Journal of Colloid and Interface Science 418 (2014) 261–272

Contents lists available at ScienceDirect

Journal of Colloid and Interface Science

www.elsevier.com/locate/jcis

The effect of oil type on the aggregation stability of nanostructured lipid carriers

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ARTICLE INFO

Article history:
Received 22 October 2013
Accepted 11 December 2013
Available online 19 December 2013

Keywords:
Solid lipid nanoparticles
Nanostructured lipid carriers
Particle aggregation
Aggregation modeling

ABSTRACT

Second generation lipid systems for the delivery of bioactive compounds have been developed by mixing a liquid carrier oil with a solid lipid to form so-called nanostructured lipid carriers (NLCs). In this study, we investigated the effect of different liquid carrier oils on the crystallization and aggregation behavior of tristearin NLC dispersions. We found that NLC suspension stability was strongly affected by the type and amount of the carrier oil. As the oil concentration was increased, the crystallization and melting temperatures decreased, the polymorphic transformation rate increased, the particles became more spherical, and suspension stability was enhanced. These results suggest that oil trapped within the growing crystal matrix accelerated polymorphic transformation but retarded the large shape change normally associated with the transformation. We also found that considerably less surfactant was necessary to produce stable NLC suspensions than was required to stabilize solid lipid nanoparticle (SLN) suspensions without a carrier oil. Based on preliminary simulation results, we hypothesized that improved NLC suspension stability was attributable to both reduced particle shape change, which created less new surface area to be covered by surfactant, and increased mobility of surfactant molecules, which resulted in available surfactant being more efficient at covering created surface area.

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1. Introduction

Solid lipid nanoparticles (SLNs) offer great potential for delivery of pharmaceutical and bioactive compounds [1–8]. SLNs are commonly prepared by the hot homogenization method where a lipid emulsion is first prepared by high pressure homogenization above the lipid melting temperature followed by controlled cooling such that the lipid emulsion droplets crystallize and solid particles are formed [1,2]. Compared to other colloidal delivery systems, SLNs offer several advantages for encapsulation of active components including improved physical stability, protection to chemical degradation and precise control over release rates [1,3,4]. On the other hand, SLNs have distinct challenges including the tendency of the particles to aggregate when stored at room temperature and the associated rejection of the bioactive compound from the solid lipid matrix [1,2].

Many studies have shown that particle aggregation is driven by polymorphic transformation of the crystalline SLNs [9–11]. Triglycerides commonly used to form SLNs exhibit three different crystal polymorphs: the metastable α form, the unstable β′ form and the stable β form that have hexagonal, orthorhombic, and triclinic unit structures, respectively [2]. Following cooling, SLNs initially consist of α-form crystals that produce spherical particles. During storage at ambient temperatures, the α-form crystals transform into β-form crystals that produce platelet-shaped particles [12], resulting in a large increase in total particle surface area. Although the detailed mechanism is not known, this surface area increase appears to produce a decrease in surfactant coverage and the exposure of hydrophobic surfaces on the particles [10,12]. The exposed hydrophobic surfaces create attractive forces between particles that can result in aggregate formation [10]. We previously developed a population balance equation (PBE) model that captured this dynamic mechanism and qualitatively predicted the polymorph content and particle size distribution of aggregating SLN dispersions [13].

Although not included in our model, particle shape change alone is known to affect attractive forces between nanoparticles [14–16]. At separation distances smaller than the mean diameter, the attraction between anisometric particles such as plates, rectangular rods and cylinders is larger than for spherical particles of equal volume because a greater number of atoms are in close proximity [14]. Therefore, both the particle shape change and the resulting creation of hydrophobic surfaces caused by the polymorphic transformation are likely to play a role in SLN aggregation. Several studies have shown that the change in crystal packing that accompanies the polymorphic transformation leads to partial rejection of the encapsulated compound from the solid lipid matrix [1,2,6]. Consequently, SLN dispersion stability is intimately

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0021-9797/$ - see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.jcis.2013.12.024

connected to the bioactive compound encapsulation effectiveness of these colloidal delivery vehicles.

An effective means to improve the encapsulation efficiency of lipid nanoparticles is to mix the solid lipid with a liquid carrier oil prior to homogenization to form so-called nanostructured lipid carriers (NLCs) upon cooling of the emulsion [17–22]. Many studies have been performed to investigate the effects of the lipid/carrier oil system on NLC drug loading and release properties [23–32]. These studies suggest that incorporation of the carrier oil into the solid lipid matrix improves loading capacity, physical and chemical stability and triggered release by disrupting the crystal packing structure [20]. Moreover, NLC crystallization and melting temperatures and polymorphic content have been shown to be strongly dependent on the amount of oil added [17,19]. However, the effect of oil type on NLC polymorphic behavior and shape change remains poorly understood [18,20].

