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Resveratrol nanodispersion with high stability and dissolution rate

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ABSTRACT

Resveratrol is a highly polyphenolic substance which possesses extensive physiological activities. However, its application is limited by light instability and poor aqueous solubility. In this paper, resveratrol nanodispersion with high light stability and water dissolution rate was prepared by a combination of antisolvent precipitation in the presence of nontoxic polymer and spray-drying. The active ingredients of the unprocessed raw resveratrol decreased 80 wt% when exposed to sun light directly, while that of the resveratrol nanodispersion only reduced 14 wt% at the same condition. The resveratrol nanodispersion dissolved completely in less than 45 min, while raw resveratrol didn't dissolve completely after 120 min. Meanwhile, resveratrol nanodispersion exhibited better antioxidant activity compared to that of raw resveratrol when added in artificial intestinal juice. This study is helpful to promote the application of resveratrol and provides a routine for enhancing stability and water solubility of photosensitive lipophilic materials.

1. Introduction

Resveratrol (trans-resveratrol; trans-3,5,4'-trihydrox-ystilbene) belongs to a class of polyphenolic substances, naturally existing in grapes, red wine, peanuts and other peanut products (Sobolev & Cole, 1999). Nowadays, considerable researches have been devoted to investigating the extensive biological activities and synthesis routes of resveratrol (Athar et al., 2007; Gresele et al., 2011; Halls & Yu, 2007; Ruan et al., 2011). It was found that severe oxidative stress resulting in chronic degenerative conditions can be combated by the body with antioxidants and free radical scavengers. The biological activity of resveratrol as an antioxidant is due to its three-dimensional crystal structure owning flip-flop hydrogen-bonding scheme which results in dynamic mobility of electrophilic hydrogen atoms (Caruso, Tanski, Estrada, & Rossi, 2004). As a polycyclic aromatic hydrocarbon antagonist, resveratrol can act as an effective anticarcinogenic agent against several tumor cells, inhibiting cancer cell proliferation through its interaction with the cytochrome P450 enzyme system (Casper et al., 1999). Some studies show that resveratrol may have some physiological functions such as anti-angiocardiopathy, anti-tumor, anti-inflammatory, and anti-platelet effects (Baur & Sinclair, 2006; Fan, Zhang, Jiang, & Bai, 2008).

Therefore, resveratrol is of evident value as a cancer preventive (Delmas et al, 2002), cardio-protective (Milner, McDonald, Anderson, & Greenwald, 2001) and neuro-protective substance. It may provide an alternative intervention approach that could prevent or delay disease onset, emend the course of disease and prevent further damage.

However, the utilization of beneficial effects of resveratrol is limited because it is easily oxidizable and extremely photosensitive. It is well known that trans-resveratrol is unstable in solution when exposed to light (Trela & Waterhouse, 1996), and the half-life of trans-resveratrol is only 30–45 min (Bertelli et al., 1996). In addition, the water solubility of the highly lipophilic resveratrol is poor (López-Nicolás, Núñez-Delicado, Pérez-López, Barrachina, & Cuadra-Crespo, 2006). In order to enhance its bioavailability it is desirable to not only stabilize resveratrol and but also improve its water solubility.

From the reports on resveratrol, most of the studies have focused on the demonstration of its biological activities, evidence for its potent biological effects from clinical studies, and research for synergistic effect of resveratrol with other diet components. In recent years, several studies have focused on novel formulation approaching to stabilize resveratrol and increase its solubility in water. Monodisperse cyano-functionalized porous polymeric microspheres have been prepared to stabilize the resveratrol (Nam, Ryu, Kim, Chang, & Suh, 2005). Complexation of resveratrol with β-cyclodextrin (β-CD) or hydroxypropyl-β-CD (HP-β-CD) has been

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investigated to improve the water solubility (Lu, Cheng, Hu, Zhang, & Zou, 2009). Shi et al. (2008) used cell encapsulation technology to stabilize resveratrol and improve its water solubility. They encapsulated resveratrol into yeast cells to prepare yeast-encapsulated resveratrol. The microcapsule was more stable under illumination stresses and showed higher water solubility (Shi et al., 2008). Although important advances have already been made, the technology is still encountering some obstacles. The cell encapsulation technology may bring about the problem of biocompatibility between microcapsules and their biomaterials' components (Murua et al., 2008). Hence, there is a growing need for a better strategy to stabilize resveratrol and increase its dissolution rate in water.

In regard with the Noyes–Whitney equation, reducing particle size is a promising way to improve dissolution rate of poorly soluble substances (Date & Patravale, 2004). However, the ultrafine pure particles have a high tendency to agglomerate and grow because of their higher surface energy, which leads to decrease in the dissolution rate (Swanepoel, Liebenberg, de Villiers & Dekker, 2000). It is necessary to keep ultrafine particles dispersed in a matrix during production. Loading hydrophobic nanoparticles on hydrophilic materials such as polymers has some advantages. First, it can improve the flowability of the powder, leading to effective formulation. Second, wetting can be effectively realized due to hydrophilicity of polymers and re-agglomeration of particles during dissolution can be prevented (Sanganwar & Gupta, 2008). Moreover, the active ingredients can be protected from decomposition.

