Journal of Membrane Science 448 (2013) 190–197

Contents lists available at ScienceDirect

Journal of Membrane Science

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

Polymeric microspheres preparation by membrane emulsification-phase separation induced process

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ARTICLE INFO

Article history:
Received 30 January 2013
Received in revised form
2 June 2013
Accepted 23 June 2013
Available online 28 June 2013

Keywords:
Polymeric microspheres
Membrane emulsification
Non-solvent induced phase separation
Polyethersulfone (PES)
Oil-in-oil emulsions

ABSTRACT

Uniform Polyethersulfone (PES) microspheres of target size in the range of 30–60 μm were successfully prepared by combining membrane emulsification technology and phase separation induced process in one step. An emulsion is generated by injecting the polymeric solution through a microporous membrane into the continuous phase which allows also the phase separation induced process and precipitation of the polymer (coagulation bath). Therefore, the droplets formation and solidification occur in a single step. Furthermore, the preparation of non-aqueous (O/O) emulsions by membrane emulsification as well as the preparation of polymeric microspheres by non-solvent induced phase separation has never been reported previously. The effect of continuous phase-coagulation bath composition, hydrophobic emulsifier, dispersed phase flux and shear stress on size and uniformity of PES microspheres has been investigated. Key factors in microspheres production by membrane emulsification and phase separation induced process mechanism include the solvent/non-solvent system type, non-solvent composition and O/O interface composition. Polymeric microspheres with spherical morphology have been produced by tailoring such key factors.

1. Introduction

Polymeric microspheres are spherical microscopic particles in the range between 1 and 1000 μm manufactured from various natural and synthetic materials. They are used to deliver, protect, stabilize or control the release of the encapsulated compounds in medical, food, cosmetic and pharmaceutical field. Polymeric microspheres are produced by physical or chemical methods, however, three main common steps can be identify: (i) dispersion or emulsion preparation; (ii) deposition of the material that forms the particle wall and (iii) solidification to transform the droplets into solid microspheres. Usually microspheres are produced starting from oil-in-water (O/W), water-in-oil (W/O) or water-in-oil-in water (W/O/W) emulsions while the solidification is obtained by cross linking, polymerization, solvent evaporation/extraction. Non-aqueous emulsions (i.e., oil-in-oil (O/O)) can also serve as a versatile tool for the synthesis of new types of polymeric particles. They are obtained by mixing two different immiscible polar aprotic/organic nonpolar solvents. The introduction of the non-aqueous emulsions can be traced back to Molau (1965) [1] while Periard et al. (1970) [2] are amongst the first to talk about O/O emulsion. These systems have been successively used in the synthesis of particles based on water sensitive monomers or catalysts that cannot usually be achieved by classical approaches. Some examples include the use to perform polyadditions, [3] polycondensations, [4] or oxidative polymerization [4] for the preparation of polymer nanoparticles or even core/shell particles by a combination of different polymerization methods [5–8]. In recent years, hydrophilic and hydrophobic, smooth and rough, solid and hollow, porous and uniform particles with controlled size and uniform size distribution have been successfully produced by combining microengineering techniques and appropriate solidification process. Polymeric particles can be made from emulsions containing the dissolved polymer or monomer in the dispersed phase and an emulsion stabilizer in the continuous phase. The method used for microspheres preparation depends on the attributes of the polymer (such as physic-chemical parameters) in order to obtain microspheres with properties tailored for a specific application. However, the preparation of polymeric microspheres with controlled and uniform size distribution is still a challenge. For this reason, the key step in the production of polymeric microspheres is the manufacturing of emulsions droplets. Emulsions are usually generated by "droplet break-up" mechanism in conventional emulsification devices and highly polydisperse and uncontrolled size droplets are obtained. Over the past two decades novel microengineering techniques have been developed for the controlled production of uniform droplets such as membrane emulsification, microchannel emulsification

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http://dx.doi.org/10.1016/j.memsci.2013.06.038

and microfluidic emulsification [9–11]. The dispersed phase is injected through microchannels or membrane pores into another immiscible liquid that is the continuous phase. To form the particles, the solvent for the polymer is removed by evaporation [12] or alternatively by means of cross-linking agent [13] or initiator [14] which are added in the continuous phase to promote the suspension polymerization. However, few papers reported the combination of phase separation induced technique with membrane process concept but in two separate steps [15–17]. In our previous work, a "model membrane" consisting of a monopore polyethylene film, was used to prove the concept idea of making the formation of the polymeric drop in an organic media (emulsion formation) and, as second step, its solidification (particle formation) in the coagulation phase. Modified polyetheretherketone (PEEKWC), polyvinilydene fluoride (PVDF) and polyethersulfone (PES) particles in the range between 800 and 1500 μm have been prepared [15–17]. The polymer is dissolved in a polar aprotic solvents such as dimethyl formamide (DMF) while an organic nonpolar solvent such as dodecane was used as oil phase. Non-aqueous (O/O) emulsions have been produced and the phase separation was induced by the non-solvent phase (isopropanol–water mixture), used as coagulation bath, for solidifying the polymer drop solution in a second step.

