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Controlled release and enhanced antibacterial activity of salicylic acid by hydrogen bonding with chitosan☆

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ABSTRACT

Microcapsules of salicylic acid (SA) with chitosan were prepared by spray drying method. Various analytical methods were used to characterize the nature of microcapsules. Fourier-transform infrared spectroscopy (FTIR) confirmed the presence of intermolecular interactions between chitosan and SA. Particle size analysis showed that the average size of microcapsules ranged from 2 to 20 μm. Scanning electron microscopy (SEM) studies indicated that the microspheres were spherical and had a relatively smooth surface. Microbiological assay of antibacterial activity for SA and its microcapsules was measured using different bacterial strains. It was found that the antibacterial activity of SA was improved after the formation of microcapsules. The *in vitro* release profile showed that the microcapsules could control SA release from 1 h to 4 h. Kinetic studies revealed that the release pattern follows Korsmeyer–Peppas mechanism. Enhanced antibacterial activity of the SA microcapsules was attributed to the synergistic effects of intermolecular hydrogen-bonding interactions N–H···O and O–H···O=C between SA and chitosan. It was also confirmed by quantum chemical calculation.
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1. Introduction

Skin is one of the most important organs of human body which provides an overlaying protective barrier against environment. However, 54% of the world population is affected by skin disease each year [1]. Acne is a very common skin disease, and it affects more than 96% of teenagers. A study indicated that acne can cause some serious psychological problems *e.g.* depression, suicidal ideation and anxiety [2]. Medicinal plants containing salicylic acid have been used to treat various skin disorders [3]. Salicylic acid (SA) is a phenolic compound widely distributed in many plants, especially white willow, meadowsweet and wintergreen [4,5]. SA has been used to relieve pain, reduce fever and prevent heart attack and stroke [6]. SA is also a key ingredient in many skin-care products for the treatment of acne, psoriasis, calluses, corns, keratosis pilaris and warts [7,8]. However, application of SA has been limited due to its low solubility in water ($2\ g\cdot L^{-1}$ at 20 °C) and strong irradiation on skin. Incorporation of SA into polymer matrix has been regarded as the most efficient method.

Microencapsulation is a way in which liquid droplets, solid particles or gaseous compounds are entrapped. The technology has been widely applied in pharmaceutical, food, pesticide, cosmetic, textile and other related fields [9–11]. It provides an effective method for controlled release and protection of active substances. In addition, SA is an analgesic and antipyretic drug. Drug released from microcapsules or hydrogels is usually trigged or controlled by environment and pores of the matrix materials [12,13]. Therefore, selection of proper wall materials is important for improving performance of active compounds.

Chitosan is a natural polysaccharide derived from alkaline deacetylation of chitin. It is the second most abundant biopolymer after cellulose, and is an environmentally-friendly material with many superior properties *e.g.* biocompatibility, biodegradability and non-toxicity and can be used in many areas, such as wastewater treatment, food processing, pharmaceuticals, biomaterials, and agriculture [14–17]. In addition, it is a very promising compound as natural antioxidants in biological systems [18]. Therefore, chitosan is suitable as the wall material.

The aim of this work is to study encapsulation of SA and improvement of its release effectively with chitosan as wall material. Structure of the microcapsule has been characterized with various physico-chemical techniques. Release performance, mechanism, and Minimum Inhibitory Concentration (MIC) of the encapsulated SA were investigated with both experiments and quantum chemical

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calculations systematically. The results indicate that the method has great potential applications for functional materials in cosmetics industry.

2. Experimental

2.1. Materials

SA (A. R.) was purchased from Aladdin Industrial Corporation (Shanghai), China. Chitosan (degree of deacetylation ≥ 90.0%, $M_w = 1.43 \times 10^5$ Da) was purchased from Zhejiang Aoxing Biotechnology Co. Ltd., China. All other reagents and solvents are of analytical grade and used without further purification unless indicated. Distilled water was used throughout.

2.2. Preparation and characterization of SA/chitosan microcapsules

Chitosan solution was prepared by dissolving 3.0 g chitosan in 100 ml acetic acid (3.0%, by mass) under vigorous stirring. Different amounts of SA dissolved in 10 ml 95% ethanol were slowly added to the chitosan solution and refluxed at 60 °C for 4 h. An aqueous emulsion could be obtained from this mixture with a Fluke homogenizer at 18000 $r \cdot min^{-1}$ for 60 min. The emulsion was continuously stirred with a magnetic bar throughout the drying process. Spray drying was used for preparing SA/chitosan microcapsules due to its relatively low cost, rapid, reproducible and easy scale-up [19]. The operation conditions for a Lab Plant SD-06 atomizer were: diameter of the atomizer nozzle (0.5 mm), liquid flow rate (8 $ml \cdot min^{-1}$), and inlet and outlet air temperatures were 170 and 85–90 °C, respectively. The dried microcapsules collected in a cyclone were stored in plastic bottles at 4 °C for further analysis.

