European Journal of Pharmaceutics and Biopharmaceutics 109 (2016) 206–213

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

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

Research paper

Industrialization of lipid nanoparticles: From laboratory-scale to large-scale production line

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ARTICLE INFO

Article history:
Received 6 May 2016
Revised 13 August 2016
Accepted in revised form 23 October 2016
Available online 25 October 2016

Keywords:
Large-scale
Modular
NLC
Emulsification temperature
Homogenization pressure
Homogenization cycle

ABSTRACT

This work aimed at developing a large-scale modular production line, which referred to coenzyme Q_{10} loaded-NLC as well as its continuous and scalable emulsification and homogenization process. The production line exhibited good control over the emulsification and homogenization process and enabled the particle size of NLC below 210 nm at a throughput of 25 kg/h (for lipid solution at a flow rate of 0.4 kg/min). Among the several process parameters investigated, the size of the NLC was mainly influenced by the pre-emulsification temperature, homogenization pressure and homogenization. Suitable emulsification temperature (70 °C), homogenization pressure (600, 800 bar), and homogenization cycle (3, 4 cycles) resulted in relatively smaller particles. These results proved that coenzyme Q_{10}, a model active, had been successfully loaded into the NLC. Meanwhile, the large-scale production line can be effectively applied for continuous and modular production of NLC. The line had modern networking features-essential in the Internet age-and a modular design that was easily modified and upgraded. In addition, the long-term stability over 6 month was monitored at 30 °C and at 40 °C to assess a potential effect of the laboratory scale and large scale on stability. All batches at room temperature and below were stable, and only a negligible increase in size was observed.

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1. Introduction

Nanostructured lipid carriers (NLCs) are derived from solid lipid nanoparticles (SLNs) by simply blending solid lipids with liquid lipids (oils), this blend also being solid at body temperature [1]. One major advantage is that NLC could increase loading with actives compared to SLN and lead to a firmer inclusion of the active inside the particle matrix during the shelf life [2]. Many researchers studied NLC over the time for various applications [3–5]. Ability of production of lipid nanoparticles at laboratory scale, pilot and large scale is essential, and the latter should provide not only the quantity but also lipid nanoparticles produced with optimized process parameters comparable to the laboratory scale. Some reports are available in the literature about the optimized process parameters of lipid nanoparticles from laboratory scale [6,7]. However, there is limited optimized process parameter data available when produced on a large scale.

High pressure homogenization (HPH) is capable of generating intense disruptive forces that break up the oil and water phases, leading to the formation of tiny oil droplets and increasing the surface activity of the emulsifying molecules [8]. This kind of high-energy approach utilizing mechanical devices is used since the 1950s for the production of emulsions. The first publications about the use of HPH for large-scale production of lipid nanoparticles date back to around 2000 [9]. Gohla developed medium scale production of SLN by HPH at a throughput of 60 kg/h in a continuous or discontinuous homogenization mode [10]. Then, Müller compared homogenizers with stepwise increasing capacity from laboratory scale (40 g) to medium scale (10 kg) and large scale (20/60 kg) [9]. To the best of our knowledge, a systematic study has not been published when introducing a reliable large-scale modular line (up to 24 kg/h) in the literature.

The major benefits of NLC are enhanced chemical stability of actives, controlled occlusion, skin hydration and increased bioavailability. Therefore, NLCs are on the market as concentrates to be used as cosmetic excipients [11]. Coenzyme Q_{10} (CoQ_{10}) is

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http://dx.doi.org/10.1016/j.ejpb.2016.10.018
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a crucial component in a variety of cellular processes, and it could undergo oxidation/reduction reactions by clearing reactive oxygen species and protecting cells against oxidative stress [12]. In addition, epidermis may represent a tissue that benefits most from topically applied CoQ_{10} against UV radiation and other environmental factors [13]. CoQ_{10} was determined to be effective against UVA-mediated oxidative stress in human keratinocytes [14]. Therefore, CoQ_{10} was chosen as a model active of low solubility and poor bioavailability due to the barrier function of stratum corneum [15].

In the present study, we demonstrated the industrial approach to produce NLC for topical administration of CoQ_{10} using biocompatible excipients (GMS, CCT, A25, and P135). Effects of several process parameters, such as the number of pre-emulsification temperature, homogenization pressure, and number of homogenization cycles on the size of CoQ_{10}-NLC were investigated. The developed formulations were characterized by quality systems. We also present a flexible production line and full automatic large-scale production line.

