



Short communication

Aerosol synthesis of macroporous silica adsorbents with high performance in paclitaxel purification from plant cell cultures

Hye Ran Jang, Jin-Hyun Kim^{**}, Kyeong Youl Jung^{*}

Department of Chemical Engineering, Kongju National University, 1223-24 Cheonan-Daero, Seobuk-gu, Cheonan, Chungnam 330-717, Republic of Korea

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1. Introduction

Paclitaxel is a diterpenoid anticancer agent found in the bark of a yew tree, which have been widely used for the treatment of ovarian cancer, breast cancer, and Kaposi's tumors [1,2]. The direct extraction of paclitaxel from the yew tree is limited because the quantity and contents in the raw materials are different with the change of climate and environment [3,4]. For the mass and stable supply, paclitaxel is extracted from an artificial plant-cell culture [5,6]. Thus, many bioengineers have given a great interest to develop a high efficient production process by which the purity and yield of paclitaxel from the plant-cell culture can be increased [7–14]. In order to obtain high-purity (>98%) paclitaxel from plant cell cultures, multiple-step processes are required such as extraction of paclitaxel from biomass, pre-purification processes (liquid–liquid extraction, hexane precipitation, and fractional precipitation), and a final purification using high performance liquid chromatography (HPLC). Among those consecutive processes, the pre-purification process is important to obtain the high purity and yield of final paclitaxel products as well as the production cost. Therefore, the purity of paclitaxel should be increased as high as possible in the pre-purification step.

The crude paclitaxel extracts have a low purity (less than 10%) and considerable tar and waxy compounds. If a lot of tar and waxy compounds are remained after the liquid–liquid extraction, they cause many problems lowering the purification efficiency and increasing the solvent quantity in the final HPLC process. Specially, the tar and waxy compounds cause a lifetime shortening of the column-packing materials. Thus, they should be removed in the pre-purification step [8,9]. A simple and efficient method to remove the tar and waxy compounds in the pre-purification step is to use adsorbent before going to the hexane precipitation [15–20]. The adsorbent treatment was reported to make it possible to effectively remove plant-derived tar and waxy compounds. An effective adsorbent (sylopute), which is commercially available for the purification of paclitaxel, mainly consists of SiO₂ (60%), MgO (28%) and others (12%) [21]. Given this, porous silica compared with activated carbon is considered as a potential adsorbent for the purification of paclitaxel.

The physical properties of adsorbents affect the performance for the purification of paclitaxel. In general, large surface area is a key property for adsorbents to have. However, the purification efficiency of paclitaxel has not a linear relation with the surface area of adsorbents [19]. Beside the surface area, the pore size is an important factor. Given that the tar and waxy compounds should diffuse into the inner pores of adsorbents, macroporous silica may be more effective than the microporous or mesoporous one in the removal of impurities. Nevertheless, to our best knowledge, there was no study on the macroporous silica as an adsorbent for the purification of plant-derived paclitaxel. In this work, an ultrasonic spray pyrolysis was used to prepare mesoporous and macroporous

^{*} Corresponding author. Tel.: +82 41 521 9365; fax: +82 41 554 2640.

^{**} Corresponding author. Tel.: +82 41 521 9361; fax: +82 41 554 2640.

E-mail addresses: jinyun@kongju.ac.kr (J.-H. Kim),
kyjung@kongju.ac.kr (K.Y. Jung).

silica particles. The spray pyrolysis known as a representative aerosol process makes it possible to continuously produce porous materials. The self-assembly of organic templates in the spray pyrolysis can be completed within several seconds or less, whereas the conventional liquid-phase route requires longer than a day to achieve the highly ordered mesopores by self-assembly. Also, the pore size can be readily controlled by changing the template size. In special, the macropore size in SiO₂ matrix can be controlled by only changing the size of polystyrene (PS) nanoparticles initially dispersed in the spray solution. So, in this work, macroporous silica particles were prepared by an ultrasonic spray pyrolysis process and compared the purification performance of paclitaxel with mesoporous silica and commercial sylopute.

2. Experimental

2.1. Synthesis of adsorbents

Porous silica particles were synthesized by an ultrasonic spray pyrolysis process which consists of an ultrasonic aerosol generator with seven vibrators (1.7 MHz), quartz tube (inner diameter = 55 mm and length = 1000 mm), and a Teflon bag filter. A schematic diagram showing the spray pyrolysis apparatus was shown in Fig. 1. Tetra-ethyl-orthosilicate (TEOS, Aldrich, 97%) was used as a silica source. Cetyltrimethylammonium bromide (CTAB, Aldrich) and polystyrene (PS) nanoparticles were used as a pore-directing agent. PS nanoparticles of two different sizes (44 and 86 nm) were synthesized by an emulsion-free polymerization [22,23]. The names of silica samples were given as 'S1', 'S2', and 'S3' for the template CTAB, 86 nm PS, and 44 nm PS, respectively. To prepare the spray solution, TEOS was dissolved in purified water of 500 mL with HNO₃ of 10 mL and followed by adding the templates (CTAB or PS nanoparticles). The concentration of TEOS was fixed at 0.2 M. The CTAB/TEOS and PS/TEOS ratios were 0.2 in mole and 0.5 in weight, respectively. The prepared precursor solutions were atomized by the aerosol generator to produce droplets which were carried by air (10 L/min) into the reactor maintained at 700 °C. The silica powders were collected by the Teflon bag filter and calcined at 550 °C in order to remove organic compounds remained.

