Solid Lipid Nanoparticles/Nanostructured Lipid Carriers in Acne VulgarisTreatment

Subjects: Pharmacology & Pharmacy

Contributor: Romchat Chutoprapat , Peerawas Kopongpanich , Lai Wah Chan

Acne vulgaris (acne) is one of the most common dermatological problems affecting adolescents and young adults. Although acne may not lead to serious medical complications, its psychosocial effects are tremendous and scientifically proven. The first-line treatment for acne is topical medications composed of synthetic compounds, which usually cause skin irritation, dryness and itch. Therefore, naturally occurring constituents from plants (phytochemicals), which are generally regarded as safe, have received much attention as an alternative source of treatment. However, the degradation of phytochemicals under high temperature, light and oxygen, and their poor penetration across the skin barrier limit their application in dermatology. Encapsulation in lipid nanoparticles is one of the strategies commonly used to deliver drugs and phytochemicals because it allows appropriate concentrations of these substances to be delivered to the site of action with minimal side effects. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are promising delivery systems developed from the combination of lipid and emulsifier. They have numerous advantages that include biocompatibility and biodegradability of lipid materials, enhancement of drug solubility and stability, ease of modulation of drug release, ease of scale-up, feasibility of incorporation of both hydrophilic and lipophilic drugs and occlusive moisturization, which make them very attractive carriers for delivery of bioactive compounds for treating skin ailments such as acne.

solid lipid nanoparticles nanostructured lipid carriers topical application phytochemicals acne vulgaris

1. Introduction

The cause of acne is multifactorial, with four primary factors including excess sebum production, *Cutibacterium acnes* (formerly *Propionibacterium acnes* (*P. acnes*)) colonization, follicular hyperkeratinization, and release of inflammatory mediators into the skin. There are standard acne treatments that vary according to the stage or severity of the disease. The first-line treatment for mild to moderate *acne vulgaris* is topical medications composed of synthetic compounds or their combination with oral antibiotics. However, most of these topical medications usually cause side effects such as irritation, dryness, scaling and itch to the skin. Therefore, the use of phytochemicals has been studied as an alternative treatment to resolve unpleasant side effects due to the synthetic compounds.

Nevertheless, the major challenges of phytochemicals derived from the plants are their instability and poor penetration across the skin barrier which may limit their application in dermatology. The use of lipid carriers, such

as solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), can increase the absorption rate and facilitate the sustained release of active substances. Moreover, these carriers can protect the active substances from degradation [1]. Solid lipid nanoparticles (SLNs) are nanospheres prepared from solid lipids and surfactants. SLNs have been applied in a wide variety of cosmetics and pharmaceutical preparations due to their various advantages such as good stability, rigid morphology, good biocompatibility, ease of scale-up, ease of modulation of drug release, and the avoidance of organic solvents in the preparation [2][3]. Moreover, SLNs have an occlusive property which can reduce the trans-epidermal water loss and make the skin hydrated [4]. However, SLNs show a low drug loading capacity. Therefore, nanostructured lipid carriers (NLCs), the second generation of lipid nanoparticles, were developed to address this problem of SLNs. NLCs are prepared by incorporating liquid lipid to solid lipid in order to impart imperfections to the crystal order of the solid lipid, thereby facilitating the incorporation of higher amount of drug while preserving the stability of the NLCs [3]. Both SLNs and NLCs can play an important role in anti-acne therapy owing to their ability to penetrate into the hair follicle and sebaceous gland, occlusive and skin hydration effects [5].

2. Solid Lipid Nanoparticles (SLNs)

The SLNs are nanosized lipid particles comprising solid lipids dispersed in aqueous surfactant media. The lipids commonly used in the preparation of SLNs are biodegradable lipids with high melting point such as triglycerides, partial glycerides, fatty acids, fatty alcohols, and waxes [6]. Surfactants are used to stabilize the structure of SLNs by decreasing surface tension between aqueous media and lipid [7]. It was reported that the higher the surfactant concentration, the smaller the particle size of SLNs obtained. However, a high concentration of surfactants may cause toxicity [8]. Therefore, the surfactant concentration used in the development of SLNs has to be optimized. Particle size of SLNs is one of the most important parameters affecting the drug delivery efficiency. Some studies have shown that the skin permeability of SLNs increases when their particle size decreases, and the sub-100 nm size range is optimal for skin delivery because they can penetrate into deeper skin layers through hair follicles [9]. In addition, SLNs may enhance the penetration of drugs through the stratum corneum due to their occlusive property [4]. The incorporation of drugs into SLNs can be described by three models, namely homogeneous matrix, drug-enriched shell, and drug-enriched core (**Figure 1**).

