

Effect of microchannel confluence angles on size reduction of curcumin nano-suspension *via* liquid anti-solvent precipitation process

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ABSTRACT

In this paper, an experimental evidence is provided to investigate the potential of microchannel reactors (MCRs) for uniform particle size distribution (PSD) of curcumin nano-particles *via* liquid anti-solvent precipitation (LASP) technique. For this purpose, three arrangements of microchannel reactors (MCRs) were designed with 800 μm in diameter by 30 mm in length in various confluence angles of 45°, 90°, and 135°. The influence of confluence angle was investigated in terms of particle size reduction, short-term, and physical stability. PSD, SEM imaging, XRD, DSC, FTIR, and zeta potential measurements were also employed to characterize the produced nano-suspensions.

Upon application of the MCR with confluence angle of 135°, the precipitated particle size was found 181 nm, indicating that this geometry of micromixer can establish higher micromixing efficiency. The superior performance of MCRs with large contact angle and understanding of mixing phenomena was further linked to pressure drop, dissipation rate and size of generated nano-particles under various total liquid flow rates.

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1. Introduction

Curcumin, commonly called diferuloyl methane, is a natural hydrophobic polyphenol compound derived from the rhizome (turmeric) of the herb “*Curcuma longa*”. It has been traditionally used as medicine for many ailments because of its extensive variety of curative property such as antioxidant, anti-inflammatory [1], anti-HIV [2], antimicrobial, anti-allergic, anti-carcinogenic [3,4], and antitumor activities [5]. However, the main difficulty of translating these beneficial effects of curcumin to human medicinal purposes is its bioavailability [6]. The major problems of curcumin bioavailability are low serum levels [7–10], limited tissue distribution [8,11,12], apparent rapid metabolism [13–15] and short half-life [15–17]. As an illustration, negligible amounts of curcumin in blood plasma of rats after oral administration of 1 g/kg of curcumin showed that curcumin was poorly absorbed from the gut [7]. In addition, Ravindranath et al. evaluated the tissue

distribution of curcumin. They showed that after oral administration of 400 mg of curcumin to rats only traces of unchanged drug were found in the liver and kidney. At 30 min, 90% of curcumin was found in the stomach and small intestine, but only 1% was present at 24 h [8]. Systemic elimination or clearance of curcumin from the body is also an important factor, which determines its relative biological activity. An early study by Wahlstrom and Blennow reported that when 1 g/kg curcumin was given orally to rats, 75% of it was excreted in the feces and negligible amounts were found in the urine [15].

Formulations of diverse types were employed to increase the aqueous solubility of curcumin, thereby improving its bioavailability and pharmacokinetic properties. Nanotechnological processes like liposomes [18], nano-emulsions [19], and addition of microemulsions [20,21] are other examples. Another common approach for such a poor water-soluble drug is particle size reduction that increases its surface area, through either top-down or bottom-up techniques. However, the applicability of the available techniques is limited because of poor control of particle size, scalability, and morphology in comparison to LASP process. LASP, as a bottom-up method, is also a low energy intensive,

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Nomenclature

As/S	anti-solvent/solvent
API	active pharmaceutical ingredient
DI	deionized
DLS	dynamic light scattering
h	hour
LASP	liquid anti-solvent precipitation
m (kg)	mass
MIVM	multi-inlet vortex mixer
PSD	particle size distribution
P	pressure (Pa)
PI	polydispersity index
Q	volume flow rate (mL/min)
SEM	scanning electron microscopy
SDS	sodium dodecyl sulfate
V^0	volume flow (m ³ /s)

Greek letters

ε	dissipation rate per mass unit of fluid (m ² /s ³)
ΔP	pressure drop (Pa)
ν	liquid kinematic viscosity (m ² /s)
τ_{mix}	mixing time(s)
θ	degree (°)

cost-effective and scalable [22] approach used in a variety of applications such as paint [23,24], semi-conductor [25,26], cosmetic [27], and pharmaceutical [28–30] industries.

There are several mixing techniques reported in literature for LASP process. Some example of the equipments used for this purpose are; static mixer [31–34], confined impinging jet [35–39], high gravity precipitation [40–44], multi-inlet vortex mixer (MIVM) [45–48], Y-shaped microchannel reactor (MCR) [49,50], and T-mixer [51]. The mixing time in the order of milliseconds to microseconds can be achieved in micromixers, as they facilitate process intensification of the nano-particle formation by reducing the diffusion length between solvent (containing drug) and anti-solvent [50]. In fact, the rapid mixing helps to reach supersaturation in a short timescale, which in turn is important for formation of nano-particles due to low or negligible growth [49].

