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Process intensification approach for preparation of curcumin nanoparticles via solvent–nonsolvent nanoprecipitation using spinning disc reactor

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ABSTRACT

Continuous preparation of curcumin nanoparticles via solvent–nonsolvent (S-NS) precipitation by using spinning disc reactor was investigated. The process intensification by spinning disc reactor (SDR) along with the comparative study of conventional mechanical agitated contactor was carried out. Solvent used for curcumin precipitation in this study was ethanol whereas non-solvent deionised water. Influences of various operating parameters for spinning disc process; such as flow rate of S-NS, S-NS ratio, concentration of curcumin, disc characteristics, concentration of protecting agent and rotating disc speed were examined on the nanoparticles size. The average optimum curcumin particles size was obtained in the range 180–220 nm in consideration with particles size distribution at a flow rate of 200 mL min^{-1}; curcumin concentration of 0.5 g L^{-1} in ethanol; polyvinylpyrilodine (PVP) concentration of 1 g L^{-1} in deionised water; S:NS ratio 1:4 and operating disc speed of 1500 rpm. Particles were characterized by using XRD, FT-IR, DSC and SEM which showed decrease in the crystallinity after the nanoprecipitation of curcumin. The dissolution rates of the fabricated curcumin nanoparticle were found drastically higher than original curcumin.

1. Introduction

Spinning disc reactor (SDR) is one of the multifunctional devices which provide fast and homogenous mixing in a continuous operation. Past research studies proposed that SDR as an intensified reactor for heat and mass transfer limitation process [1–5] and also it is widely used for fast co-precipitation process such as precipitation of silver, lithium carbonate, copper oxide and chitosan [6–9]. Basic principle of SDR is seemed similar like falling film evaporators. In the falling film evaporator, thin falling liquid film on the tube wall improves the heat transfer coefficient. Whereas in the case of SDR, sheared thin film on the rotating disc is responsible for higher heat and mass transfer coefficient [1,4,10,11]. Principally SDR is a horizontal or vertical fast moving rotating disc in a circular chamber. When liquid is introduced on the centre of rotating disc, a thin liquid film appears on the disc surface under the influence of high centrifugal force which provides larger surface contact between mixing fluid. At the same time, centrifugal force also responsible for shear between disc surface and liquid leads to wave and ripple formation on the film and generates large volume of smaller eddies throughout. These phenomenon are responsible for speedy and uniform mixing of fluid on the disc [7,12–14]. In the present work, SDR is used for the continuous preparation of curcumin nanoparticles via solvent–nonsolvent (S-NS) precipitation.

Curcumin is a yellow polyphenol hydrophobic compound which is extracted from the rhizome of the herb *Curcuma longa*. Curcumin has wide varieties of therapeutic application such as an anticancer, anti-inflammatory, antioxidant, antiulcer, immunomodulatory, wound healing, neuroprotective, and anti-aging agents [15,16]. These useful applications of curcumin are limited by its hydrophobicity (solubility of pure curcumin in water 0.2 mg L^{-1}). Hydrophobic nature of curcumin hinders its successful use due to limited dissolution and hence lesser bioavailability. Nanosizing is one of the attractive techniques amongst the most commonly used methods to mitigate poor drug dissolution problem. Reduced particle size by nanosizing increases surface area and eventually enhances the solubility and bioavailability of the poorly soluble drug component. Various approaches of nanosizing

Abbreviations: SDR, spinning disc reactor; NS-S, non-solvent to solvent; S-NS, solvent and non-solvent; PDI, polydispersity index; PSD, particle size distribution; PVP, polyvinylpyrilodine.

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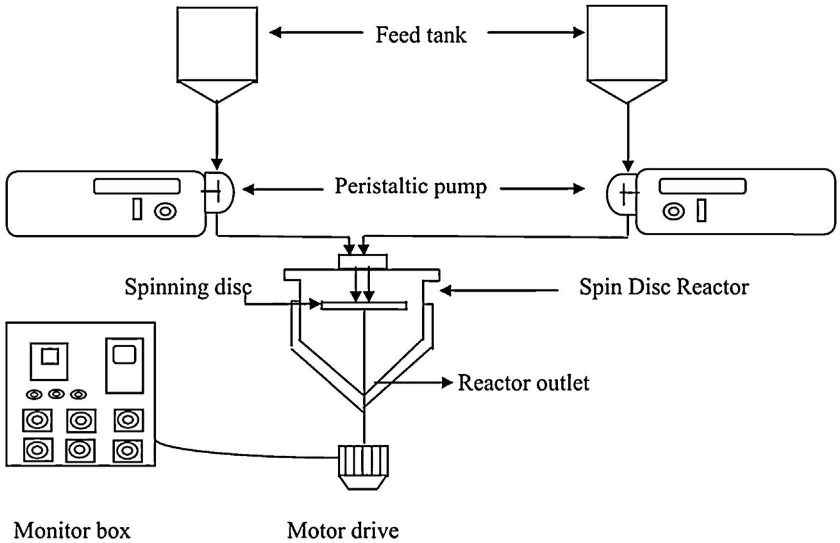

