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Research Paper

Examining practical feasibility of amorphous curcumin-chitosan nanoparticle complex as solubility enhancement strategy of curcumin: Scaled-up production, dry powder transformation, and long-term physical stability

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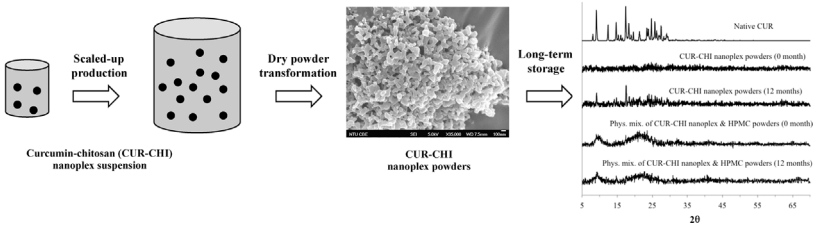
GRAPHICAL ABSTRACT

Scaled-up production of CUR-CHI nanoplex, its powder-form dissolution characteristics, and long-term amorphous state stability



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ABSTRACT

Amorphous curcumin-chitosan nanoparticle complex (or nanoplex in short) was recently developed as a new solubility enhancement strategy of curcumin (CUR) – a natural herb well known for its vast therapeutic activities. For its subsequent clinical application and commercialization, the present work aimed to address the three remaining research questions pertaining to the CUR nanoplex, i.e. (1) was the nanoplex preparation scalable? (2) could the nanoplex maintain its solubility enhancement capability in the powder form? (3) could the nanoplex resist crystallization, which would jeopardize its solubility enhancement capability, during long-term storage? First, the results showed that gram-scale production of the CUR nanoplex was readily achieved at high CUR utilization rate without significant adverse effects on the physical characteristics. Stable CUR nanoplex with size, zeta potential, and CUR payload of ≈100–300 nm, 18 mV, and 80%, respectively, was produced. The scaled-up production, nevertheless, resulted in lower yield due to lower nanoplex recovery in the purification step. Second, the CUR nanoplex powders, when formulated correctly with drying adjuvants, maintained the solubility enhancement capability of the suspension form, despite their slower dissolution velocity. High apparent solubility at approximately twice of CUR's thermodynamic solubility was demonstrated for 8 h. Third, the CUR nanoplex powders maintained its amorphous state after twelve-month storage when stored as physical mixture with crystallization-inhibiting agents. In short, the present results successfully established the CUR nanoplex as a practical and effective solubility enhancement strategy of CUR.

Abbreviations: AUC, area under the curve; C_{Sat}, thermodynamic saturation solubility; $C_{Supersat}$, supersaturated concentration; CE, complexation efficiency; CHI, chitosan; CUR, curcumin; DLS, dynamic light scattering; DTA, differential thermal analyzer; FESEM, field emission scanning electron microscope; FTIR, Fourier transform infrared spectroscopy; HPLC, high performance liquid chromatography; HPMC, hydroxypropyl methylcellulose; PBS, phosphate buffered saline; PXRD, powder x-ray diffraction; RH, relative humidity; TG, thermogravimetric; UV-Vis, ultraviolet visible spectroscopy

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1. Introduction

Curcumin – the main bioactive compound of turmeric plants – is well known for its plethora of therapeutic activities ranging from anti-inflammatory and antibacterial to anticancer and antioxidant activities [1]. The presumably immense therapeutic benefits of curcumin, however, have not been fully realized due to its low aqueous solubility (< < 1 mg/mL), which in turn causes its poor bioavailability upon oral administration [2]. Recently, nanoparticulate formulations of curcumin (nano-curcumin) have emerged as an effective solubility enhancement strategy of curcumin by virtue of the fast dissolution velocity afforded by the nanoparticles attributed to their large specific surface areas [3–5].

Previously, we developed a new class of nano-curcumin formulation in the form of amorphous curcumin-chitosan nanoparticle complex (or curcumin nanoplex in short), which were superior to the existing nano-curcumin formulations in terms of (1) the high curcumin payload (> 80%) and (2) simple, yet highly efficient, preparation involving only the mixing of curcumin and chitosan solutions under an ambient condition [6]. The solubility enhancement capability of the curcumin nanoplex was successfully demonstrated in its aqueous suspension form, where the nanoplex, upon dissolution, generated a high and prolonged apparent solubility at roughly four to five times of the thermodynamic saturation solubility of curcumin [6]. The high apparent solubility that was maintained for several hours was attributed primarily to the amorphous state of the curcumin nanoplex that was capable of producing highly supersaturated curcumin concentration upon dissolution [6].

The curcumin nanoplex was prepared by drug-polysaccharide complexation technique that relied on electrostatic binding between curcumin and the oppositely charged chitosan to form the nanoplex. As illustrated earlier in Nguyen et al. [6], the electrostatically driven complexation between curcumin and chitosan resulted in the formation of soluble curcumin-chitosan complex, which subsequently formed aggregates among themselves due to hydrophobic interactions between the bound curcumin molecules. The complex aggregates then precipitated out of the solution upon reaching a critical mass to form the curcumin nanoplex.

