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Feasibility study of silica sol as the carrier of a hydrophobic drug in aqueous solution using enrofloxacin as the model

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ABSTRACT

The aim of this study was to determine the feasibility of using silica sol to carry a hydrophobic drug in aqueous solution. Enrofloxacin, which was selected as the model drug because it is a broad-spectrum antibiotic drug with poor solubility in water, was adsorbed onto silica sol in aqueous solution during cooling from 60 °C to room temperature. The drug-loaded silica sol was characterized by transmission electron microscopy, Fourier transform infrared spectrum, thermal gravimetric analysis and ultraviolet–visible light spectroscopy. The results showed that enrofloxacin was adsorbed by silica sol without degradation at a loading of 15.23 wt.%. In contrast to the rapid release from pure enrofloxacin, the drug-loaded silica sol showed a slower release over a longer time. Kinetics analysis suggested the drug release from silica sol was mainly a diffusion-controlled process. Therefore, silica sol can be used to carry a hydrophobic drug in aqueous solution for controlled drug delivery.

1. Introduction

Various forms of silica, including silica gel, hollow silica nanoparticles, mesoporous silica and silica xerogels, have been used as drug carriers for controlled drug release because of their high levels of chemical and thermal stability, easily modified surface properties, large surface area, good biocompatibility and favourable tissue response [1–18]. The preparation of the silica carrier usually involved the synthesis of silica sol and a time-consuming and expensive gelation process, such as supercritical drying or spray-drying. These drawbacks limit their application to some fields, such as the production of veterinary drugs.

The hydrophilic surface of the silica carrier needs to be modified to improve the affinity to the drugs [19] which are poorly soluble in water, namely, hydrophobic drugs. In addition, organic solvents have been used to dissolve hydrophobic drugs [6,14,15,18]. Both of these processes increase the complexity and the cost of production.

Here, we evaluated the use of silica sol consisting of small particles (10–20 nm) of hydrophilic silicon dioxide (SiO_2) dispersed in water, as the carrier for hydrophobic drugs in aqueous solution. Enrofloxacin was selected as the drug model since it is a broad-spectrum antibiotic with poor solubility in water. There are hydrophilic groups, such as –COOH, in the molecular structure of enrofloxacin (Fig. 1), which might provide an affinity to the hydrophilic surface of silica sol in water.

2. Materials and methods

2.1. Materials

Silica sol with a silica concentration of 30 wt.% was supplied by Zhengzhou Jingwei Composite Material Co., Ltd. It is an odourless, tasteless and non-toxic material conventionally made by using a sodium silicate solution called water glass as the starting material. The sodium ions are removed by an ion-exchange method [20].

Enrofloxacin was supplied by Henan Biyun Days Animal Pharmaceutical Co. Sodium dihydrogen phosphate (NaH_2PO_3) and sodium hydrogen phosphate (Na_2HPO_3) were of analytical grade and used as received.

2.2. Drug loading

In a typical drug loading process, 0.23 g of enrofloxacin and 10 mL of silica sol were mixed and stirred with a magnetic follower in a 100 mL flask equipped with a condenser. The temperature was increased slowly and the initial turbid suspension became a light yellow and transparent solution at 60 °C, indicating that the all of the drug had been dissolved. (There was incomplete dissolution when larger amounts of the drug were used and the mixture was turbid.) The contents of the flask were allowed to cool slowly to room temperature and a white powder appeared at the bottom of the flask. The precipitate was collected by centrifugation, washed with water, dried in air at 40 °C for 24 h and finally ground to a white powder in a ceramic pestle and mortar.

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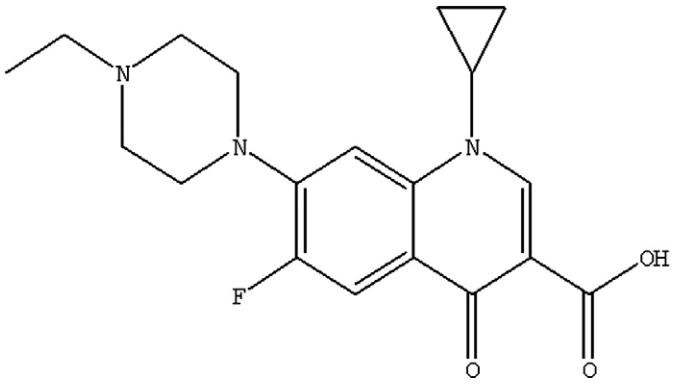

Fig. 1. Molecular structure of enrofloxacin.

