Ultrasonics Sonochemistry 24 (2015) 256–263

Contents lists available at ScienceDirect

Ultrasonics Sonochemistry

journal homepage: www.elsevier.com/locate/ultson

Modulation of particle size and molecular interactions by sonoprecipitation method for enhancing dissolution rate of poorly water-soluble drug

Thao Truong-Dinh Tran *, Kiet Anh Tran, Phuong Ha-Lien Tran *

Pharmaceutical Engineering Laboratory, Biomedical Engineering Department, International University, Vietnam National University – Ho Chi Minh City, Viet Nam

ARTICLE INFO

Article history:
Received 9 October 2014
Received in revised form 29 November 2014
Accepted 29 November 2014
Available online 5 December 2014

Keywords:
Curcumin
Polymeric nanoparticles
Molecular interactions
Crystallinity
Ultrasonication

ABSTRACT

Aim of present work was to originally elucidate the roles of ultrasonication method for modulating the size and molecular interactions in controlling release of poorly water-soluble drug. Curcumin was chosen as a model drug. Three types of polymers were investigated as carriers for preparation of polymeric nanoparticles under various ultrasonication conditions and polymer–drug ratios. Changes in drug crystallinity, particle size, and molecular interactions which would be factors enhancing drug dissolution rate were evaluated. Amorphous form of curcumin, size reduction of nanoparticles and interaction between drug and polymer in formulations were attributed to improved drug dissolution rate. Particle size was strongly affected by polymer type, polymer–drug ratio and ultrasonication conditions. Interestingly, control of those factors caused differences in molecular interactions of the hydroxyl groups and then, highly affected particle size of the nanoparticles. It was obvious that there was a reciprocal influence between the drug–polymer interactions and particle size of the nanoparticles. This relation could be modulated by polymers and ultrasonication processes for enhancing drug dissolution rate.

1. Introduction

Currently, one of the major current challenges of the pharmaceutical industry is related to strategies that improve the water solubility of drugs because over 40% of new drug candidates are water-insoluble agents [1–3]. These drugs have problems associated with rate-limiting dissolution, slow absorption and low bioavailability [4,5]. Many techniques have been investigated so far to overcome the troubles of poorly water-soluble drugs, but on the whole there are only some general rules as follows: particle size reduction, salt formation, complexation, solid dispersion, addition of solvent or surface active agents. A reduction of particle size and changes of physicochemical properties of a formulation are efficient strategies to improve dissolution rate of these drugs, resulting in a substantial increase in oral bioavailability [6–9].

The precipitation process has been widely investigated for production of nanoparticles in the last few decades. However, it has been reported that the sonoprecipitation method has been rarely used in this process to prepare polymeric nanoparticles [10]. The technique has been employed for few drugs such as cefuroxime axetil [11], griseofulvin [12,13], ibuprofen [12], itraconazole [12], sulfamethoxazole [12], nitrendipine [14], isradipine [15]. Regarding physicochemical properties of formulations of poorly water-soluble drugs, changes of drug crystallinity and molecular interactions are aspects to be concerned to investigate mechanism of enhanced drug dissolution. While an alternative structure of drug from crystalline to amorphous state may occur to improve the dissolution, an interaction among agents is another factor to contribute to the enhanced drug dissolution. Although molecular interaction between drug and polymer has been known as an important factor for improving dissolution rate [3,7,16–18], there have been no studies through sonoprecipitation method indicating modulation of molecular interactions and its interesting effects on particle size for the control of drug dissolution rate in details.

Moreover, there have been no reports on dissolution enhancement of curcumin (CUR) which is extremely poor water solubility (11 ng/ml) [19] by precipitation–ultrasonication method. In 2010, Zheng et al. has studied on sonication–assisted synthesis of polyelectrolyte-coated CUR nanoparticles [20]. Nevertheless, the CUR release was almost done after 20 h and may be only suitable for sustained release dosage forms. More recently, the precipitation–ultrasonication method has been applied for preparation of stable CUR nanocrystal without reports of drug release profiles [21]. Also, mechanisms of CUR release were not mentioned in those

* Corresponding authors. Tel.: +84 (8) 37244270x3328; fax: +84 (8) 37244271.
E-mail addresses: ttdthao@hcmiu.edu.vn (T.T.-D. Tran), thlphuong@hcmiu.edu.vn (P.H.-L. Tran).

http://dx.doi.org/10.1016/j.ultsonch.2014.11.020
1350-4177/

researches. This research would provide not only useful information about the preparation of CUR polymeric nanoparticles by the precipitation–ultrasonication method but also an interesting aspect about the modulation of molecular interaction on particle size and drug dissolution rate. The crystallinity of CUR in polymeric nanoparticles was also investigated. The report may suggest a solution for further studies in the effort of enhancing dissolution rate of poorly water-soluble drugs.

2. Materials and methods

2.1. Materials

Curcumin (CUR), acetic acid (CH_3COOH), sodium hydroxide (NaOH) were purchased from Guangdong Guanghua Sci-Tech company (China). Monopotassium phosphate (KH_2PO_4) was purchased from Wako Pure Chemical Industries (Japan). Hydrochloric acid, acetone (CH_3COCH_3), Sodium chloride (NaCl) were purchased from Xilong Chemical Industry Incorporated Company (China). Hydroxypropyl methylcellulose 6 (HPMC 6), hydroxypropyl methylcellulose 4000 (HPMC 4000), and polyethylene oxide N-60K (PEO) were provided by Dow Chemical Company (USA). Methanol–HPLC grade was purchased from Thermo Fisher Scientific Inc.

