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Short communication

Improved drying method for removal of residual solvents from paclitaxel by pre-treatment with ethanol and water

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ABSTRACT

In this study, a drying method was developed for the effective removal of the residual solvents, methylene chloride and methanol, in purified paclitaxel. When the sample purified by silica-HPLC was concentrated using a rotary evaporator, the residual methanol level easily met the ICH-specified value (3000 ppm), but methylene chloride did not meet the ICH-specified value (600 ppm). However, residual methylene chloride was easily and conveniently removed below the ICH-specified value by rotary evaporation (~1 h) alone after pre-treatment of a sample (methylene chloride: 17,600 ppm) with 95% ethanol. In addition, residual ethanol (>14,300 ppm) met the ICH-specified value (5000 ppm) after simple rotary evaporation (~1 h) alone with pre-treatment with water, and residual water also met the specified value (<4%) for active pharmaceutical ingredients.

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1. Introduction

Paclitaxel is an anticancer drug widely used for treatment of ovarian cancer, breast cancer, Kaposi's sarcoma and non-small cell lung cancer [1–3]. The main methods of paclitaxel production include direct extraction from the yew tree, semi-synthesis involving the chemical combination of side chains after obtaining a precursor from the leaves of the yew tree, and plant cell culture from the main bioreactor after inducing callus from the yew tree and performing a seed culture [4–6]. Among these methods, plant cell culture can stably mass produce paclitaxel with consistent quality in a bioreactor without being affected by such external factors as climate and environment [7,8].

For an active pharmaceutical ingredient (API), the specifications for the purified product are highly varied and strict. In particular, the concentration of residual solvents is strictly regulated because of their inherent toxicity according to the International Conference on Harmonisation (ICH) Q3C guidance [9], and residual methylene chloride, methanol and ethanol should be below 600, 3000, and 5000 ppm, respectively [10–13]. To meet the requirement of guideline for these residual solvents, it is critical to utilize a suitable drying method. In the case of rotary evaporation and vacuum drying, it is very difficult to manufacture a product with concentration of residual solvent smaller than the ICH-specified value even if samples are dried for a long time because of the phenomenon of casehardening, in which the sample surface is hardened before the residual solvent is fully removed in the process of drying paclitaxel [3,10,12]. Therefore, a drying method using supercritical carbon dioxide [10], spray drying [11], and microwave-assisted drying [12] were suggested to solve the problem. However, a drying method using supercritical carbon dioxide requires high-pressure equipment and paclitaxel can decompose due to high operating pressure [10]. In the case of spray drying, there are problems because the operation takes a long time (~24 h) and a large installation space is required [11,12]. Microwave-assisted drying also uses a rotary evaporator and vacuum drying for a long pre-treatment (>24 h) of a sample and then, additionally, a microwave (Power: 300 W) for drying (~8 h); therefore, a long drying time, additional equipment and costs are required [12]. These drying methods require a long drying time under extreme drying conditions (high pressure) and also a lot of equipment to lower the residual solvents in purified paclitaxel to meet the ICH-specified values. Therefore, it is difficult to apply to the mass production of paclitaxel, an active pharmaceutical ingredient. According to the result of a recent study, residual methylene chloride was effectively removed from homoharringtonine, an active pharmaceutical ingredient, by pre-treatment with ethanol [13]. However, microwave-assisted drying (microwave power: 400 W) had to be performed to remove the ethanol used for pre-treatment below the ICH-specified value (5000 ppm). As a result, methylene chloride was effectively removed through pre-treatment with ethanol but the method required additional equipment and costs to remove

