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Rapid communication

Continuous manufacturing of solid lipid nanoparticles by hot melt extrusion

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ABSTRACT

Solid lipid nanoparticles (SLN) can either be produced by hot homogenization of melted lipids at higher temperatures or by a cold homogenization process. This paper proposes and demonstrates the formulation of SLN for pharmaceutical applications by combining two processes: hot melt extrusion (HME) technology for melt-emulsification and high-pressure homogenization (HPH) for size reduction. This work aimed at developing continuous and scalable processes for SLN by mixing a lipid and aqueous phase containing an emulsifier in the extruder barrel at temperatures above the melting point of the lipid and further reducing the particle size of emulsion by HPH linked to HME in a sequence. The developed novel platform demonstrated better process control and size reduction compared to the conventional process of hot homogenization (batch process). Varying the process parameters enabled the production of SLN below 200 nm (for 60 mg/ml lipid solution at a flow rate of 100 ml/min). Among the several process parameters investigated, the lipid concentration, residence time and screw design played major roles in influencing the size of the SLN. This new process demonstrates the potential use of hot melt extrusion technology for continuous and large-scale production of SLN.

1. Introduction

Solid lipid nanoparticles (SLN) is a potential drug delivery system that has attracted increasing attention in the recent years as a carrier system for cosmetic ingredients, nutraceuticals and pharmaceutical drugs (Dingler and Gohla, 2002). SLN differs from nanoemulsions based on the lipid nature, wherein SLN replaces the liquid lipid to high melting point glycerides or waxes. SLN has been reported for controlled drug delivery, bioavailability enhancement by modification of dissolution rate and/or improvement of tissue distribution and targeting of drugs by using various application routes. SLN are mainly formulated by non-solvent or solvent-based techniques. The solvent-based techniques utilize organic solvents to dissolve the solid lipids followed by evaporation of the solvent(s) from the emulsion to obtain SLN. Non-solvent techniques liquefy the solid lipid above its melting point and subsequently are converted to a nanoemulsion by cooling, which results in SLN.

High-pressure homogenization (HPH), microemulsions, high-speed stirring or ultra-sonication and membrane emulsification are some of the non-solvent based approaches. Solvent evaporation by precipitation in o/w emulsion processes for formulation of SLN entails disadvantages such as the very use of organic solvents as well as the requirement of large amounts of surfactants (Hou et al., 2003). HPH (hot and cold homogenization) has been explored for its feasibility in scaling-up. R. H. Muller in 2010 conducted the scale up studies for production of stavudine-loaded SLN from laboratory scale (40 g) to medium scale (10 kg) and large scale (20/60 kg). This scale up study is very significant; however, it is only related to one part of the SLN production process, which is the homogenization step for size reduction (Muller et al., 2011). However, these methods for SLN preparation involve multistep processes (melting of lipids, dispersion or dissolution of the drug in melted lipids, preparation of aqueous dispersions and finally size reduction), hence, rendering it a batch process. In the pharmaceutical industry, a continuous process is almost always preferred over batch processes as continuous processing decreases the cost of production by decreased space requirements, labor and resources. A continuous process can provide higher efficiency and improved product quality attributes, whereas risks of batch-to-batch variation require careful and complex procedures and controls that can lead to variable product outcomes such as different particle size, polydispersion indices, zeta potential and variations in entrapment efficiency of the drug into the SLN. New approaches are therefore needed, both to increase the quality of the product and to reduce the production time. Hot melt extrusion is an innovative technology for the production of a variety of dosage

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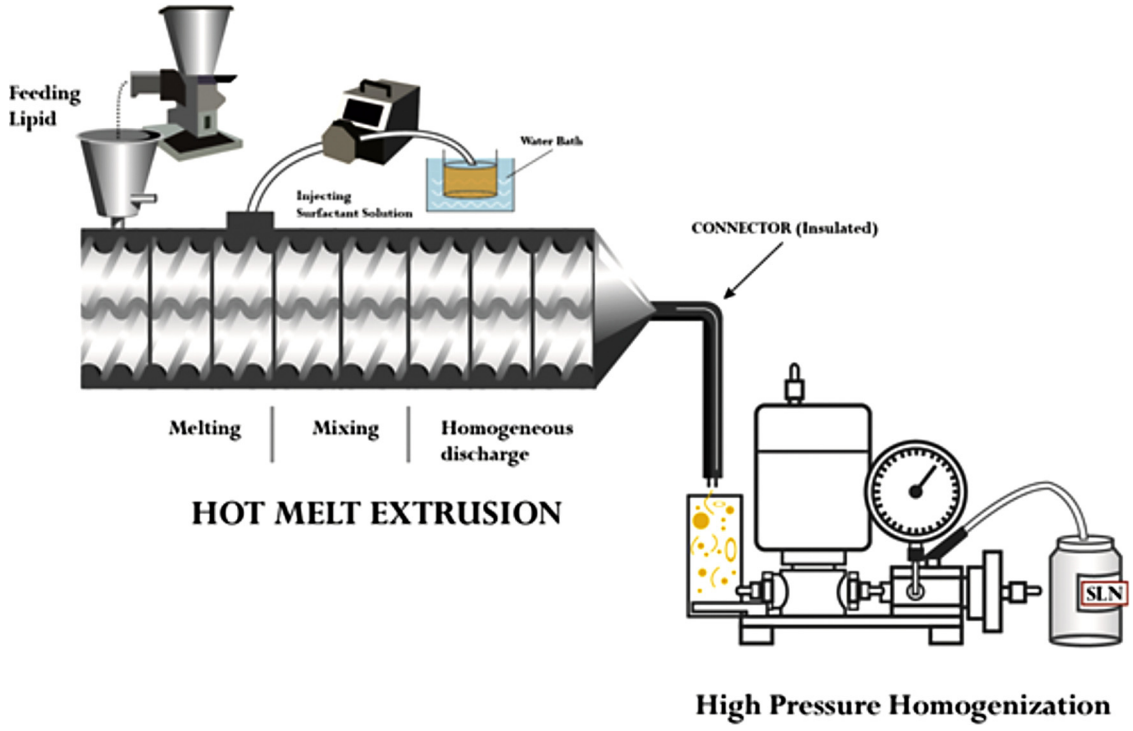

