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Release-controlled curcumin proliposome produced by ultrasound-assisted supercritical antisolvent method

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ABSTRACT

Curcumin proliposome (CPL) was prepared using supercritical antisolvent technique assisted with ultrasound. The effects of the process parameters, such as weight ratio of starting material, pressure, temperature, and ultrasound power, on the entrapment efficiency (EE) and the drug loads were investigated. The latter three parameters were optimized using response surface methodology in terms of their effects on EE. The morphology and structure of the generated CPL were characterized by SEM, XRD and DSC. The in vitro release of the curcumin proliposome (CL) formed via hydration of the CPL was studied. The results indicated that the release of the curcumin could be controlled by manipulating the morphology of the CPL including the precipitation form of the starting materials, the particle size, and the particle fusion. The CPL was stable for at least 3 months at low temperature storage.

1. Introduction

Curcumin, 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadione-3,5-dione, is a major active phytochemical compound obtained from the rhizome of the Curcumin longa L. Since ancient times, such turmeric plant has been commonly used in traditional Chinese Medicine, as an anti-inflammatory, antiseptic and wound curing compound. It is also used as food additives as a preservative, a pigment, or a flavoring. Current researches show that curcumin has a wide spectrum of beneficial bioactivities, such as antioxidant [1], anti-cancer [2,3], antibacterial and anti-mutagenic properties [4]. However, its poor water solubility resulting in its low bioavailability, limiting its clinical application [5].

Liposomal formulation is a good way to circumvent this limitation [6–8].The curcumin liposome (CL) has exhibited favorable performances such as antitumor and antiangiogenesis effects [9], suppressing the growth of head and neck squamous cell carcinoma [10], and enhancing the gastrointestinal absorption of curcumin [11]. However, liposomes are physical and chemical instable, suffering such problems as aggregation, fusion, degradation, hydrolysis and oxidation of phospholipids [12]. Proliposome, a kind of dry free-flow powder, can overcome disadvantages of liposome mentioned above, and can form liposome easily via hydration of it on-site [13]. The proliposome cannot only solve the stability issues of liposome, but also extend the liposome application especially in the area of oral delivery [14,15]. However, the study on the preparation of curcumin proliposome (CPL) and its release are few yet.

The proliposome was previously prepared using carrier-deposition [16], freeze drying [17] and spray drying [18]. However, these methods suffer from problems in either requiring proper auxiliary materials, or treating heat-sensitive drugs. The supercritical carbon dioxide antisolvent technique (SAS) is an attractive alternative for preparation of proliposome because of its mild operation [19]. Additionally, the particle morphology can be conveniently manipulated by adjusting the operational conditions [20]. Therefore, the quality of proliposome can be controlled using this method in terms of investigating the relationship between the morphology of solid particle and the release system of liposome formed via hydration.

The aim of this work was to prepare stable and release-controlled curcumin proliposome (CPL) using SAS assisted with ultrasound. The melting point of the common used phosphatidylcholine, such as soya or egg lecithin, is low due to existing double bounds. Therefore, the extra ingredient, like crystalline compound, is often required in the formulation to get desired proliposome, but it results in complicated process and unnecessary components in the formulation. The extra ingredient is not required if the HSPC is utilized because it has a higher melting point. Therefore, it can simplify the process of forming proliposome. So, the HSPC was utilized as the wall materials in this study. The influence of the process parameters on the forming CPL was investigated, and its stability

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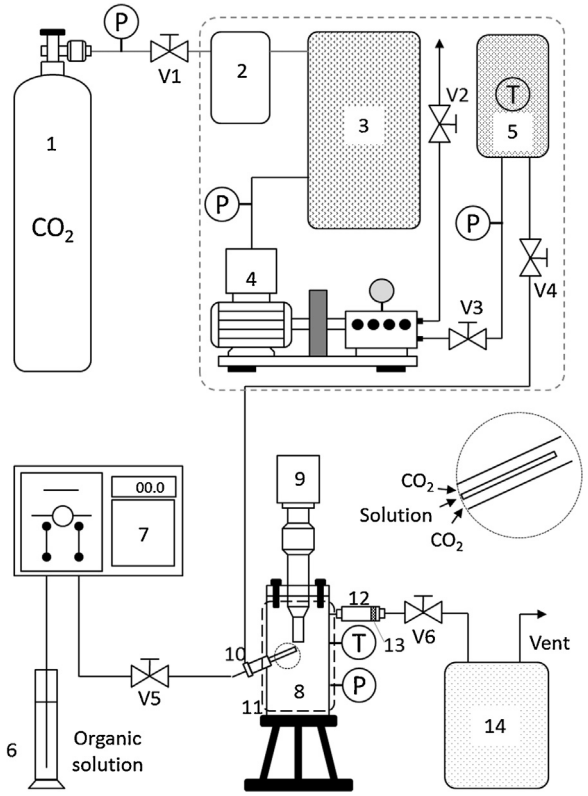