- Homogeneous matrix model: the drug is dispersed in lipid matrix without the use of solubilizers or surfactants. This model is usually prepared by the cold homogenization technique [10].
- The drug-enriched shell model: a mixture of lipid and drug is heated at temperature above the melting point of the lipid. On rapid cooling, lipid precipitates at the core whereas the drug is concentrated at the outer melted lipid. The drug-enriched shell is completely formed when the melted mixture is cooled to room temperature [11].
- The drug-enriched core model: the concentration of drug in the melted lipid is close to its saturation solubility. The cooling process creates supersaturation of the drug in the melted lipid, resulting in drug precipitation at the core prior to lipid crystallization. Further cooling will lead to the crystallization of the lipid surrounding the drug

core as a shell [12]. The drug-enriched shell and the drug-enriched core models are usually produced by hot homogenization technique.

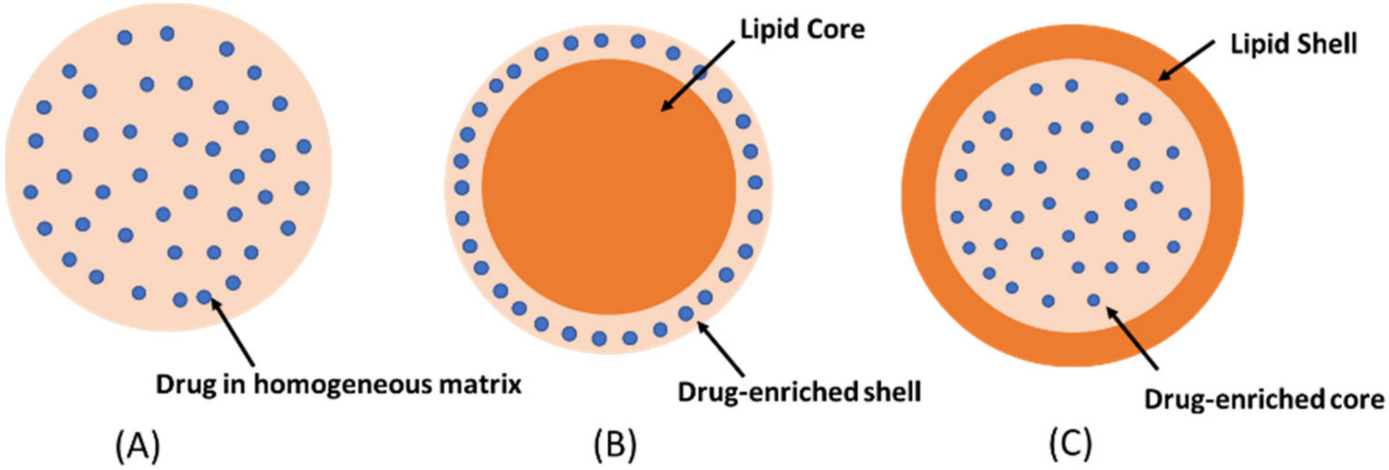

Figure 1. The drug incorporation models of SLNs (**A**) homogeneous matrix, (**B**) drug-enriched shell, (**C**) drug-enriched core.

3. Nanostructured Lipid Carriers (NLCs)

Nanostructured lipids carriers (NLCs) were developed to improve encapsulation capacity and storage stability of SLNs. The NLCs are composed of a mixture of solid and liquid lipids, with typical percentage of liquid lipid in the range of 10–30%. The presence of liquid lipid in the lipid mixture produces a nanostructure matrix which can accommodate a greater load of drug [13]. In addition, the high loading capacity of NLCs will enable a high drug concentration gradient on the skin, which will in turn improve drug permeation [4]. NLCs also have various advantages similar to SLNs such as the use of biodegradable and biocompatible lipids, controlled drug release, enhanced drug penetration and stability, ease of fabrication and avoidance of organic solvents in preparation [14]. Based on the nature of lipid content and ratios of solid and liquid lipids, NLCs can be classified into three types including imperfect crystal type, amorphous type, and multiple oil-in-fat-in-water (O/F/W) type (**Figure 2**) [15].