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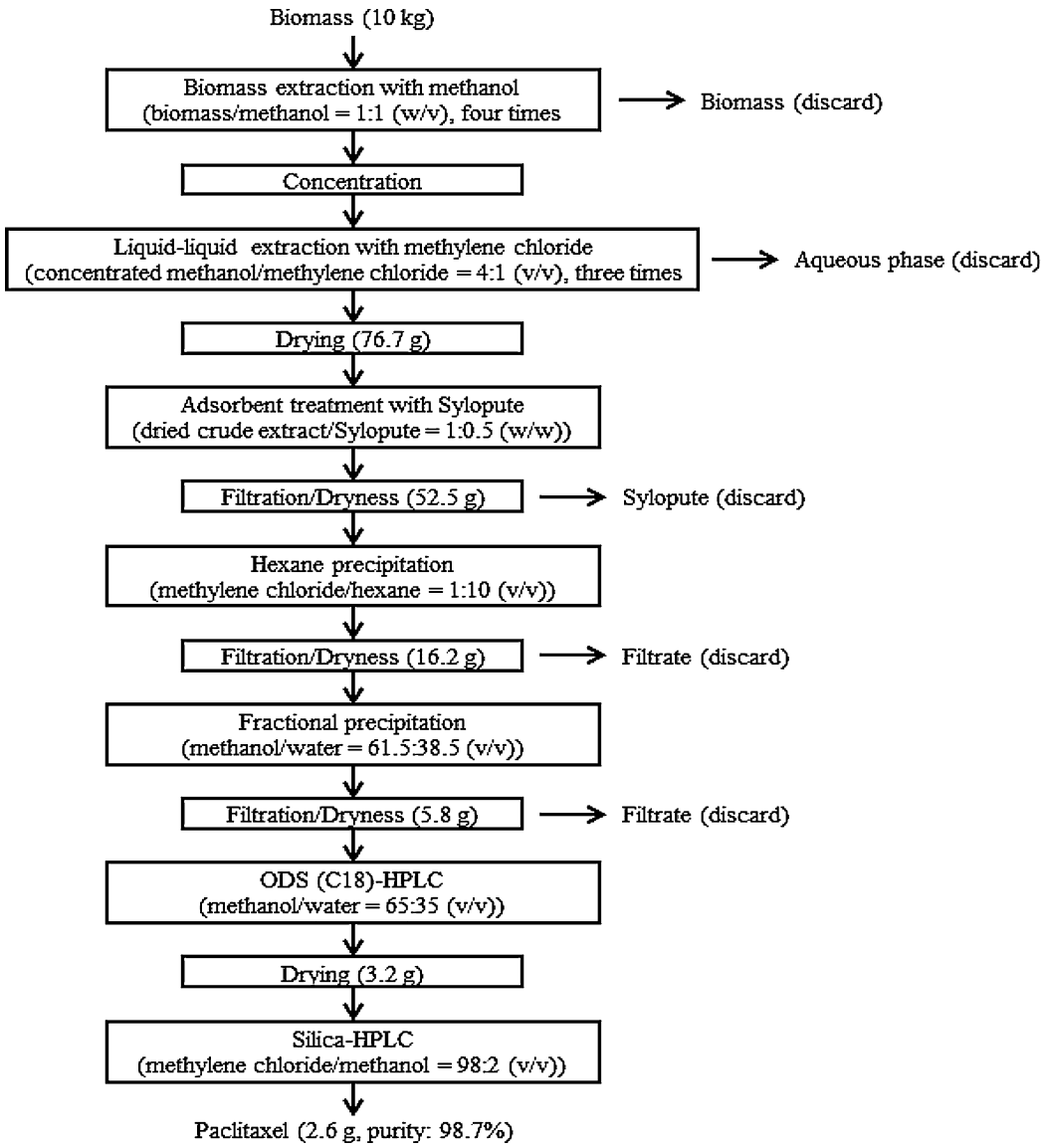

Fig. 1. Preparation of sample for the removal of residual solvents [12].

ethanol used for pre-treatment and also a long drying time, and had a complicated process. Thus, it was difficult to apply it to a mass drying process. In this study, we aimed at developing a drying method to simplify equipment, which is required to remove residual solvents in purified paclitaxel, an anticancer agent, and also dramatically reduce the time required for removal of residual solvents. In other words, the method can effectively remove residual solvents and residual water by simple rotary evaporation due to pre-treatment of a sample with ethanol and water before drying. In addition, the surface of a dried sample was investigated by SEM analysis to identify a correlation with removal of residual solvents. These results should prove useful for the removal of residual solvent in the mass production of APIs by providing an efficient drying method.

2. Materials and methods

2.1. Plant materials

The cells originating from *Taxus chinensis* were cultured in modified Gamborg's B5 medium supplemented with 30 g/L sucrose, 10 mM naphthalene acetic acid, 0.2 mM 6-benzylaminopurine, 1 g/L casein hydrolysate, and 1 g/L 2-(*N*-morpholino) ethanesulfonic acid in darkness at 24 °C with shaking at 150 rpm. The cell cultures were transferred to fresh medium every 2 weeks. During prolonged culture for production purposes, 4 mM $AgNO_3$ was added at the initiation of the culture as an elicitor, and maltose (1 and 2%, w/v) was added to the medium on day 7 and 21, respectively. Following cultivation, the biomass was recovered using a decanter (CA150 Clarifying Decanter; Westfalia) and high-speed centrifuge (BTPX 205GD-35CDEFP; Alfa-Laval). The biomass was provided by the Samyang Genex Company, South Korea.

2.2. Preparation of sample for drying

A purified paclitaxel was prepared from biomass obtained from *T. chinensis* cultures using the following steps. (i) Biomass was mixed with methanol at a ratio of 1:1 (w/v) and extracted at room temperature for 30 min. The mixture was filtered under vacuum in a Buchner funnel through filter paper. Extraction was repeated at least four times. Each methanol extract was collected, pooled and concentrated at a temperature of 40 °C under reduced pressure to reduce the volume of the methanol extract to 30% of the original. (ii) Methylene chloride (25% of concentrated methanol extract)

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