2.3. Characterization

The amount of drug adsorbed to the carrier was determined with an American Diamond thermal gravimetric analyzer (TGA). Colloidal particles of silica sol were collected by centrifugation and dried for comparison. The samples were heated at a rate of 10 °C/min in a stream of nitrogen gas. Details of the calculations based on weight loss are described below. Samples were observed by transmission electron microscopy (TEM) with a JEM 100CX-a instrument. The Fourier transform infrared (FTIR) spectrum was obtained with a CARY Eclipse FTIR spectrophotometer.

2.4. Drug release

The drug release in vitro experiments consisted of placing 0.1 g of the dry enrofloxacin-loaded silica sol powder into 50 mL of phosphate-buffered saline (PBS, pH 7.4) at 37 °C. For comparison, dissolution of enrofloxacin alone was investigated under the same conditions.

At each sampling time-point, 0.5 mL of sample was withdrawn and diluted to 10 mL with distilled water. The concentration of enrofloxacin released into solution as a function of time was determined from measurement of the absorbance at 270 nm (CARY 300 spectrophotometer), the characteristic absorption wavelength of enrofloxacin in PBS. Enrofloxacin standards were prepared by dissolving weighed amounts of the drug in PBS.

3. Results and discussions

3.1. TEM study

Fig. 2 shows TEM images of silica sol (a) and enrofloxacin-loaded silica sol (b). The colloidal particles of silica sol alone were spherical with a diameter of 15–20 nm and no aggregation was seen. Conversely, the enrofloxacin-loaded silica sol showed severe aggregation (Fig. 2b), suggesting that enrofloxacin had been adsorbed onto the surface of the silica sol, which changed its hydrophilicity. The size of the particles did not appear to be increased by the adsorption of enrofloxacin, suggesting that the drug is adsorbed to the surface of the silica sol as a thin layer that was not detected by TEM.

3.2. Drug adsorption

The FTIR spectrum of the drug-loaded silica sol was recorded and compared with that of pure enrofloxacin and silica sol alone. As Fig. 3 shows, the characteristic peaks of drug-loaded silica sol were identical with those of silica sol alone and enrofloxacin, except for the overlapping region between 1400 cm^{-1} and 1000 cm^{-1}, where a broad absorption peak was found. This result suggests that the drug is physically adsorbed onto the surface of the carrier and no degradation of drug occurred during the loading procedure.

The loading weight percentage (W) of enrofloxacin on silica sol was determined by TGA (Fig. 4). It was clear from the TGA profile of enrofloxacin that drug molecules were decomposed completely at a temperature of 900 °C. There was a small weight loss for the silica sol blank below 900 °C, which might be caused by the decomposition of some unidentified organic component of the silica sol. Therefore, the calculation of W was a little more complicated than that for pure silica hosts. Lu [7] proposed that W can be calculated as:

$$\frac{B - W_1}{100 - B} = \frac{T - W - W_2}{100 - T} \quad (1)$$

where W_1 and W_2 are the weight loss of the physically and chemically adsorbed water at <200 °C of the blank silica sol and the drug-loaded silica sol, respectively; B is the weight loss corresponding to the adsorption of water and organic content by the silica sol; and T is the sum of the weight loss of adsorbed water and organic part of drug-loaded silica sol. With $B = 4.92\%$, $W_1 = 3.05\%$, $T = 19.59\%$ and $W_2 = 2.78\%$, W is calculated by Eq. (1) as 15.23%.

