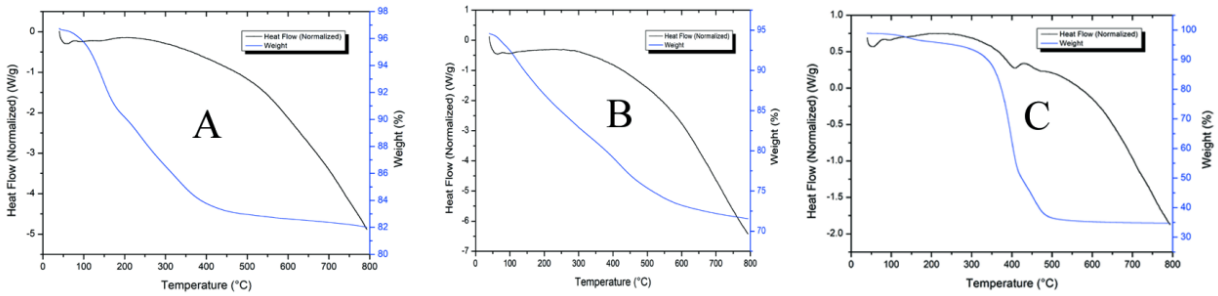

Fig. 5: Differential scanning calorimetry and thermogravimetric analysis (A): MSNs; (B): Chitosan grafted MSNs (CS-MSNs) and (C): BJO loaded CS-MSNs (BJO@CS-MSNs)

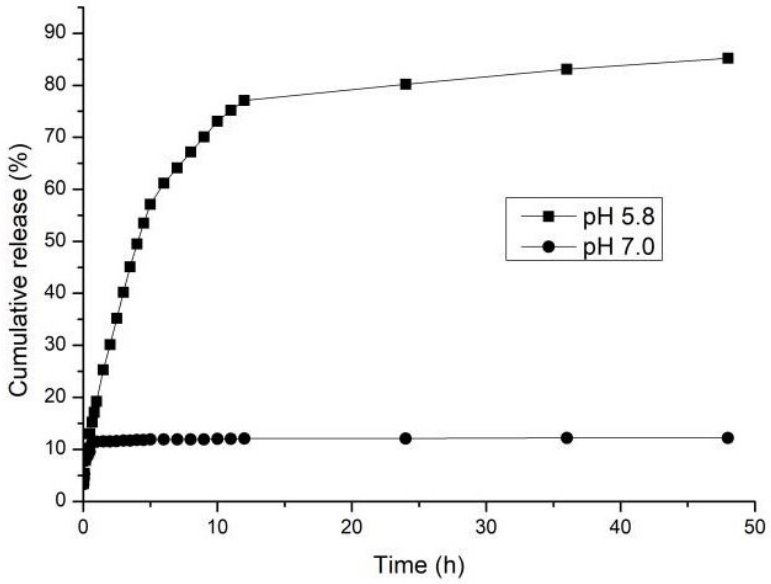

Fig. 6: *In vitro* calculated release from BJO loaded chitosan grafted mesoporous silica nanoparticles (BJO@CS-MSNs) in Phosphate Buffered Saline (PBS) of pH 7.0 and pH 5.8
Note: (—■—): pH 5.8 and (—●—): pH 7.0

The supercritical solution impregnation method can significantly increase the encapsulation rate of BJO to over 90 %, with a much better encapsulation effect than traditional methods. Furthermore, this technology eliminates the need for organic solvents, aligning perfectly with the principles of green pharmaceuticals. The successful construction of BJO@CS-MSNs was confirmed by multiple techniques such as SEM, FT-IR, XRD and thermal analysis, laying a structural foundation for subsequent mechanism research. The oleic acid dissolution rate of BJO@CS-MSNs at pH 5.8 was much higher than that at pH 7.0 in the *in vitro* release experiment. This responsive release can minimize drug leakage in healthy tissues and facilitate targeted controlled release at tumor sites, overcoming the limitations of traditional dosage forms regarding controlled release and targeting. This study constructed a pH-sensitive BJO mesoporous silica Nano drug delivery system through supercritical CO2 fluid technology, achieving significant results in encapsulation effect, structural characterization and *in vitro* release performance, providing a new strategy for the efficient delivery of anti-tumor components of traditional Chinese medicine.

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Author's contributions:

Huaping Lei: Conceptualization, methodology, data curation, writing-original draft preparation, project administration, funding acquisition. Yachao Jiang: Methodology, formal analysis. Bowen Ou, Shirui Mao and Jinhao Tang: investigation. Hui Zhang: writing-review and editing. Jie Wang: validation, data curation. Zhonglu Peng: Writing-review and editing, supervision. All authors have read and agreed to the published version of the manuscript.

Conflict of interests:

The authors declared no conflict of interests.

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