Fig. 1. The configuration of the SEDS-AU apparatus. 1-CO_2 cylinder; 2-surge tank; 3-chiller; 4-high-pressure pump; 5-preheater; 6-container; 7-HPLC pump; 8-precipitation vessel; 9-ultrasound probe; 10-nozzle; 11-heating mantle; 12-collector; 13-filter membrane; 14-recyclable vessel;V1–V6-valves.

and the curcumin release from it were also studied. The response surface methodology (RSM) was applied to optimize the operation parameters. The ultrasound was utilized to improve SAS process in terms of manipulating the particle morphology [21]. The influence of the CPL morphology on the drug release and the stability were investigated.

2. Materials and methods

2.1. Materials

Curcumin (purity >97%) was purchased from Sinopharm Co. (Shanghai, China). Hydrogenated soy phosphatidylcholine (HSPC, purity >98%, average molecular weight of 790 g/mol) was purchased from Toshisun (Shanghai, China). CO_2 was supplied by SJTU chemical store (Shanghai, China). Absolute ethanol was purchased from Shanghai Lingfeng Chemical Reagent Co., Ltd (Shanghai, China).

2.2. Apparatus and preparation of CPL

The experimental apparatus is shown in Fig. 1. It is mainly consisted of a CO_2 high-pressure pump (4) (Hangzhou River Equipment Co., China), a HPLC solution pump (7) (HLP-1040, Yanshan Instrument Co., China), a windowed precipitation chamber of 200 mL (8), and an ultrasound system (9). To prepare the CPL, CO_2 was firstly pumped through the outer tubule of a coaxial nozzle (10) into the preheater (5) and the precipitation chamber at a constant flow rate (40 mL/min), until the system pressure achieved a desired value and kept stable by adjusting the valve V6. Meanwhile, the precipitation chamber was heated to a certain temperature by a temperature-controlled heating mantle (11). Then, pure ethanol was pumped into the precipitation chamber through the inner tube (100 μm in diameter) at 1 mL/min to obtain steady state composition conditions of the fluid phase. Then, the ultrasound system was turned on at a fixed ultrasound power (USP). After that, the ethanol solution of curcumin (7.5 mg/mL) and HSPC was pumped into the chamber instead of pure ethanol at the same flowrate. When finishing solution delivery, the CO_2 was continually pumped for a fixed time for eliminating ethanol residues as completely as possible. Finally, the chamber was smoothly depressurized to atmosphere pressure, and the CPL products were collected from both the chamber and a collector (12) loaded with filter membrane (13) for analysis. The organic solvent was recycled by a vessel (14) in the end.

2.3. Curcumin content analysis

Curcumin content in the CPL was measured by an ultraviolet spectrophotometry detector (UV, 765PC, Shanghai Spectrum

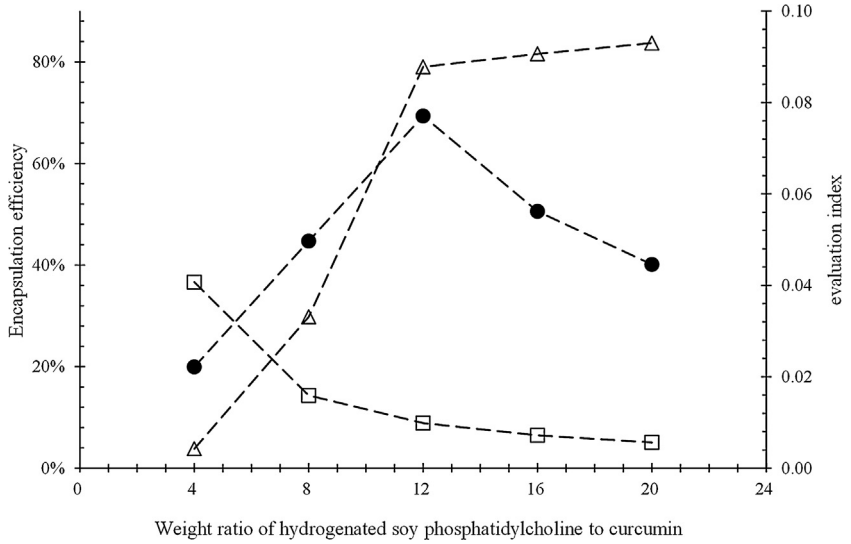

Fig. 2. The variation of entrapment efficiency (△, left axis), drug load (□, left axis) and evaluation index z (●, right axis) with the weight ratio of hydrogenated soy phosphatidylcholine to curcumin.