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Membrane emulsification technology: Twenty-five years of inventions and research through patent survey

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ABSTRACT

Membrane emulsification technology is a drop-by-drop emulsification method through a porous membrane, introduced in Japan in 1988. Ever since, the attention on the method has increased significantly from both the scientific and technological point of views. After around twenty-five years of research and inventions, directions and trends in the development of membrane emulsification can be obtained through a critical analysis of the patents in this field. Patents are a powerful tool to assess the development stage of a technology and predict the potential impact on a productive scale. This paper aims to discuss critically innovation promoted worldwide during this half a century. A total of 103 patents from 1988 to 2013 were used as the database for the analysis. Patents distribution per year, country and field of the inventions will be illustrated, demonstrating territorial excellence and technological specialization. Significant examples of patents in process development and applications will be also presented. Thirty-one per cent of patents are on process development and only 11% of these are specifically related to membranes construction/modification for emulsions preparation. The rest is mainly dedicated to formulation. Many uses for membrane emulsification have been successfully achieved and medicine is the main field of application.

Contents

1. Introduction

Membrane emulsification technology has received increasing interest over the last 25 years as an alternative method to produce emulsions and particles. The method allows the generation of emulsions by a drop-by-drop mechanism through a microporous membrane (Fig. 1). The dispersion phase in the form of droplets can be as a pure liquid or an emulsion. In the first case, simple emulsions are produced such as oil-in-water (O/W) or water-in-oil (W/O) droplets in which an immiscible liquid is used as continuous phase. In the second case, an emulsion of an emulsion is generated e.g. water-in-oil-in-water (W/O/W) and oil-in-water-in-oil (O/W/O) emulsions, also termed multiple or double emulsions.

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A coarse emulsion may be, alternatively, refined upon passage through a microporous membrane. The process is referred to as premix membrane emulsification to distinguish from the direct process (Fig. 1B).

Benefits of membrane emulsification include: (i) production of uniform particles, (ii) droplets size controlled by appropriate membrane pore size selection, (iii) low shear stress, (iv) energy requirement reduction, (v) high flexible plant use, (vi) operation in mild conditions on a variety of scales and (vii) precise, selective and flexible manufacturing of different types of particles such as simple and multiple emulsions, microspheres, liposomes, etc.

Two main types of membrane emulsification can be identified by using: (i) a "moving continuous phase" (Fig. 2) or (ii) a "moving membrane" (Fig. 3). The forces acting on a droplet at the membrane pore level include detaching forces, driving droplets off the pore, and retaining forces, holding droplets on the pore (Fig. 4). Detaching forces are: drag (F_D), buoyancy (F_{BG}), inertial (F_I), lift (F_L) and static pressure (F_{SP}) force while the main retaining force is the interfacial tension (F_γ). The drag force (F_D) is created by the continuous phase flowing parallel to the membrane surface; the buoyancy force (F_{BG}) is due to the density difference between the continuous phase and the dispersed phase; the inertial force (F_I) is caused by the dispersed phase flow moving out from the pore outlet; the dynamic lift force (F_L) results from the asymmetric velocity profile of the continuous phase near the droplet; static pressure (F_{SP}) force is due to the pressure difference between the dispersed phase and the continuous phase at the membrane surface; the interfacial tension force (F_γ) is provided by the effects of dispersed phase adhesion around the edge of the pore opening. In the case of "moving membrane" emulsification, additional forces have to be considered. For rotating membrane emulsification, the additional forces are the centrifugal force to aid droplet detachment and the tangential velocity differences between the droplet and the continuous phase. For an oscillating membrane system where the membrane is transversally excited, an additional drag force and an inertial force appear in the direction parallel to the membrane. The forces acting on the droplets at the membrane pore level are associated with different parameters influencing droplets detachment such as

- operating parameters: wall shear stress, transmembrane pressure, disperse phase flux, and temperature,
- membrane parameters: pore size, pore size distribution, pore border morphology, number of active pores, distance between pores, porosity, and surface wetting property and
- phases parameters: emulsifier type and concentration, viscosity and density of dispersed and continuous phase.

