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The controlled aggregation and tunable viscosity of nanostructured lipid carrier dispersions

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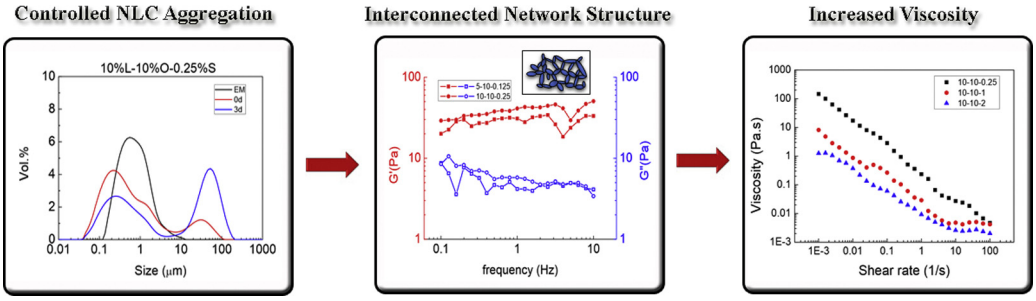
GRAPHICAL ABSTRACT



HIGHLIGHTS

- NLC suspension viscosity can be modified by controlling particle aggregation.
- The degree of aggregation can be controlled by tuning surfactant and/or oil content.
- Non-aggregated dispersions exhibited typical behaviors of a viscoelastic liquid.
- Aggregated dispersions exhibited typical behaviors of a viscoelastic solid.
- Aggregated samples appeared to have an interconnected network structure.

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ABSTRACT

Applications of solid lipid nanoparticles (SLNs) in drug delivery and the encapsulation of bioactive, lipophilic compounds have been hindered by the tendency of SLN suspensions to undergo uncontrolled aggregation due to polymorphic transformation of the lipid crystals. Second generation lipid nanoparticle systems have been developed by mixing liquid lipid with solid lipid to form more stable nanostructured lipid carriers (NLCs). In this study, we investigated the effect of chemical formulation on the aggregation behavior and rheology of NLC dispersions. We found that NLC suspension viscosity could be modified by an order of magnitude by controlling particle aggregation with different surfactant and/or oil concentrations. The viscosity could be tuned by decreasing the amount of surfactant and/or oil to achieve a desired level of particle aggregation. Oscillatory sweep tests showed that non-aggregated and aggregated dispersions exhibited typical behaviors of a viscoelastic liquid and a viscoelastic solid, respectively. Modeling

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results suggested a stronger particle–particle bonding force and a higher aggregation efficiency as the amount of surfactant and/or oil was decreased. Both experimental and modeling results indicated that aggregated samples had an interconnected network structure, while no indication of network formation was observed for non-aggregated samples. Collectively these results suggest that controlled NLC aggregation can be exploited to develop dispersions with tunable viscosity for applications such as rheology modification.

Nomenclature

a	particle radius, m
d_f	fractal dimension of aggregates, dimensionless
d_l	chemical dimension of chains, dimensionless
F_c	bonding force between particles, N
G^*	complex modulus, Pa
G'	storage modulus, Pa
G''	loss modulus, Pa
h_c	equilibrium value of the gap width between particles, m

Greek letters

α	aggregation efficiency, dimensionless
γ	shear rate, s^{-1}
δ	phase angle, °
η	viscosity of the dispersion, Pa s
μ	viscosity of the continuous phase, Pa s
σ^*	yield stress, Pa
ϕ_a	volume fraction of aggregates, dimensionless
ϕ_m	maximum packing fraction, dimensionless
ϕ_p	volume fraction of particles, dimensionless

Acronyms

NLC	nanostructured lipid carrier
SLN	solid lipid nanoparticle

1. Introduction

Solid lipid nanoparticles (SLNs) hold considerable promise for the delivery of pharmaceutical and other bioactive compounds [1–8]. Compared to alternative colloidal delivery systems, SLNs offer several advantages for encapsulation of bioactive components including improved physical stability, protection against chemical degradation, no biotoxicity, precise control over release rates, and easier manufacturing scale-up [1,3,4]. On the other hand, a major obstacle to the industrial use of SLNs is their strong tendency to undergo uncontrolled aggregation during storage at room temperature and the associated rejection of the bioactive compound from the solid lipid matrix [1,2]. Several studies have indicated that particle aggregation is driven by the creation of hydrophobic surfaces when the lipid undergoes a polymorphic transformation from unstable α-form crystals into stable β-form crystals. These hydrophobic patches cannot be covered due to surfactant immobility and induce interparticle attraction that eventually results in uncontrolled aggregation [9–13]. More ordered crystal packing that accompanies the polymorphic transformation leads to partial rejection of the encapsulated ingredient from the solid lipid matrix [1,2,6].

The second generation of lipid nanoparticles, commonly termed nanostructured lipid carrier (NLC), was developed by mixing a liquid lipid (carrier oil) with the solid lipid prior to particle formation [6,14–19]. The incorporation of carrier oil into the solid lipid matrix improves physical and chemical stability, loading capacity, and allows for controlled release by disrupting the crystal packing structure [16]. Many studies have been performed to investigate the effects of the solid lipid/carrier oil system on drug loading and release properties [20–29]. Moreover, the stability of the dispersion against aggregation has been shown to be highly improved [15,30].

Rheological properties such as viscosity are critical parameters of lipid nanoparticle dispersions for typical applications such as pharmaceutical, and cosmetic products [31–37]. A common method to produce lipid nanoparticle systems with the desired rheological properties involves incorporating the SLN or NLC dispersion into topical vehicles such as creams or hydrogels [38–40]. This approach has several disadvantages, including limited SLN/NLC loading, possible incompatibilities with the added viscosity enhancer and more complex manufacturing steps [34,41]. Consequently, the creation of NLC dispersions with rheological properties that can be tailored without the use of additional ingredients is highly desirable.

A few previous studies have focused on the influence of key SLN properties (particle size, physical state of the lipid, emulsifier amount) on the rheological properties of the dispersion as well as understanding how the formulation can be modified to produce dispersions with the desired rheological properties without adding further ingredients [32–34]. Our previous study on NLC aggregation stability demonstrated that aggregation can be essentially eliminated by increasing the oil content of the particle and/or the amount of surfactant [30]. We hypothesized that the rheological properties of NLC dispersions could be tuned by controlling the degree of aggregation since properties such as viscosity should depend on the aggregated particle network structure [34,42,43]. To the best of our knowledge, the rheological properties of NLC dispersions with controlled aggregation have not been investigated.

In this study, we investigated the effect of formulation variables (dispersed phase, carrier oil and surfactant concentrations) on particle aggregation and rheological properties of NLC dispersions. Tristearin and triolein were selected as the solid lipid and carrier oil, respectively, since we have used this model system in our previous work on NLC dispersion stability [30]. A previously developed model for weakly aggregated dispersions [42,43] was fit to our experimental data to provide insights into the aggregation effect. We believe that our study represents the first comprehensive investigation focused on controlling aggregation to tune the rheological properties of NLC dispersions and therefore an important step toward developing rational NLC design strategies for bioactive compound delivery and rheology modification.

2. Materials and methods

2.1. Materials

Tristearin and triolein were purchased from TCI America (Portland, OR). The surfactant Tween 60 was supplied by Procter and Gamble. All materials were used as received.