3.3. Drug release

The controlled release of a drug from its carrier has become increasingly important for oral, transdermal and implantable therapeutic systems. Fig. 5 shows the concentration change of enrofloxacin released into solution as a function of time for enrofloxacin alone and for the drug-loaded silica sol under the same conditions. There is a major difference between the curves. Enrofloxacin alone showed a rapid release into the solution within the first 2 h, reaching a concentration of 0.00029 g/mL and remained at 0.00031 g/mL after 9 h. In contrast to the brief, short-term release from pure enrofloxacin,

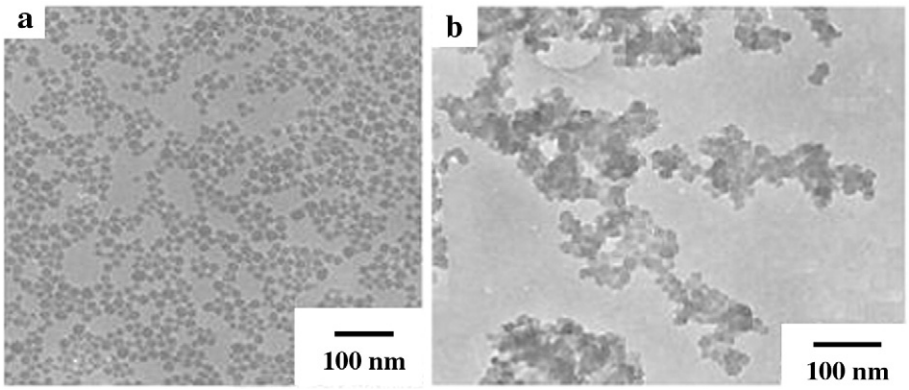

Fig. 2. TEM images of silica sol (a) and enrofloxacin-loaded silica sol (b).

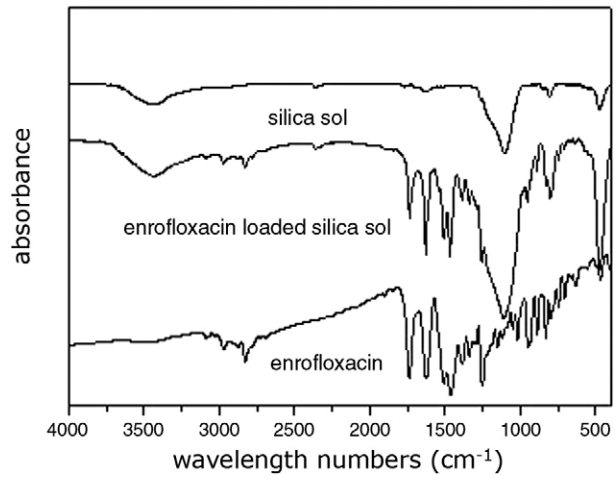

Fig. 3. FTIR spectra of silica sol, enrofloxacin and silica sol loaded with enrofloxacin.

the drug adsorbed onto silica sol showed a slower, longer-term release, where the concentration of enrofloxacin was only 0.00013 g/mL after 10 h and 0.00022 g/mL after 48 h and it took nearly 168 h to reach a concentration of 0.00030 g/mL. It is clear from these results that adsorption onto the silica sol markedly delays release of the

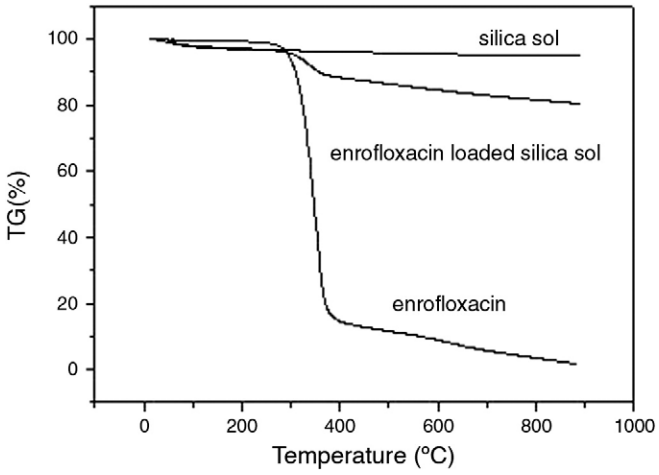

Fig. 4. TGA profiles of silica sol, enrofloxacin and silica sol loaded with enrofloxacin.