- Imperfect crystal type: this type involves mixing of spatially different liquid lipids such as glycerides and solid lipids which introduce imperfections in the crystal order leading to more space for drug loading. The imperfection can be increased by using a mixture of various glycerides which vary in saturation and length of carbon chains.

- Amorphous type: this type is formed by incorporating special liquid oils such as isopropyl myristate or hydroxyoctacosanyl hydroxystearate in a lipid matrix. The matrix will solidify in an amorphous form that potentially reduces the expulsion of the loaded drug by delaying the crystallization of lipids during the preparation and storage of the NLCs

- Multiple O/F/W type: this type is formed by adding high amount of liquid lipid beyond its solubility in the lipid matrix. This will create oil nanocompartments distributed in the solid matrix. Drug solubility in oil nanocompartment is higher than in solid matrix which enables higher drug loading. Moreover, a solid lipid matrix around the oil nanocompartments acts as a barrier that prevents drug leakage and provides controlled drug release.

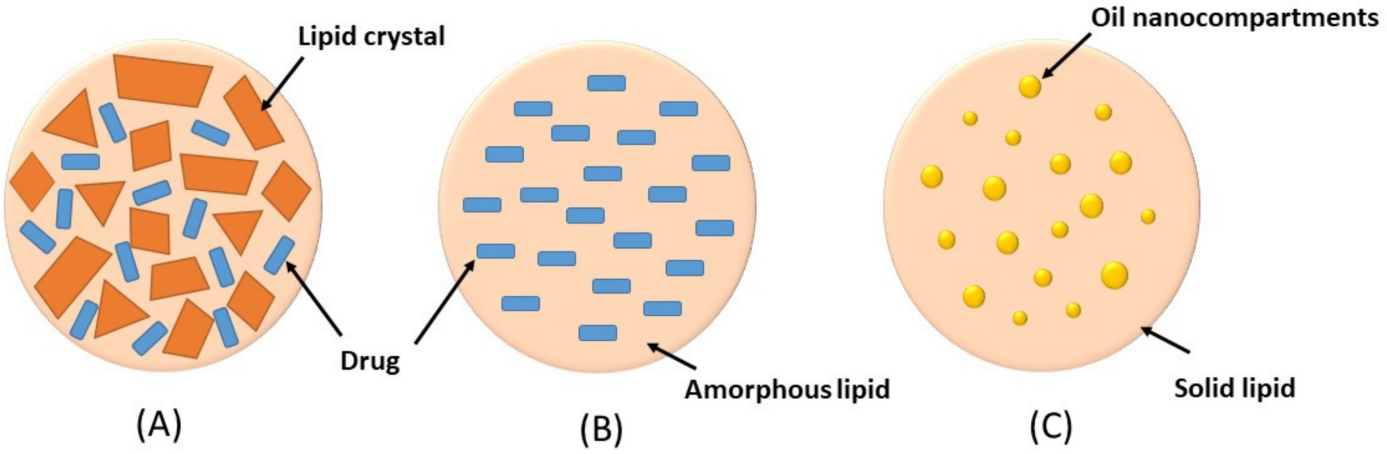

Figure 2. Types of NLCs (**A**) imperfect crystal type, (**B**) amorphous type, (**C**) multiple oil-in-fat-in-water type.

4. SLNs and NLCs as Topical Carriers for Anti-Acne Phytochemicals

SLNs and NLCs were broadly studied and used in a wide variety of pharmaceutical and cosmetic applications including anti-acne.

