Chemical Engineering Journal 248 (2014) 107–121

Contents lists available at ScienceDirect

Chemical Engineering Journal

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

Multiple orifices in customized microsystem high-pressure emulsification: The impact of design and counter pressure on homogenization efficiency

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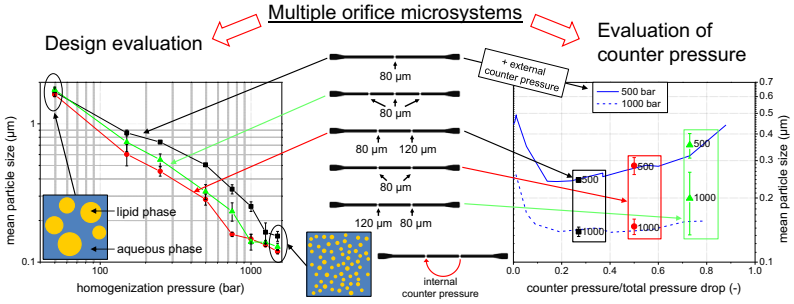
HIGHLIGHTS

- Systematical evaluation of double orifice design parameters.
- Identification of mechanism of droplet disruption and stabilization.
- Induced counter pressure is crucial for improved emulsion processing.
- Specific double orifice superior for common formulations due to stabilization zone.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 10 July 2013
Received in revised form 12 December 2013
Accepted 16 December 2013
Available online 18 March 2014

Keywords:
Nanoemulsion
Customized micro fluidics system
Multiple orifices
Droplet break-up efficiency
High-pressure homogenization
Counter pressure

ABSTRACT

A continuous production of nanoemulsions (or solid lipid nanoparticles) via a single passage through a homogenization device is a challenging, yet essential prerequisite of upstream or downstream processes in an integrated overall microsystem.

Multiple orifice microsystems with consecutive orifice arrangements were identified as especially efficient tools for this purpose. Design, process, and formulation parameters were studied to evaluate their influence on the process efficiency and the underlying mechanisms affecting the droplet breakup and droplet stabilization efficiency.

The application of multiple orifices in one microsystem reduces the coalescence of broken up droplets due to the establishment of a turbulent mixing zone. Therein, the frequency of droplet collision is elevated and, in turn, their collision time is shorter than the coalescence time. Thus, the droplets are fluid dynamically stabilized against coalescence. Double orifices are found more efficient than triple orifices because the breakup is superior due to higher energy density. The combination of differently wide orifices as well as the orifice order and the inter-orifice distances also influence the homogenization result. The combination of orifices must be selected to yield a counter pressure in the range of Thoma numbers between 0.1 and 0.4, as described for common two-stage homogenizers.

The variation of formulation parameters displayed that the improved double orifice efficiently produces small particle sizes virtually independent of the emulsifier properties and the viscosity of the continuous phase.

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http://dx.doi.org/10.1016/j.cej.2013.12.105

In conclusion, a versatile microsystem design has been developed and characterized for a highly efficient processing of a broad range of formulations and to suit a complex process chain by consuming only a minimum of pressure drop (e.g. 1000 bar).

1. Introduction

The processing of nanodisperse systems, either emulsions or suspensions, is a demanding challenge for manufacturing devices. Nevertheless, these processes have continuously been developed and well been characterized to provide high quality products. These nanodisperse products are of high interest in many fields of research and manufacturing because the nanoscale dimensions may provide advantageous and innovative properties to materials well known from macroscale.

Many efforts are carried out in the field of dairy processing (e.g. milk, yoghurt, butter). Development in this field is primarily focusing on high throughput and energy efficiency. With the manufacturing of pharmaceutical formulations, however, the production volume is likely to be smaller while the product properties are more critical and have to be met in a narrow range. In pharmaceutical applications, nanoemulsions and solid nanoparticles (especially solid lipid nanoparticles, SLN) are promising vehicles for drug delivery. Nanoemulsions and nanoparticles may facilitate the application of hardly soluble drugs, enhance their bioavailability and permeation through biological barriers, enable drug targeting, sustain drug release, and protect drugs against degradation [1]. Furthermore, these particulate systems allow many ways of administration such as by parenteral [2], peroral [1,3], dermal [4–7], ocular [8,9] or respiratory [10,11] route. Regarding the tolerance of nanodisperse lipid systems *in vivo*, nanoemulsions are routinely used for parenteral nutrition since the 1950s [12]. Since many years, nanoemulsions have also been used as commercial drug delivery systems e.g. for diazepam [13].