2.2. Methods

2.2.1. Preparation of polymeric nanoparticles

Polymeric nanoparticles were prepared in the following steps. CUR used in all of the formulations was firstly dissolved in acetone. PEO (or HPMC 4000 or HPMC 6) was dissolved in distilled water. The CUR solution was quickly introduced into the polymer solution under stirring. The precipitated sample in 1000 mL-glass beaker was continuously treated with tip of ultrasonicator (QSONICA, USA) at a controlled room temperature (25 °C). The temperature of each sample was measured before and after ultrasonication. Acetone was completely evaporated under stirring. The nanosuspension was then lyophilized at −50 °C until powder was obtained for physicochemical analyses. The detailed formulations including ultrasonic powers (W) are described in Table 1.

2.2.2. Dissolution studies

Dissolution rate of CUR was tested in enzyme-free simulated gastric fluid (pH 1.2) and enzyme-free simulated intestinal fluid (pH 6.8) by dissolution tester (DT 70 Pharma Test, Germany). The samples equivalent to 30 mg CUR were exposed to 900 mL of dissolution medium at 37 ± 0.5 °C and the paddle was set at 50 rpm. At regular time intervals (10, 20, 30, 60, 90 and 120 min), 1 ml of medium was withdrawn for determination of drug release. An equivalent amount of fresh medium was replaced to maintain a constant dissolution volume.

Table 1
Formulation compositions and precipitation–ultrasonication conditions for preparation of polymeric nanoparticles. CUR and polymer were dissolved in acetone and water with concentration 30 mg/ml and 1 mg/ml, respectively.

Codes	CUR (mg)	PEO (mg)	HPMC4000 (mg)	HPMC6 (mg)	Power (W)	Time (min)
FN1	30	180	–	–	15	20
FN2	30	–	180	–	15	20
FN3	30	–	–	180	15	20
FN4	30	–	–	180	15	10
FN5	30	–	–	180	15	5
FN6	30	–	–	180	9	20
FN7	30	–	–	180	12	20
FN8	30	–	–	60	15	20
FN9	30	–	–	120	15	20

2.2.3. HPLC analysis

The quantification of CUR was performed by HPLC system (Dionex, USA). The mixture of methanol and acetic acid solution (2%) was used as the mobile phase with ratio 8:2. The flow rate was maintained at 1.2 mL/min. Luna 5 μ C18 analytical column (150 × 4.6 mm) was maintained at 25 °C ± 0.5 °C. The UV–Vis detector was set at 425 nm. 20 μL of sample were injected into HPLC system for analysis.

2.2.4. Particle size analysis

After treating by ultrasonication, the nanosuspension sample was immediately analyzed particle size by the Particle Size Distribution Analyzer (LA-920, HORIBA, Japan).

2.2.5. Powder X-ray diffraction (PXRD)

CUR, physical mixtures of drug and polymer (HPMC 6, HPMC 4000 and PEO), polymeric nanoparticle powders were analyzed the crystallinity by X-ray Diffractometer (Bruker D8 Advance, Germany) using Cu-Kα radiation at a voltage of 40 kV, 50 mA. The samples were scanned in increments of 0.02° from 5° to 60° (diffraction angle 2θ) at 1 s/step, using a zero background sample holder.

2.2.6. Fourier transform infrared spectroscopy (FTIR)

A FTIR spectrophotometer (Bruker Vertex 70, Germany) was used to investigate the spectra of CUR, physical mixtures of drug and polymer (HPMC 6, HPMC 4000 and PEO), polymeric nanoparticle powders. The wavelength was scanned from 500 to 4000 cm^{-1} with a resolution of 2 cm^{-1}. KBr pellets were prepared by gently mixing 1 mg of the sample with 200 mg KBr.

2.2.7. Transmission electron microscopy

Transmission electron microscopy (TEM) was used to observe the encapsulation of CUR in polymeric nanoparticles, as well as size and shape of the nanoparticles. The samples were examined using JEM-1400 Transmission Electron Microscope (Jeol, Japan).

3. Results and discussion

3.1. Dissolution enhancement of polymeric nanoparticles: the role of particle size formation

Dissolution enhancement of CUR was firstly investigated with three polymers: PEO, HPMC 4000 and HPMC 6. In the preliminary experiments, the dissolution of physical mixture (drug and polymer at the ratio 1:6) demonstrated insignificant effect on CUR release. Percent of drug release from three polymers after 2 h in dissolution medium were under 40%. For an investigation of ultrasonication, drug and polymer ratio was also fixed at the ratio 1:6 and ultrasonication conditions were fixed at ultrasonic power 15 W in 20 min. All of the polymeric nanoparticles showed a potential dissolution enhancement of CUR significantly at both pH 1.2 and pH 6.8 (Fig. 1A and B). However, among polymers, HPMC 6 showed the best ability to increase the dissolution rate of CUR. Meanwhile, drug release from the nanoparticles of PEO or HPMC 4000 was lower. Specially, the same amount of drug was released from HPMC 4000 nanoparticles at the first 10 min as compared to HPMC 6. However, CUR was immediately precipitated after 10 min and then had the same release profile as that of PEO nanoparticles at both pH 1.2 and pH 6.8. These results indicated that polymer type played a critical role on formation of nanoparticles which directly affected dissolution of CUR. HPMC 6 could form a nano size of particles to enhance the dissolution (Table 2, FN3). In contrast, HPMC 4000 or PEO still showed a micro scale of particles (Table 2, FN1 and FN2). Different size of the