4.1. SLNs as a Promising Carrier System for the Topical Delivery of Anti-Acne Phytochemicals

SLNs loaded with resveratrol, vitamin E, and epigallocatechin gallate (EGCG) for skincare applications have been developed by Chen et al. in 2017. The study showed that lipid nanoparticles provided protective effect against UV-induced degradation of resveratrol and vitamin E and improved skin penetration of resveratrol [16]. Previous studies showed that the topical formulations containing resveratrol and EGCG were effective in reducing inflammation, sebum production, and the viability of *P. acnes* [17] as well as reducing the severity of *acne vulgaris* in patients [18]. Shrotriya et al. (2018) developed SLNs gel loaded with curcumin with the aim of improving its efficacy. Curcumin is a phytochemical extracted from the rhizome of *Curcuma longa* (Zingiberaceae family). Curcumin has anti-inflammatory and antimicrobial activities which may combat the bacteria that contribute to acne. The results demonstrated that SLNs-based gel gave better occlusive effects and skin accumulation of curcumin compared to plain gel. The optimized curcumin-loaded SLNs had mean particle size of 51 nm and entrapment efficiency of 93% [19]. According to Kakkar et al. (2018), SLNs loaded with tetrahydrocurcumin (THC), a partially reduced derivative of curcumin, provided great occlusive effect. The THC- loaded SLNs in gel formulation demonstrated better

therapeutic effects than free THC [20]. It was also found that the formulation containing just 10% SLNs resulted in better occlusion properties than the gold standard (Vaseline) [21]. Talarico et al. (2021) reported that the controlled release of Quercetin, a poorly water-soluble flavonoid, over 26 h was achieved with SLNs composed of stearic acid as core lipid and Arabic Gum as stabilizer. In addition, the SLNs were found to enhance antioxidant activity compared to free Quercetin [22]. Eugenol is a natural compound widely found in many aromatic plant species such as clove, holy basils, and betel vine. It has shown anti-acne activity by suppressing *P. acnes*-induced inflammatory reaction [23].

4.2. NLCs as a Promising Carrier System for the Topical Delivery of Anti-Acne Phytochemicals

Rapalli et al. (2020) developed curcumin-loaded NLCs with the aim of improving its skin permeability. The results indicated that the skin permeation of curcumin-loaded NLCs was three times higher than that of curcumin alone. Moreover, curcumin loaded-NLCs showed extended in vitro release up to 48 h [24]. Lacatusu et al. (2017) studied the anti-inflammatory activity of the marigold extract and azelaic acid co-loaded NLCs. The results showed that the NLCs could reduce inflammatory IL-6 and IL-1β cytokines tested by ELISA method and paw edema in rats challenged with carrageenan [25]. Moreover, a synergistic effect of carrot extract (CE) combined with azelaic acid (AA) in NLCs on anti-inflammatory and anti-acne activities was observed by Lacatusu et al. (2020). The results revealed that the NLCs exerted superior anti-inflammatory effect compared with the commercial product. Furthermore, the expression of inflammatory IL-1β and TNF-α cytokines was decreased in the cells treated with CE-AA loaded NLCs [26][27]. Salicin is an alcoholic β-glucoside found in willow bark extract which is used to treat skin diseases such as acne due to its anti-inflammatory and high comedolytic activities. According to Arsenie et al. (2020), NLCs loaded with a mixture of white willow bark extract (WBE), azelaic acid and panthenol were able to improve the epidermal cell reconstruction. The gel containing the NLCs gave a degree of hydration of 84 % in the T-zone for type-III skin (predisposed to acne) [28]. Asiaticoside, madecasosside, asiatic acid, and madecassic acid are the phytochemicals found in *Centella asiatica* which exhibit multi-therapeutic effects including antioxidant, anti-inflammatory, antimicrobial, and anticarcinogenic activities [29]. NLCs were found to enhance the membrane fluidity of stratum corneum which enabled the asiaticoside in *Centella asiatica* to penetrate the skin [30].

5. Conclusions

The SLNs and NLCs are attractive and promising lipid nanocarriers for topical delivery of phytochemicals due to their desirable properties that include skin penetration enhancement, promising occlusive effect, possibility to modulate drug release kinetics, ability to prevent the degradation of phytochemicals and suitability as carriers for both hydrophilic and lipophilic active substances. Moreover, the SLNs and NLCs can be applied onto damaged or inflamed skin because they are composed of biocompatible and non-toxic lipids. However, it is worth highlighting that although remarkable results of SLNs and NLCs as delivery systems for anti-acne phytochemicals have been demonstrated by many research groups, their in vivo efficacy in treating acne has not been fully established yet. Hence, further investigation on the potential of these lipid carriers in clinical setting is highly warranted and strongly

encouraged. This would bring a new perspective on SLNs and NLCs as phytochemical carriers for topical treatment of acne.

