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An insight on reducing the particle size of poorly-water soluble curcumin via LASP in microchannels

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ABSTRACT

The potential of microchannel reactors (MCRs) was investigated to prepare curcumin nanoparticles, via liquid anti-solvent precipitation (LASP) technique. Three various arrangements of double jet impingement microchannels were proposed with confluence angles of 45°, 90°, and 135°. The understanding of mixing phenomenon was further linked to the size of precipitated particles, pressure drop, and dissipation rate. The effect of stabilizers and their concentrations have also been studied on the size of precipitated hydrophobic particles in the optimum cylindrical microchannel. Particle size distribution (PSD), SEM imaging, and zeta potential were employed to characterize the precipitated nanoparticles. The analysis of obtained data showed that the mean particle size of curcumin suspension decreased from 28.96 μm to 77.72 nm, and the specific surface area of freeze-dried powder increased from 3.88 to 17.50 m^2/g after the LASP process in MCR. In particular, curcumin precipitated from PVP 0.03% and PVP 0.3% have demonstrated the smallest median particle sizes.

1. Introduction

Curcumin is a natural polyphenol compound with many important pharmacological properties. It exhibits anti-oxidant, anti-inflammatory [1–4], anti-microbial, and anti-carcinogenic [5–9] activities. Additionally, the hepato-and nephro-protective [10,11], thrombosis suppressing [12], myocardial infarction protective [13–16], hypoglycemic [17–20], and anti-rheumatic [21] effects of curcumin are well established. Various animal models [22,23] or human studies [24–26] proved that curcumin is extremely safe even at very high doses. In this regard, the pharmacological safety, and efficacy of curcumin makes it a potential compound for treatment, and prevention of a wide variety of human diseases. In spite of its efficacy and safety, curcumin has not yet been approved as a therapeutic agent, and the relative bioavailability of curcumin has been highlighted as a major problem for this issue. In other words, its bioavailability is limited by its solubility and dissolution rate [27]. The dissolution rate can be improved by decreasing particle size [28]. Decrease in size will subsequently increase the surface area, which results in increasing the rate of dissolution of these drugs in aqueous media of body fluid [29]. While there are many techniques available for size reduction, their applicability is limited, because of poor control of particle size, morphology, and scalability in comparison with liquid anti-solvent (LAS) precipitation [30,31]. In LAS, precipitation of a solid solute is achieved by an increase in molar volume of solution, and hence a decrease in solvent power for solute by the addition of a non-solvent (anti-solvent) [32]. It should be noted that the precipitation process mainly involves nucleation due to supersaturation, attained by mixing [33], and simultaneous growth of nuclei by coagulation and condensation [34]. In order to control the particle size (PSD), and improve the stability, it is necessary to increase the nucleation rate, inhibit the particle growth, and control the agglomeration of particles driven by hydrophobic effects, electrostatic interactions, as well as weak van der Waals attractive forces.

Experimental results reported in literatures showed that micromixing (mixing on the molecular scale) has a significant effect on PSD, especially for rapid chemical processes [35,36]. Indeed, micromixing devices facilitate process intensification and intensify the nanoparticles formation by reducing the diffusion length between solvent (containing drug) and anti-solvent [37].

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Nomenclature

Abbreviations

As/S	Anti-solvent/solvent
BET	Brunauer–Emmett–Teller
d	Diameter
DI	Deionized
F. G.	Functional group
HPMC	Hydroxypropyl methyl cellulose
h	Hour
LAS	Liquid anti-solvent
LASP	Liquid anti-solvent precipitation
m (kg)	Mass
min	Minute
mV	Milli volt
MCR	Microchannel reactor
PSD	Particle size distribution
PVP	Poly(vinylpyrrolidone)
P	Pressure (kPa)
PdI	Polydispersity index
Q	Volumetric flow rate (mL)

Greek letters

ε (m^2/s^3)	Dissipation rate
θ (°)	Degree

Besides, the relatively small design in geometry of the microchannels will provide an intense mixing to create interfacial areas at high rates. At the interface, diffusive mixing is the key to accomplish the final steps in small scale homogeneous mixing, as it is necessary for precipitation of nanoparticles. It also allows performing very fast mixing with a residence time in the range of seconds. Short residence times are of a great interest to limit the particle growth.