While the use of NLCs to enhance bioactive compound encapsulation and delivery has received considerable attention, the impact of the carrier oil on NLC dispersion stability has not been extensively investigated. In one study in which NLCs were prepared with tripalmitin as the lipid and fish oil as the carrier oil, the oil was shown to inhibit the large shape change normally associated with the polymorphic transformation, putatively reducing hydrophobic attraction between particles [19]. The NLC lipid crystals appeared to be less ordered than SLN crystals as lower melting and crystallization temperatures were observed in the presence of oil. In another study with glyceryl behenate (Compritol 888 ATO) used as the lipid and caprylic/capric triglycerides (Miglyol 812) used as the oil, NLC dispersions were shown to be most stable in the absence of oil and at high oil concentrations [17]. The large fraction of monoglycerides and diglycerides in Compritol was argued to be responsible for the long-term stability of SLN dispersions in the absence of oil. The highly disordered state of Compritol NLCs with high concentrations of Miglyol was believed to delay recrystallisation and improve physical stability. However, another series of studies on Compritol/Miglyol NLCs showed that the lipid crystals were not disturbed in their structure as expected by oil addition [33–35]. Instead, these studies indicated that the NLCs consisted of an external liquid compartment on the particle surface that strongly interacted with the solid lipid. Therefore, NLCs may not be solid lipid nanoparticles with embedded liquid droplets as reported in the literature [18,20], but rather they may consist of an oil layer between the solid lipid and the surfactant layer [33–35].

In this paper, we investigate the effect of carrier oil type and concentration on the polymorphic behavior and aggregation stability of NLCs prepared with the model lipid tristearin. Four pure oils with different structures and two naturally occurring oil mixtures were tested to understand the factors that govern the melting and crystallization temperatures, polymorphic form, particle shape and size distribution of the NLC dispersions. The surfactant concentration was varied for one tristearin/oil system to further examine NLC dispersion stability. To better understand the effect of particle shape change, we modified our previously developed population balance equation model of SLN aggregation dynamics to account for the presence of the carrier oil. We believe that this study represents the first comprehensive investigation of the effect of carrier oil on NLC dispersion stability and represents a first step towards developing rational NLC design strategies.

2. Materials and methods

2.1. Materials

Tristearin, triolein and tricaprylin were purchased from TCI America (Portland, OR). Oleic acid, pentadecane and palm oil were purchased from Fisher Scientific (Pittsburgh, PA). Colavita olive oil was purchased from a local grocery store. As shown in Table 1, the four pure oils provided a wide range of different melting points and molecular structures. Typical carbon chain distributions of the two common oils listed in Table 2 shows the heterogeneous nature of these materials [36]. The surfactant Tween 60 was supplied by Procter and Gamble. All materials were used as received.

2.2. SLN and NLC preparation

SLNs and NLCs were prepared by using the hot homogenization method. The lipid phase for NLCs was prepared by mixing tristearin and a particular oil at a temperature of 85 °C, approximately 10 °C above the melting point of tristearin. The lipid phase for SLNs consisted of tristearin without additional oil. The aqueous phase was prepared by mixing deionized nanopure water with Tween 60 surfactant followed by heating to 85 °C. Coarse oil-in-water emulsions with 10 wt% total lipid (tristearin and oil) and 2 wt% surfactant were prepared by mixing the lipid and aqueous phases at 85 °C using a high speed blender (Ultra-Turrax Model T18, IKA-Works Inc.) for 5 min at 13,000 rpm. For tristearin/triolein NLCs, the triolein content of the lipid phase was varied from 2.5 wt% to 50 wt%. For the other oils, the oil content was varied from 2.5 wt% to 20 wt%. Fine emulsions were prepared by passing the coarse emulsion through a high pressure homogenizer (Emulsiflex C-3, Avestin Inc.) 5 times at 500 bar. The temperature was maintained at 85 °C throughout the homogenization process. The coarse and fine emulsions were cooled in a refrigerator (5 °C) for 12 h to obtain SLN and NLC dispersions, which were subsequently stored at room temperature.

2.3. SLN and NLC characterization

2.3.1. Particle size distribution

Particle size distributions of SLN and NLC dispersions were measured by static light scattering (Mastersizer 2000, Malvern Instruments). Refractive indices of 1.54 for the particles and 1.33 for water were used to calculate particle size distributions [37]. The Mastersizer analyzer calculates the size of non-spherical particles as the diameter of a volume equivalent sphere. We assumed that aggregate breakage within the Mastersizer was negligible.

2.3.2. Differential scanning calorimetry (DSC)

A differential scanning calorimeter (Q100-0416, TA Instruments) was used to determine melting and crystallization temperatures and the polymorph content of SLN and NLC dispersions. A 7–10 mg sample drawn from the dispersion was placed in a hermetic aluminum pan and sealed. An empty pan was used as a reference. The dispersions were scanned in the temperature range of 40–90 °C with constant heating and cooling rates (10 °C/min). The melting and crystallization temperatures were identified from the peak heat flow of the melting and crystallization cycles. To better understand the rate of polymorphic transformation, a so-called quick DSC scan was performed for each sample. The sample was fully melted by holding the temperature at 90 °C for 1 min and then cooled to 0 °C at rate of 10 °C/min to reform solid particles.

Table 1
Physicochemical property data for the pure oils.

Material	Melting point (°C)	Structure
Tristearin	73	C18:0 triglycerides
Triolein	5	C18:1 triglycerides
Tricaprylin	10	C8:0 triglycerides
Oleic acid	13	C18:1 fatty acid
Pentadecane	12	C15 hydrocarbon

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