The aim of this work was to investigate PES microspheres generation combining membrane emulsification process with phase separation induced method. In particular, the use of a non-aqueous (continuous) phase allowed both the formation of the emulsion and, at the same time, the starting of the polymer precipitation (slower demixing than water) thanks to the weaker phase inducer employed. An emulsion is generated by injecting the polymeric solution through a microporous membrane into the non-aqueous continuous phase that works at the same time as phase separation inducer and allow the particle formation. In this case, droplets formation and solidification occur in a single step. To our knowledge, the preparation of non-aqueous (O/O) emulsions by membrane emulsification as well as the preparation of polymeric microspheres by non-solvent induced phase separation has not been previously reported. A summary of the main advances, introduced in this paper, is reported:

1. microspheres are produced at much higher throughputs because the number of drop generation units (pores) compared to just one drop generation unit (monopore);
2. the continuous phase is homogeneous solutions obtained mixing the non-solvent (organic non-polar solvent) and the surfactant solution (hydrophobic surfactant) and particles production and solidification occurred in a single step;
3. microspheres size is reduced more than 30 times the size obtained with the monopore.

Therefore, the main emphasis of this work was to investigate the effect of hydrophobic emulsifier, shear stress, dispersed phase flux, dispersed phase concentration on the size and uniformity of PES generated droplets. Different non-solvents were used in the preparation of the continuous phase-coagulation bath in order to evaluate the effect on the induced phase separation process.

2. Experimental section

2.1. Materials

Polyethersulfone (ICI VICTREX) was dried in an oven at 50 °C for 48 h and dissolved in N, N-Dimethylformamide (DMF, Sigma Aldrich, Italy) and used as polymeric dispersed phase. Paraffin oil (Carlo Erba Reagenti, Italy) containing polyglycerol fatty acid ester (SY-Glyster PO-55, Sumitomo Corporation, Japan) as surfactant and dodecane or isooctane or butanol or isopropanol (all purchased from Carlo Erba reagent, Italy) is used as continuous phase-coagulation bath.

Brookfield DV-II viscometer (Brookfield Engineering Laboratories, Inc. Stoughton, MA) was used to evaluate the viscosities of the polymer solutions and the solutions used as continuous phase-coagulation bath.

2.2. Membrane and membrane module

The emulsions were obtained using a stirred cell with a nickel flat disc membrane under the paddle blade stirred. A ringed

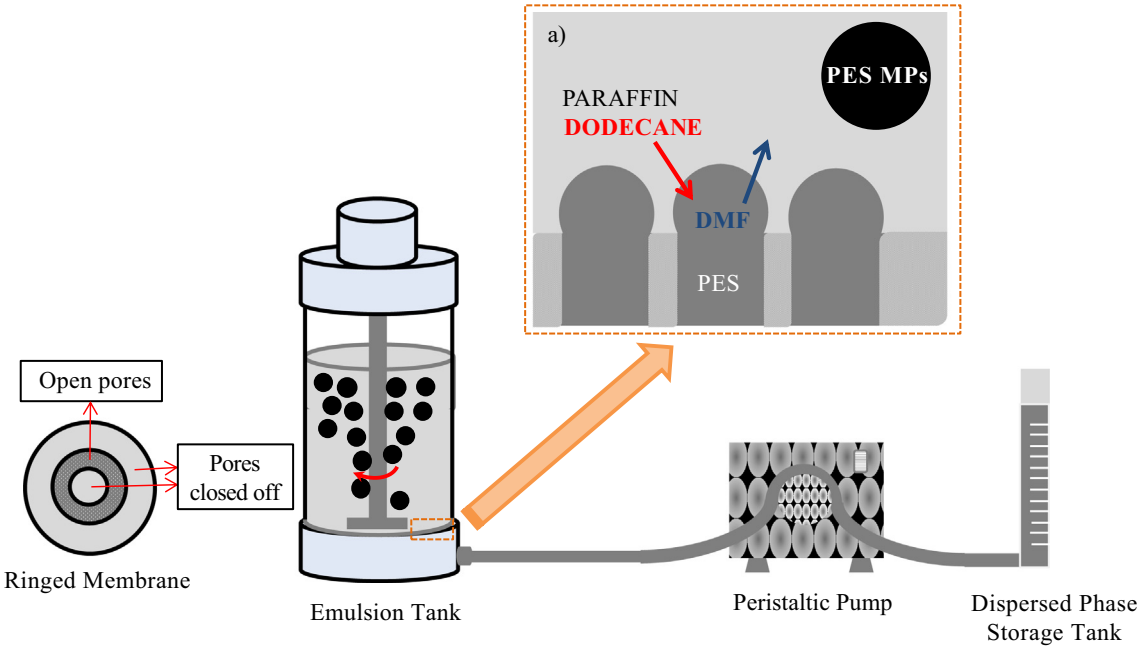

Fig. 1. Illustration of the dispersion cell and the ringed membrane used in microspheres preparation. (a) Microspheres generation by membrane emulsification combined with phase separation induced process.