On the other side, surveys on the mixing performance of micromixers in the literature mostly focus on the transition of flow patterns, geometry, and external power input to the system. Besides, micromixing process was mostly chosen for single component system, i.e., water–water system [52–54]. However, actual and practical systems such as nano-drugs preparation by anti-solvent methods always involve both aqueous and organic solutions [55]. Therefore, proper evaluation of the mixing behaviors of these systems in different micro-scale mixers is quite important.

In this study, the main aim is to reduce the size of drug particles by uniform precipitation of them. This was done *via* liquid anti-solvent precipitation process in designed microchannels. As far as the mixing performance is quite important in this process, the way that mixing takes place is quite important. For this purpose, three microchannels were proposed to establish various mixing pattern and to control growth and agglomeration of the formed curcumin nano-particles. The authors believe that though apparently simple, no general validation rules have already been presented about the influence of MCR geometry on the size of final precipitated particles that would be the novelty of this study.

2. Experiments

2.1. Materials

Raw curcumin (C₂₁H₂₀O₆) with a mean particle size of 28.9 μm (95%) was supplied from Merck-Schuchardt, and used without further purification. The solvent used for experiments, ethanol, was obtained from Mojallali chemical laboratories, Iran. An anionic surfactant, Sodium Dodecylsulfate (SDS), was also obtained from Merck-Schuchardt, Germany and used as a stabilizer. All chemicals were chosen from analytical grade and used as received. The structural formulas of both curcumin and dodecylsulfate were given in Fig. 1.

2.2. Methods

2.2.1. Preparation of organic and aqueous phases

Briefly, 89.1 mg of curcumin was dissolved in 20 mL of ethanol to prepare an organic solution of curcumin with concentration of 4.455 g/L. The prepared solution was then filtered through a 0.45 μm syringe filter. The anti-solvent solution was prepared by dissolving 1 mg of water-soluble surfactant, SDS, in 100 mL of (deionized) DI water (0.001% w/v). A small amount of surfactant will help achieve formation of fine and small particles of poorly water soluble APIs (Active Pharmaceuticals Ingredients), and also prevent agglomeration [56]. The aqueous solution of surfactant was mixed continuously at the room temperature in a mixer. The agitation was stopped after 1 h in order to settle the mixture. Before processing, the surfactant solution was filtered through a 0.22 μm syringe filter to remove any possible particulate impurities.

2.2.2. Design of microfluidic device and experimental procedures

Fig. 2 exhibits the three designed microchannels with various confluences, namely S_2 (45°), S_3 (90°), and S_4 (135°). The whole channels were fabricated on a flat plate of poly methyl methacrylate (Plexiglas) by precise milling and were of 800 μm in diameter by 15 mm in length and a circular cross-section positioned centrally opposite each other. Based on the figure, the solvent flow was visualized by the use of violet color dyes, whereas the anti-solvent streams were fed through two other inlets.

In LASP process, the two liquid streams came into contact at the crossing of the channels and precipitation immediately occurred. Referring to Zhao et al. [50] study, the presence of water in ethanol decreases the solute concentration on the formed precipitated particle surface. There are some reasons for this observation; first, the instantaneous supersaturation level of the solution is greatly increased due to the reduction of the solvent concentration from the enhancement of the AS/S ratio when the curcumin solution and DI water are mixed.

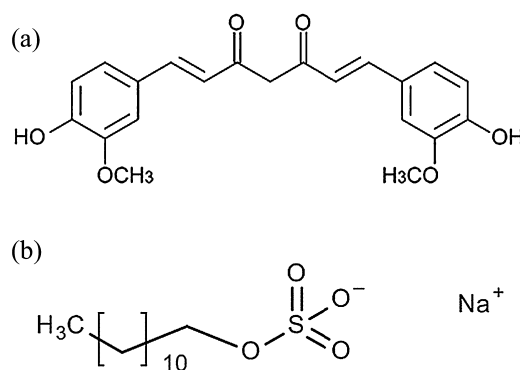


Fig. 1. Chemical structure of (a) drug (curcumin) (b) sodium dodecyl sulfate (SDS) as the stabilizer.

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