The particle size distribution of SA/chitosan microcapsules was measured using a laser particle size analyzer (Mastersizer 2000, Malvern Instruments Limited, Malvern, UK). Particle size was measured using the dry sample adapter and the volume mean diameter (V_d) was recorded. IR spectra of the microcapsules was recorded on a Bruker TENSOR 37 FTIR spectrometer. SEM was used to observe the morphology of the microcapsules (FE-SEM, JSM-6330F). Samples were coated with thin layer of gold prior to examination under the electron beam. An operating voltage of 25 kV was used.

2.3. Determination of SA content in microcapsules

SA/chitosan microcapsules were washed with ethanol solution twice. The amount of surface SA in the solution was measured on UV-2450 spectrophotometer (Hitachi, Japan). The absorbance at 297 nm as the absorption maximum of SA was measured at 298 K. The microcapsules were further suspended in phosphate buffer saline (PBS) pH 7.2 (USP XXIII), and treated with ultrasonic irradiation twice at 15 min intervals. The amount of incorporated SA was measured with the same method. Encapsulation efficiency (EE) and loading capacity (LC) of the microcapsules were calculated as:

$$\mathrm{EE} = \frac{(\text{Total SA} - \text{Surface SA}) \text{ in the the microcapsules}}{\text{Total SA}} \times 100\% \quad (1)$$

$$\mathrm{LC} = \frac{(\text{Total SA} - \text{Surface SA}) \text{ in the the microcapsules}}{\text{The microcapsules}} \times 100\% \quad (2)$$

2.4. Microbiological assay

Microbiological assay was performed for blank microspheres, SA, and SA/chitosan microcapsules. MIC ($\mu g \cdot ml^{-1}$) against selected strains of *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Propionibacterium acnes* was determined using the agar dilution method in Mueller-Hinton agar medium, as previously reported [20].

2.5. In vitro release study

In vitro release study was conducted for all prepared SA/chitosan microcapsules. Microcapsules containing 20 mg of SA and a reference sample with the same amount of SA were kept in 100 ml phosphate buffer pH 7.4 (USP XXIII) at 37 °C under a constant rotation of 150 $r \cdot min^{-1}$. An aliquot of the release medium (2 ml) was sampled and its absorbance at 297 nm was measured for quantitation of SA. Another 2 ml phosphate buffer was then added to keep the volume of the release media constant.

The release data were evaluated with the release kinetics theories [21–23]:

Zero order kinetics:

$$F_t = K_0 t \quad (3)$$

here F_t represents the fraction of drug released in time t and K_0 is the apparent release constant for zero order kinetics.

First order kinetics:

$$\ln(1-F) = K_1 t \quad (4)$$

here F represents the fraction of drug released in time t and K_1 is the release constant for first order kinetics.

Higuchi model:

$$F = K_2 t^{1/2} \quad (5)$$

here F represents the fraction of drug released in time t and K_2 is the Higuchi dissolution constant.

For the Korsmeyer–Peppas model, the drug release mechanism was often derived from Fick's law, and the anomalous behavior was described by the following equation:

$$\frac{M_t}{M_\infty} = kt^n. \quad (6)$$

Here M_t is the drug released at time t, M_∞ is the quantity of drug released at infinite time, k is the kinetic constant and n is the release exponent. When $\ln(M_t/M_\infty)$ was plotted against $\ln t$, its slope gives n and the intercept corresponds to k. n obtained from the Korsmeyer–Peppas model indicates that drug release was dominated by the diffusion process. n is used to characterize different release mechanisms. $n \le 0.45$ indicates Fickian diffusion, in which the rate of diffusion is less than that of relaxation. n in the range of $0.45 < n < 0.89$ indicates that the mechanism is neither Fickian diffusion nor anomalous diffusion, where the diffusion and relaxation rates are comparable. When $n > 0.89$, the major mechanism for drug release is Case II diffusion (relaxation-controlled transport) in which diffusion is very rapid compared to the relaxation process of polymer [21].

2.6. Quantum-chemical calculations

Quantum-chemical calculations were used to access the formation of these molecular complexes at molecular level, which can provide some information regarding the energy and structure of inclusion complex. In the present investigation, chitosan is a polysaccharide with high molecular weight. It composed mainly of 2-deoxy-2-amino-D-glucopyranose units, and partially of 2-deoxy-2-acetamido-D-glucopyranose linked *via* (1 → 4)-β-glycosidic bonds. In order to explore the host–guest interaction mechanism, a basic assumption is that the binding sites are 2-deoxy-2-amino-D-glucopyranose and 2-deoxy-2-

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