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Improved antimicrobial property and controlled drug release kinetics of silver sulfadiazine loaded ordered mesoporous silica

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ABSTRACT

The present study deals with the loading of silver sulfadiazine into ordered mesoporous silica material by post-impregnation method and its effect on the in vitro release kinetics and antimicrobial property of the drug. The formulated SBA-15 silica material with rope-like morphology and SBA-15-silver sulfadiazine (SBA-AgSD) were characterized by UV–visible spectrophotometer, small and wide-angle powder X-ray diffraction (PXRD), field emission scanning electron microscope (FESEM) and high resolution transmission electron microscope (HRTEM). Thermo-gravimetric analysis of SBA-AgSD revealed a high loading amount of 52.87%. Nitrogen adsorption–desorption analysis confirmed the drug entrapment into host material by revealing a reduced surface area (214 m^2/g) and pore diameter (6.7 nm) of the SBA-AgSD. The controlled release of silver sulfadiazine drug from the mesoporous silica to simulated gastric, intestinal and body fluids was evaluated. The Korsmeyer–Peppas model fits the drug release data with the non-Fickian diffusion model and zero order kinetics of SBA-AgSD. The antibacterial performance of the SBA-AgSD was evaluated with respect to *Staphylococcus aureus*, *Bacillus subtilis* and *Pseudomonas aeruginosa*. The controlled drug delivery of the SBA-AgSD revealed improved antibacterial activity, thus endorsing its applicability in effective wound dressing.

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1. Introduction

Nowadays, mesoporous nanomaterials have gained lots of interest as a drug carrier material due to their various beneficial properties such as biocompatibility, ability to control the drug release rate, non-toxicity, etc. Recently, silica based ordered mesoporous materials, commonly known as SBA-15, have provoked special consideration in the pharmaceutical field due to its unique advantages in many aspects such as biodegradability and biocompatibility, tunable pore size and structure, large surface areas and pore volumes, controllable morphology and modifiable surfaces with desirable functional group, high chemical and thermal stabilities, etc. [1,2]. The discovery and use of triblock copolymer template give birth to a polymorphic SBA-15. It is quite easy to control the surface area and pore volume of non-toxic SBA-15 in the range of 600–1600 m^2/g and 0.6–1.3 cm^3/g, respectively [3–6], which is highly required to control the drug release. The pure SBA-15 provides silanol groups on the channel walls, which form a weak intermolecular hydrogen bond with drugs and allow storage of high amount of a drug and also able to extend the drug release cycle in a sustained manner [7]. This polymorphic silica based ordered mesoporous material (or SBA-15) shows its proficiency in control drug delivery system due to its gate like scaffold nature in pure and in functionalized form [8–11].

In human body, the outermost lipophilic epithelial layer or skin is the first and second line of defense which provides the essential immunity. The presence of sebum and acidity (pH 3–5) in skin inhibits bacterial growth. But due to the advancement of technology and fast speed of life, most of the people suffer from burns, wounds and other types of skin diseases. Therefore, in the absence of this skin like swaddle, human body provides excellent medium for the development and propagation of pathogenic microorganisms. Thus, the development of innovative wound and burn dressing advancement is in great demand [12,13]. It is well

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known that the silver and its compounds such as silver sulfadiazine (AgSD) are widely used in most of the skin complications because of their peerless antimicrobial activity [14,15]. But, the AgSD shows cytotoxicity and allergic reactions in clinical studies, which lead to hamper the healing progress of skin [16]. Therefore, a substitute scenario is required to improve drug (AgSD) efficacy. The antibacterial property requires a carrier which releases the drug for longer time but in a controlled manner. To fulfill this requirement, the SBA-15 can be used as an effective drug carrier which may reduce the drug cytotoxicity and enhance its efficacy.

In the present study, an attempt has been made to load AgSD in porous SBA-15 material in order to achieve the beneficial properties of both AgSD and SBA-15. The release kinetics of AgSD from the SBA-15 to simulated gastric, intestinal and body fluids was studied. The antibacterial performance of the SBA-AgSD was also evaluated with respect to *Staphylococcus aureus*, *Bacillus subtilis* and *P. aeruginosa*. An efficient antibacterial agent in the form of AgSD loaded SBA-15 has been developed. The SBA-AgSD proved its proficiency as an excellent and smart long range antibacterial fighter against various pathogenic bacteria.

2. Experimental

Reagents used for the synthesis of mesoporous materials: Pluronic P_{123} [ethylene oxide–propylene oxide–ethylene oxide ($EO_{20}PO_{70}EO_{20}$), Mw = 5800], tetraethoxy orthosilicate [$(C_2H_5O)_4Si$, TEOS] and HCl (35%) were procured from Sigma–Aldrich.

Reagents used for the preparation of human simulated body fluid (SBF): phosphate buffer solution (PBS), HCl (hydrochloric acid), NaCl (sodium chloride), KCl (potassium chloride), KH_2PO_4 (potassium dihydrogen phosphate), NaOH (sodium hydroxide), Na_2HPO_4 (disodium hydrogen phosphate) were procured from Merck, India.

Silver sulfadiazine drug was generously gifted by Galentic Pharma (India) Pvt. Ltd.