Various researchers have tried to improve the dissolution characteristics of curcumin particles [27,38–41]. Table 1 presents list of literature reports, available on the micronization of curcumin. A comprehensive study of the liquid mixing process in T-shaped microchannels was carried out using μ-LIF (micro laser induced fluorescence) technique, by Wang et al. [39]. They focused on the miscible liquid mixing processes with/without multi-solvents, e.g., using water–water and water–ethanol systems in this work. In another study, the effects of process parameters like temperature, drug concentration (mg/mL), flow rate of solution stream (mL/min), and ratio of anti-solvent to solvent (As:S), were studied on the supersaturation, nucleation, and growth rate with two methods: anti-solvent precipitation with a syringe pump (APSP), and evaporative precipitation of nanosuspension (EPN). Overall, the average particle size of the original drug was about 10–12 μm, and it was decreased to a mean diameter of 330 nm for the APSP method and to 150 nm for the EPN method [27]. Moreover, He et al. [41] conducted a systematic characterization of structure evolution of curcumin nanoprecipitation from a micromixer. According to Table 1, in those experiments the two liquid streams are mixed in the microfluidic devices, although the mixing performance was investigated under different total liquid flow rates, the anti-solvent to solvent ratio were 1:1. Furthermore, in these studies little attention has been paid on stabilizers, since curcumin characterization can be further improved by adding additives into the system.

During precipitation, stabilizers can also affect a multitude of mechanisms including nucleation, growth, and agglomeration. A survey of the literature reveals the existing ambiguity regarding their exact role on precipitation, including prevention of growth and/or agglomeration. Based on [42], adsorption during particle formation occurs by favorably interacting with the particles at the solid–liquid, and by shielding them from the surrounding environment through reduction of the solid–liquid interfacial tension [43,44]. One hypothesis indicates that by adding some stabilizers the nucleation rates increase, thereby the particle size would decrease [45,46]. It has been also suggested that surfactants tend to decrease the surface energy of the system, hence reducing the time needed for the beginning of crystal growth. Accordingly, screening for an optimal stabilizer(s) and its amount is very important to stabilize the nanosuspension system, and prevent aggregation and Ostwald ripening [47].

The present investigation aims to characterize and improve curcumin particle size via liquid anti-solvent precipitation (LASP) process in microchannels. For this purpose, a series of experiments were employed to screen the optimized geometry of the designed microchannels, stabilizers type, and corresponding concentrations. The particle size, BET surface area, and morphology of the as-prepared curcumin powders, as well as their chemical structure, and physical characteristics were characterized to detect the properties of nanosized curcumin. The authors believe that the results of this investigation will offer a new perspective for understanding the significance of stabilizers in MCRs. The nobility

Table 1
List of literature reports available on the micronization of curcumin.

Process	Solvent	Mixing device	As:S (v/v)	Particle size (nm)	Morphology	Comments	Ref.
Anti-solvent precipitation with droplet-based approach	Ethanol	A T-shaped microchannel $d = 250\,\mu m$)	1:1	200–450	Strip-shaped, needle-shaped clusters, nanospheres	Deionized water as anti-solvent, compressed air as the gas flow pipe, air dried at 298 K	[38]
Anti-solvent precipitation	Ethanol	T-shaped microchannels (convergent angel = 180° and 90°, $d = 300\,\mu m$)	1:1	105–125	Sphere	Deionized water as anti-solvent, SDS 0.5 wt% as surfactant, air dried at 298 K	[39]
	Ethanol	Microchannel $d = 200\,\mu m$	1:1	100	Irregular	Water as anti-solvent, electrospray dryied	[40]
	Ethanol	Syringe pump	1:10–1:20	330	Lath-like	DI water as anti-solvent, vacuum dried	[27]
Evaporative precipitation of nanosuspension (EPN)	Ethanol	Syringe pump	1:10–1:20	150	Needle-like	Hexane as anti-solvent, stirring Speed = 200–1000 rpm, Vacuum dried	[27]