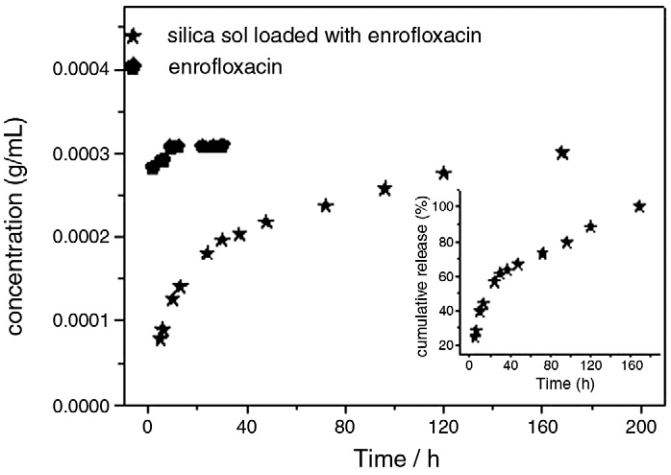

Fig. 5. The concentration changes of enrofloxacin as a function of time released from pure enrofloxacin itself and drug-loaded silica sol, respectively. Inset: cumulative release percentage of enrofloxacin from drug-loaded silica sol vs. time.

Table 1
The functions and the correlation coefficients of the three models to fit the experimental data.

Model	Functions	R^2
Zero order	$\frac{M_t}{M_\infty} = 0.01409t + 0.21653 \left(\frac{M_t}{M_\infty}\ 0.6\right)$	0.9739
	$\frac{M_t}{M_\infty} = 0.00283t + 0.52961 \left(0.6 < \frac{M_t}{M_\infty} < 1\right)$	0.99843
	$\frac{M_t}{M_\infty} = 0.00416t + 0.38583$	0.92643
First order	$\frac{M_t}{M_\infty} = (0.66713 - 0.61404e^{-t/12.88759})\% \left(\frac{M_t}{M_\infty} < 0.6\right)$	0.99865
	$\frac{M_t}{M_\infty} = 4.50269 - 3.98215e^{-t/1301.60341} \left(0.6 < \frac{M_t}{M_\infty} < 1\right)$	0.9971
	$\frac{M_t}{M_\infty} = 0.95210 - 0.71945e^{-t/48.07211}$	0.96049
Ritger–Peppas	$\frac{M_t}{M_\infty} = 0.11645t^{0.4998} \left(\frac{M_t}{M_\infty} < 0.6\right)$	0.9842
	$\frac{M_t}{M_\infty} = 0.20812t^{0.3007} \left(0.6 < \frac{M_t}{M_\infty} < 1\right)$	0.9766
	$\frac{M_t}{M_\infty} = 0.15789t^{0.3638}$	0.9662

Note: $\frac{M_t}{M_\infty}$ is the fractional of drug release.

enrofloxacin into solution. The delay might be caused by the change of the surface property of silica sol from hydrophilic to hydrophobic resulting from the adsorption of enrofloxacin. As a result, the drug-loaded silica sol aggregates readily in aqueous solution (Fig. 2b). Before the drug is released from the surface of the silica sol and diffuses away, the release fluid must moist the carrier causing desorption of the drug molecules.

The inset in Fig. 5 shows a burst release followed by a sustained release of enrofloxacin from the carrier as a function of time. The cumulative release of the enrofloxacin was 61.2% within the first 30 h, and the remainder (38.8%) was released during the following 138 h, indicating that the release of the drug was a two-step process, which requires that the kinetic model [19,21–24] describes the drug release in two stages. Three diffusion models, including zero-order, first-order, and Ritger–Peppas were considered to fit the experimental data as shown by the inset in Fig. 5. The regression functions and correlation coefficients for all data over the full release duration as well as data of the different release stages are given in Table 1. It was found that the correlation coefficients of full release analysis were lower than those obtained by two-stage analysis, and the first-order kinetics model performed better than the other models, indicating that the results were in accordance with the commonly used description of a diffusion-controlled process.

4. Conclusion

The antibiotic enrofloxacin with poor solubility in water was adsorbed onto silica sol in aqueous solution. The release of the drug from the silica sol carrier was time-dependent. In contrast to the rapid release into solution from pure enrofloxacin, the release from the drug-loaded silica sol was slower and occurred over a longer time. The kinetic analysis suggested that the release from silica sol was mainly a diffusion-controlled process. This study has demonstrated the feasibility of using silica sol as a carrier of hydrophobic drugs in aqueous solution for controlled drug delivery.

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