Current Application of DNSPEs in Drug Delivery

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A drug nanocrystal self-stabilized Pickering emulsion (DNSPE) is a novel Pickering emulsion with drug nanocrystals as the stabilizer. As a promising drug delivery system, DNSPEs have attracted increasing attention due to their high drug loading capacity and ability to reduce potential safety hazards posed by surfactants or specific solid particles.

Pickering emulsion drug delivery nanocrystals

1. Oral Administration of DNSPEs

The first drug delivery system based on a DNSPE was reported by Yi; it was used to improve the oral bioavailability of silybin [1]. Silybin is used to treat acute and chronic hepatitis, cirrhosis, and toxic liver injury in clinics due to its beneficial effects in protecting normal liver cells and helping damaged liver cells to recover. However, the oral bioavailability of silybin is low owing to its poor water solubility and membrane permeability. A Pickering emulsion stabilized by silybin nanocrystals (SN-DNSPE) was prepared by mixing silybin nanocrystals of about 300 nm with Capmul C8 by high-pressure homogenization. The resultant emulsion droplet size was 27.3 μm. SN-DNSPE was much more stable than the nanocrystal suspension of silybin. It remained stable at room temperature for more than 40 days, whereas the nanocrystal suspension began to layer after only 4 days. The AUC and the C_{max} of silybin in the DNSPE were 4.0 and 1.6 times and 3.6 and 2.5 times greater than those of the crude material suspension and nanocrystal suspension, respectively, following gavage administration to rats, indicating that the DNSPE significantly improved the oral absorption of silybin and the improvement was even better than that of the nanocrystal suspension.

Up to now, DNSPEs have been employed to deliver many other poorly water-soluble drugs orally, such as curcumin, quercetin, ginkgolide B, puerarin, and even traditional Chinese medicinal compounds. Curcumin is an effective anti-inflammatory agent extracted from turmeric’s rhizome. However, its clinical applications have been limited by its extremely low oral bioavailability. A curcumin nanocrystal self-stabilized Pickering emulsion (Cur-DNSPE) with a droplet size of 163.66 ± 6.78 nm was prepared [2]. The cumulative release of curcumin in vitro was enhanced, and the transport of curcumin across Caco-2 cells was promoted, which led to enhanced oral bioavailability and anti-inflammatory effects in rats. The expression of inflammatory factors NO, IL-6, TNF-a, MDA, IgE, and ICAM-1 was inhibited and the expression of IL-10 and SOD was improved significantly.

Quercetin exhibits a variety of pharmacological activities, including anti-inflammatory, antioxidant, anti-hypertensive, and neuroprotective. However, its solubility in water is only 0.01 $mg \cdot mL^{-1}$, restricting its oral absorption. Wang et al. [3] developed a DNSPE stabilized by quercetin nanocrystals with a drug loading of 5.35 $mg \cdot mL^{-1}$ using Labrafac Lipophile WL 1349 as the oil phase. The drug release and oral absorption of the DNSPE significantly improved compared with crude material and nanocrystal suspension of quercetin. After 24 h, the cumulative drug release rate of the DNSPE in phosphate buffer (pH = 7.4, containing 1% sodium dodecyl sulfate) was 68.88%, surpassing the rates of 20.15% for the crude material and 50.71% for the nanocrystals. The AUC_{0-t} of the DNSPE after gavage in rats was 2.76 and 1.38 times greater than those of the crude material and nanocrystals, respectively, and the C_{max} was 2.4 and 1.4 times greater.

Compared with traditional emulsions stabilized with surfactants, drugs in DNSPEs are not only dissolved in the oil phase but also adsorbed at the oil–water interface of the droplets. Differences in the structure lead to different drug loading and dissolution kinetics. It seems that the improvement in drug loading and dissolution might be related to (1) some crystals dissolving in the oil phase of the emulsions, (2) increasing the surface area of the drug crystals through homogenization, and (3) enhanced exposure of particles due to interlocking at the interface that affects their kinetics of dissolution. The clear mechanism remains to be further explored.