References

1. Garg, T. Current nanotechnological approaches for an effective delivery of bio-active drug molecules in the treatment of acne. Artif. Cells Nanomed. Biotechnol. 2016, 44, 98–105.
2. Battaglia, L.; Gallarate, M. Lipid nanoparticles: State of the art, new preparation methods and challenges in drug delivery. Expert Opin. Drug Deliv. 2012, 9, 497–508.
3. Beloqui, A.; Solinís, M.; Rodríguez-Gascón, A.; Almeida, A.J.; Préat, V. Nanostructured lipid carriers: Promising drug delivery systems for future clinics. Nanomedicine 2016, 12, 143–161.
4. Jain, S.; Patel, N.; Shah, M.K.; Khatri, P.; Vora, N. Recent advances in lipid-based vesicles and particulate carriers for topical and transdermal application. J. Pharm. Sci. 2017, 106, 423–445.
5. Verma, S.; Utreja, P.; Duvedi, D.R.; Prasad, D.; Kumar, L. Nanotechnological carriers for treatment of acne. Recent Pat. Antiinfect Drug Discov. 2018, 13, 105–126.
6. Mukherjee, S.; Ray, S.; Thakur, R.S. Solid lipid nanoparticles: A modern formulation approach in drug delivery system. Indian J. Pharm. Sci. 2009, 71, 349–358.
7. Mishra, V.; Bansal, K.K.; Verma, A.; Yadav, N.; Thakur, S.; Sudhakar, K.; Rosenholm, J.M. Solid lipid nanoparticles: Emerging colloidal nano drug delivery systems. Pharmaceutics 2018, 10, 191.
8. Smith, T.; Affram, K.; Nottingham, E.L.; Han, B.; Amissah, F.; Krishnan, S.; Trevino, J.; Agyare, E. Application of smart solid lipid nanoparticles to enhance the efficacy of 5-fluorouracil in the treatment of colorectal cancer. Sci. Rep. 2020, 10, 16989.
9. Mardhiah Adib, Z.; Ghanbarzadeh, S.; Kouhsoltani, M.; Khosroshahi, A.Y.; Hamishehkar, H. The effect of particle size on the deposition of solid lipid nanoparticles in different skin layers: A histological study. Adv. Pharm. Bull. 2016, 6, 31–36.
10. Zur Mühlen, A.; Mehnert, W. Drug release and release mechanisms of prednisolone loaded solid lipid nanoparticles. Pharmazie 1998, 53, 552–555.
11. Müller, R.H.; Radtke, M.; Wissing, S.A. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. Adv. Drug Deliv. Rev. 2002, 54 (Suppl. S1), S131–S155.
12. Wissing, S.A.; Muller, R.H. The influence of the crystallinity of lipid nanoparticles on their occlusive properties. Int. J. Pharm. 2002, 242, 377–379.