Fig. 1. Schematics representation of spinning disc reactor set-up.

are classified into two groups namely top-down and bottom-up as mentioned by Pattekari et al. [17], the former approach addresses breaking down large particles to smaller size particle mechanically by using milling or high pressure homogenization technique. Basic problems associated with this technique are, difficult to control particle size, surface property, high shear force and contamination [18,19]. On the other hand, nanoparticles in the bottom up processes are prepared from supersaturated solution of compound. In this technique, particles begin to start precipitation from its molecular state with precise control over particle size, shape and uniformity. Hence these approaches are suitable for controlling particle size and other complications which happen in the top-down approach [20].

Solvent and non-solvent (S-NS) precipitation is a cost effective as well as easily scalable bottom up approach suitable to prepare nanoparticle maintaining precise control over particle size and PSD [21–23]. Briefly this method involves dissolution of hydrophobic solute in organic solvent (S) followed by addition of an aqueous solvent (Non-Solvent; NS; water). Mixing between S-NS reduces the solubility of solute in the mixture and when it surpasses threshold limit, the mixture of S-NS become supersaturated which results in beginning of solute nuclei formation.

Precipitation process involves in two main steps, nucleation where nuclei are generated due to supersaturation and once nucleation start second step i.e. particles growth begins as a result of coagulation and condensation. For small and uniform particles precipitation, nucleation rate would be dominant over growth rate [14,21,24]. Supersaturation is the driving force for nucleation rate and higher supersaturation generates large number of smaller nuclei. Hence, rapid and uniform mixing is desired between S-NS to obtain high and uniform value of supersaturation which plays critical role over the particles precipitation. For small and uniform particles of curcumin by S-NS precipitation, literature reported various approaches used for enhancing micromixing between S-NS such as ultrasonification, homogenization and micromixer with electrospray drying [25–27].

Particle size and PSD play an important role for designing suitable drug carrier system, affecting rate of cell uptake and permeability of curcumin through tissue. In the conventional reactor, there is non-uniform mixing between S-NS at micro scale which affects particle size distribution. Thus there is a demand of mixing equipment which will provide more energy efficient mixing between S-NS. SDR offers fast mixing between fluids at micro scale level gives higher degree of supersaturation [7,8]. This supersaturation leads to formation of higher quantity of smaller size nuclei and controlled growth due to uniform mixing throughout the film.

The aim of this study is to develop smaller and uniform size curcumin nanoparticles in the spinning disc reactor (SDR) by using solvent and non-solvent (S-NS) precipitation technique. Parameters were optimized for SDR process and compared with mechanical agitated contactor. PVP was used to stabilize the curcumin particles. To the best of our knowledge; no literature is available for SDR for S-NS precipitation technique for curcumin nanoparticle preparation. Curcumin particles size and their distribution were measured by dynamic laser light scattering (DLLS) technique. X-ray diffraction (XRD) was used to determine crystallinity of particles. Thermal behaviour and chemical structure of nanoparticles were examined by DSC and FT-IR respectively. Morphology of the particles was determined by the scanning electronic microscopy (SEM). Finally dissolution study of curcumin nanoparticle and raw curcumin were carried out.

2. Materials and methods

2.1. Materials

Curcumin, PVP (poly vinylpyrilodine) and ethanol were procured from S.D Fine chemicals Ltd. (Mumbai, India). The deionised water (Mili Q) with the electrical conductivity of 0.55 μS cm^{-1} at 30 ± 0.5 °C was used. The organic solvent ethanol was used for dissolution of curcumin whereas deionised water containing PVP was used as non-solvent.

2.2. Mechanical agitated contactor

Mechanical agitated contactor was used for mixing S-NS in both batch and semi-batch process which consisted of a glass vessel having 150 mL capacity, 10 cm height, 8 cm diameter and equipped with baffle arrangement. Mixing was done by using a glass stirrer of 2.3 cm diameter (diameter of impeller/diameter of tank ratio 1/3.4) at room temperature (30 ± 0.5 °C). In the batch process, S-NS ratio was maintained at 1:4 (20 mL solvent and 80 mL non-solvent) and mixed at 1000 rpm. Whereas in the semi-batch process, reactor was first filled with solvent (20 mL) and then non-solvent (80 mL) was continuously added at defined flow rate (35 and 45 mL min^{-1}) through a vertical tube (2 mm diameter) which was located near the