Fig. 1. Schematic representation of continuous preparation of SLNs using hot melt extrusion connected to a high pressure homogenizer.

forms, offering several advantages over traditional processing techniques and is cost-effective (Khinast et al., 2013; Roblegg et al., 2011; Repka et al., 2007; Crowley et al., 2007).

Hot melt extrusion (HME) technology is a continuous process of pumping raw materials at high temperatures and pressures resulting in a product of uniform shape and density (Breitenbach, 2002; Maniruzzaman et al., 2012). To the best of our knowledge, HME has not been reported in the literature for the manufacturing of SLN. The purpose of this current work was to develop a continuous process for SLN production using hot melt extrusion for preparing a pre-emulsion and high-pressure homogenization for further size reduction. With this process, HME and HPH are connected in a sequence through an insulated connection. Process parameters, such as the zone of liquid addition (ZA), barrel zone temperature (ZT), screw speed (SS), liquid temperature (LT), screw design (SD), and lipid concentration (LC) were optimized for the formulation of SLN by this hot melt extrusion–high pressure homogenization method. First, three parameters that is ZA, ZT and SS play a very important role to ensure the lipid is completely in a molten state and the drug is completely melted and dissolved in the lipid before coming in contact with the surfactant solution. The HME barrel zone temperature for all zones between the feeding zone to the liquid addition zone and screw speed should be sufficient to melt the lipid completely when it contacts the surfactant aqueous solution and, hence, due to high shear generation within the extruder, the two phases mix with each other to form an emulsion. The scheme for continuous manufacturing of SLN is summarized in Fig. 1. SLN were prepared by the figure-illustrated hot melt extrusion and high-pressure homogenization method.

Glyceryl behenate (Compritol® 888 ATO, Gattefosse, France) was fed into the co-rotating twin-screw extruder (11 mm Process 11, ThermoFisher Scientific, Karlsruhe, Germany) using a gravimetric feeder. A 1.5% w/w Tween 80 (Sigma–Aldrich, USA) aqueous solution heated to the equivalent to the extrusion temperature was injected into the extruder barrel through an injection port using a peristaltic pump. The melt-extrusion was performed by varying the formulation parameters, process parameters and screw configuration as described in Table 1. The barrel temperature for zone 2, 3 and the rest of the zones (4–8) along with the die were varied based on the screw speed. The screw configuration with three mixing zones was used either as manufacturer's standard screw configuration or a modified

Table 1
Experimental design matrix and response variable values obtained (data represent mean ± SD, $n = 6$).

Batch	Screw speed	Zone of liquid addition	Barrel temp.[a] (°C)	Screw design	Lipid conc. (% w/w)	Z-average (nm)	PDI	Zeta potential (mV)
F1	240	3	150–100–83	Std.	6	85.1 ± 7.12	0.353 ± 0.025	−31.8 ± 0.11
F2	240	4	150–100–83	Std.	6	286.9 ± 5.12	0.312 ± 0.012	−28.6 ± 0.09
F3	240	3	150–100–83	Modi.	6	245.5 ± 6.91	0.408 ± 0.041	−33.3 ± 0.18
F4	240	3	120–85–75	Std.	6	303.9 ± 7.64	0.295 ± 0.028	−29.2 ± 0.08
F5	160	3	150–100–83	Std.	6	266.3 ± 4.71	0.264 ± 0.015	−30.6 ± 0.15
F6	160	3	150–100–83	Modi.	6	194.8 ± 5.82	0.391 ± 0.009	−34.3 ± 0.04
F7	160	3	150–100–83	Modi.	12	846.7 ± 21.52	0.625 ± 0.085	−15.7 ± 0.48
F8	Conventional process for SLN preparation				6	248.2 ± 13.42	0.412 ± 0.038	−30.6 ± 0.12

[a] The barrel temperature for zone no. 2–3–4 through the die (F6 optimized batch barrel temp. in zone 2 – 150 °C, zone 3 – 100 °C and zone 4 through the die – 83 °C).