13. Iqbal, M.A.; Md, S.; Sahni, J.K.; Baboota, S.; Dang, S.; Ali, J. Nanostructured lipid carriers system: Recent advances in drug delivery. J. Drug Target. 2012, 20, 813–830.
14. Liu, C.H.; Wu, C.T. Optimization of nanostructured lipid carriers for lutein delivery. Coll. Surf. A Physicochem. Eng. Asp. 2010, 353, 149–156.
15. Khosa, A.; Reddi, S.; Saha, R.N. Nanostructured lipid carriers for site-specific drug delivery. Biomed. Pharmacother. 2018, 103, 598–613.
16. Chen, J.; Wei, N.; Lopez-Garcia, M.; Ambrose, D.; Lee, J.; Annelin, C.; Peterson, T. Development and evaluation of resveratrol, Vitamin E, and epigallocatechin gallate loaded lipid nanoparticles for skin care applications. Eur. J. Pharm. Biopharm. 2017, 117, 286–291.
17. Yoon, J.Y.; Kwon, H.H.; Min, S.U.; Thiboutot, D.M.; Suh, D.H. Epigallocatechin-3-gallate improves acne in humans by modulating intracellular molecular targets and inhibiting P. acnes. J. Investig. Dermatol. 2013, 133, 429–440.
18. Szulc-Musioł, B.; Sarecka-Hujar, B. The use of micro- and nanocarriers for resveratrol delivery into and across the skin in different skin diseases—A Literature Review. Pharmaceutics 2021, 13, 451.
19. Shrotriya, S.; Ranpise, N.; Satpute, P.; Vidhate, B. Skin targeting of curcumin solid lipid nanoparticles-engrossed topical gel for the treatment of pigmentation and irritant contact dermatitis. Artif. Cells Nanomed. Biotechnol. 2018, 46, 1471–1482.
20. Kakkar, V.; Kaur, I.P.; Kaur, A.P.; Saini, K.; Singh, K.K. Topical delivery of tetrahydrocurcumin lipid nanoparticles effectively inhibits skin inflammation: In vitro and in vivo study. Drug Dev. Ind. Pharm. 2018, 44, 1701–1712.
21. Hamishehkar, H.; Same, S.; Adibkia, K.; Zarza, K.; Shokri, J.; Taghaee, M.; Kouhsoltani, M. A comparative histological study on the skin occlusion performance of a cream made of solid lipid nanoparticles and Vaseline. Res. Pharm. Sci. 2015, 10, 378–387.
22. Talarico, L.; Consumi, M.; Leone, G.; Tamasi, G.; Magnani, A. Solid lipid nanoparticles produced via a coacervation method as promising carriers for controlled release of Quercetin. Molecules 2021, 26, 2694.
23. Tsai, T.H.; Huang, W.C.; Lien, T.J.; Huang, Y.H.; Chang, H.; Yu, C.H.; Tsai, P.J. Clove extract and eugenol suppress inflammatory responses elicited by Propionibacterium acnes in vitro and in vivo. Food Agric. Immunol. 2017, 28, 916–931.
24. Rapalli, V.K.; Kaul, V.; Waghule, T.; Gorantla, S.; Sharma, S.; Roy, A.; Dubey, S.K.; Singhvi, G. Curcumin loaded nanostructured lipid carriers for enhanced skin retained topical delivery: Optimization, scale-up, in-vitro characterization and assessment of ex-vivo skin deposition. Eur. J. Pharm. Sci. 2020, 152, 105438.

25. Lacatusu, I.; Badea, G.; Popescu, M.; Bordei, N.; Istrati, D.; Moldovan, L.; Seciu, A.M.; Panteli, M.I.; Rasit, I.; Badea, N. Marigold extract, azelaic acid and black caraway oil into lipid nanocarriers provides a strong anti-inflammatory effect in vivo. Ind. Crops Prod. 2017, 109, 141–150.
26. Lacatusu, I.; Istrati, D.; Bordei, N.; Popescu, M.; Seciu, A.M.; Panteli, L.M.; Badea, N. Synergism of plant extract and vegetable oils-based lipid nanocarriers: Emerging trends in development of advanced cosmetic prototype products. Mater. Sci. Eng. C 2020, 108, 110412.
27. Istrati, D.; Lacatusu, I.; Bordei, N.; Badea, G.; Oprea, O.; Stefan, L.M.; Stan, R.; Badea, N.; Meghea, A. Phyto-mediated nanostructured carriers based on dual vegetable actives involved in the prevention of cellular damage. Mater. Sci. Eng. C 2016, 64, 249–259.
28. Arsenie, L.V.; Lacatusu, I.; Oprea, O.; Bordei, N.; Bacalum, M.; Badea, N. Azelaic acid-willow bark extract-panthenol—Loaded lipid nanocarriers improve the hydration effect and antioxidant action of cosmetic formulations. Ind. Crops Prod. 2020, 154, 112658.
29. Sun, B.; Wu, L.; Wu, Y.; Zhang, C.; Qin, L.; Hayashi, M.; Kudo, M.; Gao, M.; Liu, T. Therapeutic potential of Centella asiatica and its triterpenes: A review. Front. Pharmacol. 2020, 11, 568032.
30. Da Rocha, P.B.R.; Souza, B.S.; Andrade, L.M.; Dos Anjos, J.L.V.; Mendanha, S.A.; Alonso, A.; Marreto, R.N.; Taveira, S.F. Enhanced asiaticoside skin permeation by Centella asiatica-loaded lipid nanoparticles: Effects of extract type and study of stratum corneum lipid dynamics. J. Drug Deliv. Sci. Technol. 2019, 50, 305–312.