2.1. Synthesis of SBA-15 matrix

The synthesis of mesoporous silica was performed in accordance with our earlier reported work [17]. In a typical process, initially 2 g triblock copolymer, P_{123} was dissolved in 70 mL distilled water at 40 °C under high acidic conditions produced by the addition of 10 mL HCl (2 M). A clear solution was achieved after 3 h of continuous mechanical stirring of the solution. Then, 4.8 mL TEOS was added to the above mentioned solution followed by continuous stirring for another 24 h at 40 °C. Thereafter, the solution was transferred to a Teflon lined stain-less steel autoclave and hydrothermally treated at 100 °C for 24 h. After cooling down to room temperature, the solid products were filtered, washed and dried at 70 °C. Finally, the solid product was calcined at 600 °C with a heating rate of 1 °C/min for 4 h in air to remove organic templates and to obtain mesoporous powder form SBA-15.

2.2. Preparation of calibration curve of silver sulfadiazine in 0.1 N HCl at λ_{max} = 254 nm

Calibration curve of the drug silver sulfadiazine (AgSD) was prepared in 0.05% ammonia solution at λ_{max} = 254 nm as shown in Fig. 1. The AgSD of about 100 mg was weighed and dissolved in 1000 mL 0.05% ammonia solution to get a concentration of 100 μg/mL. 2 mL from this stock solution was further diluted to 10 mL with 0.05% ammonia solution to obtain a concentration of 20 μg/mL. Serial dilutions of 2–20 μg/mL were prepared using 0.05% ammonia solution. A calibration curve was obtained by recording the absorbance of each diluted solution at 280 nm in a UV–visible double beam spectrophotometer. A regression equation between the absorbance (A) and concentration (C, μg/mL) was obtained: $A = 0.009C + 0.007$, $R^2 = 0.992$, so that the concentration of drug in solution can be obtained using Eq. (1):

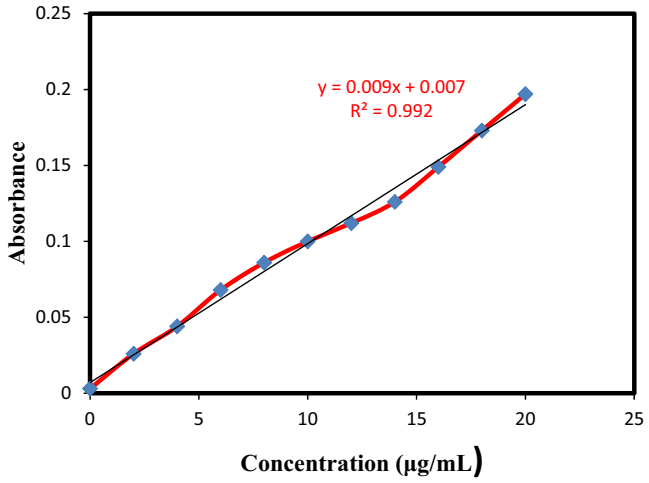

Fig. 1. Calibration curve of AgSD in 0.05% ammonia solution at λ_{max} = 254 nm.

$$C = \frac{A - 0.007}{0.009}, \quad \text{in} \quad \mu\text{g/mL} \tag{1}$$

2.3. Drug loading

The loading of AgSD was achieved by post-impregnation method. The AgSD (200 mg) was dissolved in 20 mL of 0.1 N HCl solutions and soaked with SBA-15 (250 mg) under continuous stirring for 12 h at 500 rpm. The pellet obtained after centrifugation (15,000 rpm at 4 °C for 1 h) was dried and preserved under vacuum at room temperature for further characterization.

The drug entrapment (EE%) in mg/mL and loading efficiency (P_E) in mg/g was calculated by UV–visible spectroscopy at 254 nm using respective blank following Eqs. (2) and (3).

$$\text{EE\%} = \frac{(C_i - C_f)}{C_i} \times 100 \tag{2}$$

$$P_E = \frac{(C_i - C_f)}{W} \times V \tag{3}$$

where P_E is the amount of drug absorbed into the matrix (mg/g; mg azathioprine per gram SBA-15), C_i and C_f (mg) are initial and final concentrations of the azathioprine in the reaction solution (mg/mL), respectively, V is the volume of the reaction solution (mL), and W is the weight of the SBA-15 (g).

2.4. In vitro drug release measurements

The drug release behavior of the loaded samples were investigated in simulated gastric fluid (SGF), simulated intestinal fluid (SIF) and simulated body fluid (SBF) at different pH of about 1.2, 6.8 and 7.2, respectively. To study the release of AgSD from SBA-15, the loaded powders were immersed in different fluids under magnetic stirring in a dialysis membrane. The AgSD loaded SBA-15; equivalent to 15 mg of the drug was transferred into the dialysis bag. Sample aliquots (5 mL) were withdrawn at specific time intervals and were subsequently replenished with fresh dissolution medium. Hence, a corrected method was employed to determine the real content of AgSD released from the SBA-15 material, using Eq. (4)

$$C_{t-\text{corrected}} = C_t + \frac{v}{V}\sum_{0}^{t-1} C_t \tag{4}$$

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