Antisolvent precipitation process is a promising technique to prepare ultrafine particles, which is based on the change of supersaturation caused by mixing the solution and the antisolvent. In this method, it requires two solvents that are miscible. Ideally, the materials must dissolve in the solvent, but not in the antisolvent. Precipitation occurs instantaneously by a rapid desolvation of the materials. The key to producing ultrafine particles by antisolvent precipitation is to create conditions that favor very rapid particle formation and little or no particle growth. The technique is a straightforward, rapid and easy to perform. Spray drying is a normal method for producing powder. Our group has successfully prepared nanoparticles by combining anti-solvent and spray-dry process in the presence of stabilizers (Zhang et al., 2009). Therefore, in this work, we report the preparation of resveratrol nanodispersion (RND) by combining anti-solvent precipitation in the presence of nontoxic polymer and spray-dry process. The as-prepared products were characterized by SEM, FT-IR, XRD, DSC, and BET surface area test. Dissolution performance, antioxidant activity and stability were evaluated as well.

2. Materials and methods

2.1. Materials

Resveratrol (transform, purity is 98%) was purchased from Xi'an Haoxuan Biological Science and Technology Ltd (Xi'an, China). Hydroxypropylmethyl cellulose (HPMC, E4M, molecular weight: 86,000) was obtained from Shandong Ruitai Chemicals Co. Ltd (Feicheng, China). Polyvinyl pyrrolidone (PVP K30, molecular weight: 45,000–58,000) was obtained from Beijing Chemical Reagent Company (Beijing, China). Polyethylene glycol (PEG-400, molecular weight: 380–420) was supplied by Beijing Biodee Biotechnology Co (Beijing, China). Poloxamer188 (Plurnic F68, molecular weight: 7680–9510) was obtained commercially from Beijing Chemical Reagent Co. Ltd (Beijing, China). 2, 2-Diphenyl-1-picryl-hydrazyl (DPPH) was supplied by Shanghai Hualan Chemical Science and Technology Ltd (Shanghai, China). Ethanol, sodium hydroxide (NaOH) and potassium dihydrogen phosphate (KH_2PO_4) were analytical grade and obtained commercially from Beijing Chemical Reagents Company (Beijing, China). Deionized water was prepared with Hitech-K Flow Water Purification System (Hitech Instruments Co. Ltd, Shanghai, China).

2.2. Preparation of resveratrol solid dispersion

In the typical process, the anti-solvent solution was prepared by dissolving certain amount of polymer into water. Separately, raw resveratrol was dissolved in ethanol (30 mg/mL) as the solvent solution, followed by filtration through a 0.22 μm nylon membrane to remove the possible particulate impurities. The volume ratio of solvent solution and anti-solvent solution was adjusted to be 1:20. Then, the resveratrol solution was poured into anti-solvent solution rapidly under a vigorous stirring speed of 9000 rpm provided by the high speed disperser (Shanghai Scientific Instrument Co. Ltd., Shanghai, China) and the precipitation occurred immediately. After stirring for 30 s, the precipitated resveratrol suspension was obtained. Then the suspension was dried by spray drying method to generate resveratrol solid dispersions (spray-dried powder). Spray-drying was carried out using a laboratory scale spray dryer (SD-Basic, Lab Plant, North Yorkshire, UK) under the following conditions: inlet temperature, 105 °C; outlet temperature, 50–60 °C; spray flow rate, 12 mL/min; atomization air pressure, 0.65 MPa. The active ingredient content in RND was 9.6 wt% measured by UV spectrophotometer. In order to carry out contrast experiment, physical mixture (RPM) containing the same content (9.6 wt%) of active ingredient and polymer was prepared. And in the following experiment, the active ingredient content in RND and RPM was 9.6 wt%.

2.3. Characteristics

2.3.1. Determination of particle size

The particle size was analyzed by using laser diffractometer (Malvern NANO-ZS90, Worcestershire, UK). The samples needed to be dispersed into water to make sure the concentration of particles was approximate 0.05 mg/mL. Each sample was tested in triplicate, and the results were expressed as the mean ± standard distribution.

2.3.2. Scanning electron microscopy (SEM)

Particle morphology was observed by using scanning electron microscopy (SEM) JSM-6360LV (JEOL Inc, Tokyo, Japan). The samples were fixed on a SEM stub using double-sided adhesive tape, and then coated them with Au at 50 mA for 6 min through a sputter-coater (KYKY SBC-12, Beijing, China). A scanning electron microscope with a secondary electron detector was used to obtain digital images of the samples at an accelerating voltage of 10 kV.

2.3.3. Fourier transform infrared spectroscopy (FT-IR)

FT-IR spectra of samples were recorded with a Nicolet model 8700 spectrometer (Nicolet Instrument Corporation, Madison, USA) in the wavenumber range of 500–4000 cm^{-1} to evaluate the molecular states. Samples were diluted with KBr mixing powder at 1.0 wt% and pressed into self-supporting disks.

2.3.4. X-ray diffraction studies (XRD) and differential scanning calorimetry (DSC)

The samples were placed in a glass sample holder. Cu Kα radiation was generated at 30 mA and 40 kV. Samples were scanned from 5° to 50° with a step size of 0.05°. The DSC process was performed with a heating rate of 10 °C/min using nitrogen flow (50 mL/min) and samples were weighed (approximately 4.5 mg) in open aluminum pans and the percentage weight loss of the samples was monitored from 25 to 300 °C.