The appropriate selection of each parameter allows one to obtain the production of uniform droplets with controlled size at a reasonable emulsification flux to answer to specific industrial requests.

The previous reviews on membrane emulsification focused on principles, parameters and applications of the method [1–17]. Nakashima et al. [1] described, for the first time, the membrane emulsification method by using porous glass membrane, including fundamentals and applications. Joscelyne et al. [2] and Charchosset et al. [3] reviewed the experimental studies which focused mainly on investigations of process parameters such as: the membrane type, average pore size and porosity, shear stress, transmembrane pressure and emulsifier and the applications of membrane emulsification on the industrial scale and small-scale. Other reviews focused on specific aspects related to the process, such as cross-flow membrane emulsification [4] and premix membrane emulsification [8], and to the manufacturing of particulate materials (simple o/w and w/o emulsions, multiple emulsions, solid-in-oil-in-water (S/O/W) dispersions, coherent solids (silica particles, solid lipid microspheres, solder metal powder) and structured solids (solid lipid microcarriers, gel microbeads, polymeric microspheres, core–shell microcapsules and hollow polymeric microparticles) [5,14] and double-emulsions [6]. The application of membrane emulsification in a specific field such as food [7,15], drug delivery [9] and cell delivery [17] was also reviewed. Vladisavljević et al. [10] described the production of uniform droplets not only by using a membrane but also by microchannel and microfluidic emulsification devices. In a recent review, Spyropoulos et al. have focused on novel membrane materials and engineering advantages and the limitations of a range of membrane techniques [11]. Special attention paid to models developed to predict droplet size, flow behavior and other phenomena involved in membrane emulsification process (such as droplet–droplet interactions) were reviewed in [12,13]. In order to assess the technological innovation promoted so far and perspectives at industrial level of the membrane emulsification process, the present review will mainly focus on patents, which play a fundamental role in disclosing information about innovations thereby fostering further technological progress. The work will therefore illustrate technological details, reveal business trends, inspire novel industrial solutions, as well as guide investment policy.

A patent search was conducted using Questel Intellectual Property Portal (www.orbit.com) that allows searching more than 90 patent authorities worldwide. A general research was carried out using two specific keywords: membrane and emulsion. The keywords were searched in the title, abstract and text while classifications, names, numbers, data country, restrictions were not specified in order to make the search as general as possible without excluding some useful results. A total of 103 patent documents published from 1988 to 2013

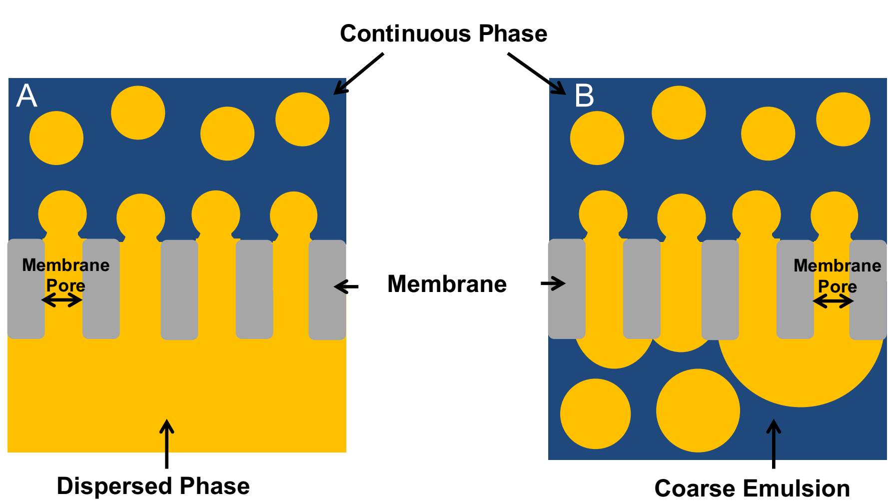

Fig. 1. Particles production by direct and premix membrane emulsification. (A) Direct membrane emulsification and (B) Premix membrane emulsification.