2. Materials and methods

2.1. Materials

Glycerin monostearate (GMS) and caprylic capric triglyceride (CCT) were purchased from ShenXian Nova Oil Co., Ltd. (Shandong, China), Coenzyme Q_{10} (CoQ_{10}) from Haotian Bioengineering Technology Co., Ltd. (Xi'an, China) and PEG 30 Dipolyhydroxystearate (P135) from Croda International Plc. (UK). Cremophor® A25 was purchased from BASF SE (Ludwigshafen, Germany). Ultrapure water was used in all the experiments. All other chemicals used were of analytical grade and commercially available products.

2.2. Laboratory scale production

The CoQ10-loaded NLC was prepared by the hot high pressure homogenization (Fig. 1). The formulation contains 1 % (w/w) CoQ10, 6 % (w/w) solid lipid (GMS) and 6 % (w/w) liquid lipid (CCT) used as oil phase, while 5 % (w/w) A25 and 3 % (w/w) P135 were used as stabilizer. Briefly, the desired amount of CoQ10 was dispersed in the melting lipid phase at around 70 °C. The obtained hot lipid phase was mixed to the isothermal dispersion medium (ultrapure water and stabilizer) by high-speed stirring by using an Ultra-Turrax (FM200, FLUKO Technology, Germany). The formed hot pre-emulsion was homogenized by high pressure homogenizer for three cycles at 600 bar. Eventually, lipid nanoparticles were formed by recrystallization of the dispersed lipid when the resulting dispersion was cooled at ambient conditions to room temperature. Laboratory-scale production of NLC is performed using a laboratory scale homogenizer (ATS, AH-80D). The batch size varied from 50 g to 200 g. As the process is discontinuous, the small product container collecting the homogenized dispersion needs to be almost emptied, and the dispersion poured back into the central feeding cylinder for the next homogenization cycle. When production is expanding, this kind of discontinuous process would become more inefficient.

2.3. Modular design of large-scale production line

Laboratory scale production is inefficient and discontinuous, thus not suitable for the industrial application. We tried to find an efficient and continuous way to realize the industrial requirements. Modular design is the answer. A continuous large-scale production line used in this work is shown in Fig. 2A and B. The line was composed of assist-process module, pretreatment module, operation module and after treatment module. The connecting pipes and containers were all double-walled allowing temperature control of pre-emulsification and homogenization. All modules allow also aseptic production. The whole line is made of high quality 304 stainless steel, which is malleable and highly corrosion-resistant. So, all the modules can be sterilized by streaming steam. Less thermal conductivity of the stainless steel also benefits temperature control.

The assist-process module could provide water of different temperature to water tank or clean-in-place (CIP). Temperature control is based on a water bath. The design is double-walled vessel with the corresponding circulation loop to achieve the constant temperature. Deionized water was heated by the assist-process module, and then pumped into the water tank, which belongs to the pretreatment module. CIP is a method of cleaning the interior surfaces of pipes, vessels, process equipment, filters and associated fittings, without disassembly.

For the emulsification and homogenization pretreatment, pretreatment module was used at specified frequency (range 0–50 kHz) for needed time (Fig. 2C). To ensure excipients in the oil tank could be completely discharged, we design a flush pump between the water tank and oil tank. Therefore, the delicate design could reduce risk of less active in the final product. Another noteworthy design is determination of place of oil tank. The place of the oil tank is obviously higher than that of other vessels, and the height difference was used to reduce pump energy consumption and control the production cost.

For the high pressure homogenization treatment, an operation module was used as shown in Fig. 2C, which consists of a HPH and a circulating tank. The sample was forced by a positive displacement (piston and plunger pump) and pumped into the homogenizing valve where the work is done. The sample was passed through a gap between the valve and the seat at specified pressure (range 0–1800 bar). The average size of the sample will be reduced by the shear stress when it was released externally by cavitation. In this process, shear stress is generated in the bulk of the product stream, which preserves the nanostructure of lipid carriers and leads to reduction of particle size. The other advantage of this module over laboratory scale emulsification is that it also can easily be scaled up because flow rate of sample solution could increase up to 0.4 kg/min. The last module is the after treatment module, which consists of a filtrator and final sample tank. When a failure happens on one HPH, then this spare machine in the middle of Fig. 2B takes over homogenization from the operation module. A batch size was 100 kg and the first run of production took 4 h for the continuous mode, but the next production cycle time could be shortened.

Thanks to the modular design of this large-scale production line, and the declarative way that pipes are configured rationally, assist-process module can easily be used across different modules and also can easily be combined with creative leverage of other modules, especial core module (operation module). Besides, the modular design was easily modified and upgraded.

2.4. Procedure of large-scale production

A large-scale production of CoQ10-NLC was prepared by several steps procedure as follows:

Step 1. Preparation of production

We received the material after the application was approved on the Enterprise Resource Planning (ERP) base on the production planning and task list. Then open the water pumps after heating the water to 70 °C to make the tanks warm up gradually. Excipi-

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