Thus far, the drug-polysaccharide complexation technique had only been carried out in a very small production volume (i.e. 2 mL) in which good mixing between curcumin and chitosan, which was required for their electrostatic binding to take place, was readily achieved. For the curcumin nanoplex to gain traction as the preferred formulation platform for nano-curcumin, the scalability of the curcumin-chitosan complexation technique ought to be demonstrated. Thus, the first objective of the present work was to investigate the scalability of the curcumin nanoplex preparation by assessing (1) the physical characteristics (i.e. size, zeta potential, curcumin payload, solid concentration, and colloidal stability), and (2) preparation efficiency (i.e. complexation efficiency of CUR, overall yield) of nanoplex prepared at larger production volumes.

Next, as solid dosage forms (e.g. tablets, capsules) remain the formulation of choice for oral drug delivery [7], the curcumin nanoplex, which currently is prepared as aqueous suspension, must undergo transformation to dry powders for it to be readily processed into solid dosage forms. Previous studies on other drug nanoplexes, however, showed that the dry powder transformation in the absence of drying adjuvants had adverse effects on the drug nanoplex's dissolution characteristics, which was caused by irreversible aggregation of the nanoplex upon drying [8,9]. Therefore, the second objective of the present work was to examine the solubility enhancement capability of the dry powder form of the curcumin nanoplex prepared in the presence of drying adjuvants.

Lastly, while the amorphous state of the nanoplex had been established as the primary reason for its solubility enhancement capability, the amorphous state stability of drug nanoplex powders during long-term storage had not been investigated before. In this regard, amorphous solid dispersions of drugs, if they are not formulated correctly, are notoriously prone to recrystallization during storage due to its metastable state, resulting in the loss of their solubility enhancement capability [10,11]. Thus, the third objective of the present work was to evaluate the amorphous state stability of the curcumin nanoplex powders during long-term storage.

In a nutshell, the outcomes of the present work provided answers to three of the most important remaining research questions regarding the curcumin nanoplex, i.e. (1) could the curcumin nanoplex be prepared at a larger scale and how did the production scale affect its physical characteristics and preparation efficiency? (2) could we maintain the solubility enhancement capability of the curcumin nanoplex after its dry powder transformation when drying adjuvants were used? and lastly (3) did the curcumin nanoplex powders remain in their amorphous state during long-term storage and whether the inclusion of crystallization-inhibiting agent was needed? The results of these three studies demonstrated the definite potential of the curcumin nanoplex as the solubility enhancement strategy of curcumin.

2. Materials and methods

2.1. Materials

Curcumin (CUR) (98%) and low molecular weight chitosan (CHI) (50–190 kDa with 75–85% deacetylation) were purchased from Alfa Aesar (Singapore) and Sigma-Aldrich (Singapore), respectively. Ethanol (absolute) and phosphate buffered saline (PBS) (pH 7.4) were purchased from Merck Millipore (Singapore) and 1st Base (Singapore), respectively. D-Trehalose, hydroxypropyl methylcellulose (HPMC), potassium hydroxide (KOH), sodium chloride (NaCl), and glacial acetic acid (AA) were purchased from Sigma-Aldrich (Singapore).

2.2. Methods

2.2.1. Scaled-up preparation of CUR-CHI nanoplex

CUR with pK_a of 8.4, 9.9, and 10.5 [12] was dissolved at 5 mg/mL in 0.1 M KOH (pH 13) resulting in the formation of anionic CUR molecules. CHI with pK_a of 6.5 [13] was dissolved separately at 6 mg/mL in 1.2% (v/v) acetic acid solution (pH 4.4) resulting in the formation of cationic CHI molecules. Next, equal volumes of the CUR and CHI solutions were mixed under gentle stirring using magnetic stirrer, immediately after their preparation to minimize alkaline degradation of CUR. The resultant CUR-CHI nanoplex suspension was ultrasonicated for 15 s at 20 kHz (VC 505, Sonics, USA) to disperse the nanoplex aggregates that might form. Subsequently, the nanoplex suspension was washed by two cycles of centrifugation (14,000 × *g*) to remove excess CUR and CHI after which the washed nanoplex suspension was re-suspended in deionized water for characterizations.

In the scaled-up production, the production volume (i.e. CUR + CHI volumes) was gradually increased from 2 mL to 800 mL (i.e. 2, 10, 50, 200, 400, and 800 mL). The upper limit for the production volume was dictated by the maximum capacity of the high-speed centrifuge (Sorvall ST 16, Thermo Fisher Scientific, USA) available in our laboratory. The centrifugation time was gradually increased from 25 min at 2-mL production volume to 2.5 h at 400-mL production volume at a fixed centrifugation speed (14,000 × *g*). The centrifugation for the 800-mL volume was carried out in two rounds at 400-mL each time for a total of 5 h centrifugation time. Likewise, the ultrasonication was gradually increased from one cycle at 2-mL production volume to nine cycles at 800-mL production volume (15 s for each cycle) at a fixed ultrasonication frequency (20 kHz).

2.2.2. Physical characterizations of CUR-CHI nanoplex

The size and zeta potential of the CUR-CHI nanoplex in its aqueous suspension form were characterized by dynamic light scattering (DLS)