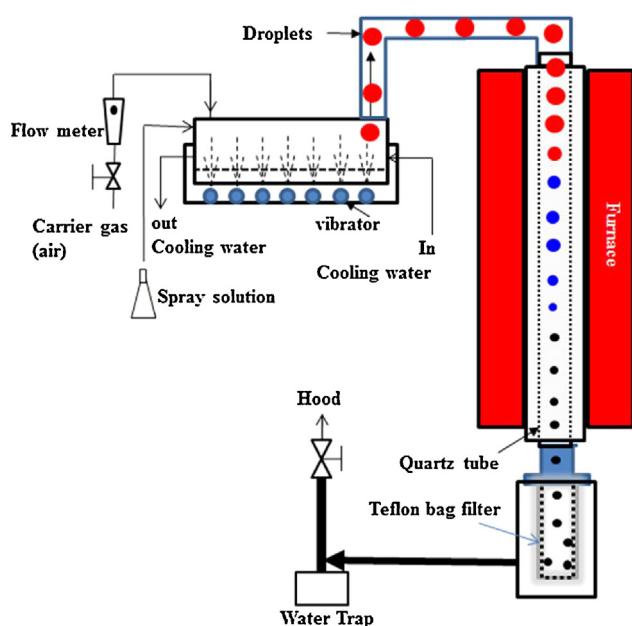


Fig. 1. Schematic diagram showing the experimental setup (spray pyrolysis apparatus) used for the preparation of porous silica particles.

The synthesized silica particles were analyzed by N₂ adsorption–desorption isotherms (Micrometrics ASAP 2010), mercury porosimetry (Micrometrics), transmission electron microscopy (TEM, Philips Tecnai F20), and small-angle X-ray diffraction (SAXS, Rigaku D/Max-2500). Particle morphology was monitored by scanning electron microscopy (SEM, TESCAN, MIRA LMH) and the particle size distribution of PS nanoparticles was measured by using a particle size analyzer (DLS, Photal Otsuka Electronics).

2.2. Performance evaluation of adsorbents for the purification of paclitaxel

Dried crude extract (purity: 10.6%) supplied from Samyang Genex company (South Korea) was dissolved in methylene chloride at a ratio of 20% (v/w). Thereafter, the synthesized silica or sylopute (Fuji Silysia Chemical Ltd., Japan) particles of 50 wt% with respect to the dried crude extract were added to the crude extract solution. The mixture was agitated at 40 °C for 30 min and followed by a filtration and drying at 30 °C in a vacuum oven. The dried filtrate was dissolved again in methylene chloride for a hexane precipitation processing in which the hexane was slowly added (methylene chloride/hexane = 1/10, v/v) in order to get more purified paclitaxel precipitate. After the precipitated paclitaxel was withdrawn by filtration and drying in the vacuum oven at 30 °C, the yield and purity was evaluated by high performance liquid chromatography (HPLC) to determine the performance of the adsorbents.

2.3. Paclitaxel analysis

Dried residue was redissolved in methanol for quantitative analysis using an HPLC system (Waters, USA) with a Capcell Pak C18 column (250 mm × 4.6 mm; Shiseido). Elution was performed in a gradient using a distilled water-acetonitrile mixture varying from 65:35 to 35:65 within 40 min (flow rate = 1.0 mL/min). The injection volume was 20 μL, and the effluent was monitored at 227 nm with a UV detector. Authentic paclitaxel (purity: 97%) was purchased from Sigma–Aldrich and used as a standard.

3. Results and discussion

3.1. Adsorbent characterization

Fig. 2(a) shows nitrogen adsorption/desorption isotherms of the commercial sylopute and the mesoporous silica prepared by using CTAB as a template. The pore size distribution curves were also displayed in the inset of Fig. 2(a). Two samples showed a typical type IV isotherm [24]. The mesoporous silica (S1) synthesized by spray pyrolysis has no hysteresis curve, whereas the commercial sylopute showed a hysteresis curve (H1 type) corresponding to opened cylindrical pores. To identify the uniformity and the structuring ordering of pores, SAXS analysis of silica S1 was performed and shown in Fig. 2(b). Three distinct diffraction peaks were observed, indicating that the mesoporous silica S1 has the pore structure of highly ordered hexagonal phase. To confirm the ordered structure of mesopores, TEM analysis for the silica S1 was carried out and the result was shown in Fig. 2(c). From the TEM images, the prepared silica particles were confirmed to have a spherical shape and well-ordered pores. The physical properties obtained from the nitrogen adsorption/desorption isotherms were summarized Table 1. The pore sizes of the prepared silica (S1) and sylopute were 2.2 nm and 16.8 nm, respectively. The specific surface area of the mesoporous silica was 1574 m²/g, which was much larger than that of sylopute ($S_{\text{BET}} = 331 \text{ m}^2/\text{g}$).

To prepare macroporous silica (S2 and S3), PS nanoparticles were used as a template. SEM photos and particle size distributions

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