However, pharmaceutical application poses special requirements towards product quality concerning defined, small particle sizes, narrow particle size distributions, and high stability.

As the most common production technique, the top-down manufacturing method of high-pressure homogenization has extensively been developed and characterized for the production of nanosized particles [14,15]. Different principles in homogenization devices are applied: radial diffusers, axial flow nozzles (or orifices) and counter jet dispersers [16,17]. The latter two principles are commonly implemented without movable parts, yielding advantages towards human error, mechanical failure, and wear.

In this study, the intensified development and characterization of customized microsystems is described, which provide several advantages: a high surface-to-volume ratio, a defined residence time distribution, and a defined input of stresses to the product stream (by customizing microchannel design). Additionally, the application of small educt batches and a good product recovery, due to small dead volumes, are facilitated. This is of special interest for applications in early pharmaceutical development if just small amounts of active pharmaceutical ingredients (APIs) are available for formulation screening. The use of such microsystems offers cost reduction and simultaneously decreases process times and hazardous potentials.

With regard to an integrated overall microsystem that comprises further process steps – both prior (e.g. the dispersion of solid APIs in the oil phase and the initial junction of the oil phase and the aqueous phase) and subsequent ones (e.g. defined cooling and crystallization of solid lipid nanoparticles) to the high-pressure homogenization – a continuously operating system is required. Thus, the homogenization must yield small particle sizes with a narrow size distribution by the application of a single passage through the microsystem. According to that, the homogenization efficiency of the microchannel design is of special interest.

In previous work, we showed that microsystems are generally able to meet these requirements [18–20]. The results rose questions about the underlying mechanisms and influences on droplet disruption and stabilization that needed further investigation of the microsystem design as well as the process parameters. Most promising candidates were orifice microchannels due to their simple structure in combination with high homogenization efficiency. Especially the application of multiple orifices showed interesting results and perspectives [19] which are investigated in detail in this study. The number of orifices, the distance between orifices, and the combination of different orifice widths are evaluated over a wide pressure range.

In the literature, the addition of a second consecutive homogenization stage or structure has been described to lead to an enhanced reduction in droplet size [21–24]. This is most likely explained by the application of counter pressure towards the first orifice, fostering the cavitation intensity which is understood to contribute to droplet disruption [23,25]. The applicability of this counter pressure theory to explain the effects in the present microsystems was studied with regard to design modifications and the application of external counter pressure.

In addition, the effects of formulation variations regarding the emulsifier (faster adsorption to interfaces) and the viscosities of continuous and disperse phases were examined. These experiments furthermore provide insight regarding the differentiation of the breakup efficiency and the stabilization efficiency of the microsystems.

2. Materials and methods

2.1. Materials

Medium chain triglycerides (MCT; Miglyol® 812, Caelo, Hilden, Germany) were used as liquid oil for emulsion preparations. Macrogol-15-hydroxystearate (MHS; Solutol® HS 15, BASF, Ludwigshafen, Germany) was used in aqueous solution as nonionic emulsifier/stabilizer. It consists of polyethylene glycol mono- and diesters of 12-hydroxystrearic acid and approx. 30% free polyethylene glycol. Sodium dodecyl sulfate (SDS; Texapon® L100, Henkel & Cie, Düsseldorf, Germany) was used as anionic emulsifier in aqueous solution. Critical micelle concentration is 0.021% (w/v) for MHS [26] and 0.024% (w/v) for SDS [27]. Water was used in double distilled quality.

To adjust viscosities, refined castor oil (CO; Caelo, Hilden, Germany) was added to the lipid phase or polyethylene glycol 20,000 (PEG; Mainland Pharmazeutische Fabrik GmbH, Frankfurt am Main, Germany) was added to the aqueous phase, respectively.

2.2. Microstructures

2.2.1. Design and production

The microsystem generally consists of a structured bottom plate with customized microchannels for emulsification on its