The above DNSPEs mostly employed medium-chain fatty acid glycerides or polyethylene glycol glycerol oleate as the oil phase. Given the abundance of insoluble and volatile pharmacodynamic components in many traditional Chinese medicine (TCM) formulations, the idea of DNSPEs utilizing mixed nanocrystals of different active compounds from TCM formulas as solid particles and the volatile oil as an oil phase was proposed. The initial successful application of the idea was for puerarin. Puerarin has favorable pharmacological effects, such as the inhibition of atherosclerosis, improvement of microcirculation, anti-myocardial ischemia, and anti-arrhythmia, etc. However, it belongs to class IV according to the BCS classification system, and its oral bioavailability in rats is limited. Chuanxiong Rhizoma has the effects of dilating blood vessels, improving microcirculation, and relieving pain, and is frequently used in the treatment of many cardiovascular and cerebrovascular diseases. Volatile oil is one important active component of Chuanxiong Rhizoma. With Ligusticum chuanxiong oil and Labrafil M 1944 C (9:1, *v*/*v*) as an oil phase, a DNSPE stabilized by puerarin nanocrystals was developed [4]. A study on its oral bioavailability in rats showed that the DNSPE significantly enhanced the oral absorption of puerarin. The AUC was increased by 1.6, 0.56, and 1.24-fold, respectively, compared with the crude material, nanocrystals, and emulsions stabilized by Tween 80.

Ginkgolide B, a naturally occurring platelet-activating factor antagonist, is widely used for the treatment of cardiovascular and cerebrovascular ailments. Its limited oral bioavailability, however, impedes its practical application. A ginkgolide B nanocrystal self-stabilized Pickering emulsion (GB-DNSPE) was prepared using a miniaturized wet bead milling method with Ligusticum chuanxiong oil as the oil phase [5]. In contrast to Ginkgolide B nanocrystals, GB-DNSPE demonstrated superior efficacy in enhancing the oral bioavailability of GB due to the slow release and absorption of the intact nanoparticle. The relative oral bioavailability of GB-DNSPE was approximately 5.96 times and 1.63 times greater than crude GB powder and GB nanocrystals, respectively. Hence, the anti-ischemic stroke efficacy of GB was significantly improved by the DNSPE.

DNSPEs have even been used for TMC formulas containing multiple medicinal ingredients. Tongmai is a traditional TCM remedy with effects of promoting blood circulation and removing blood stasis. It is comprised of Puerariae lobatae radix, Chuanxiong rhizoma, and Salvia miltiorrhiza. Puerarin, ferulic acid, salicylic acid B, tanshinone IIA, and Ligusticum chuanxiong oil are the primary pharmacodynamic components. A DNSPE with the Tongmai formula was prepared using a nanocrystal mixture comprising puerarin, ferulic acid, salicylic acid B, and tanshinone IIA as an aqueous phase, and a mixture of Ligusticum chuanxiong oil and Labrafil M 1944 C (9:1, *v*/*v*) as an oil phase [6]. The DNSPE exhibited superior physical stability in comparison to nanocrystal suspensions due to the strong adsorption film formed by the adsorption of 15.40% of the puerarin, 15.39% of the ferulic acid, 10.97% of the salvianolic acid B, and 31.51% of the tanshinone IIA onto the surface of the Ligusticum chuanxiong oil droplets. The results of the Caco-2 cell monolayer transport experiment indicated that the apparent permeability coefficient (P_{app}) from the apical side to the basal side (AP → BL) increased 1.21-fold and 0.93-fold for puerarin and salicylic acid B, respectively, when compared with the unprocessed crude material dispersion. Crude tanshinone had a negligible capacity to traverse the Caco-2 cell monolayer, whereas its $Papp_{AP \rightarrow BL}$ in the DNSPE increased to 5.78 × 10^{-6} cm·s^{-1}. Puerarin, ferulic acid, salicylic acid B, tanshinone IIA, and Ligusticum chuanxiong oil were all classified as both ‘excipients’ and ‘drugs’ in the DNSPE, potentially exhibiting synergistic effects. This kind of DNSPE is particularly promising for oral preparations of TCM formulas containing complex active compounds.

2. Injectable Drug Delivery of DNSPEs

Up to now, there have only been a few studies on the injection administration of Pickering emulsions. These injectable Pickering emulsions have been primarily investigated for subcutaneous delivery of vaccines and immune adjuvants [7][8][9] utilizing PLGA-based nanoparticles, such as Chinese yam polysaccharide PLGA nanoparticles and Lentinan PLGA nanoparticles as solid particle stabilizers. An intra-articular DNSPE was reported recently. Sinomenine has anti-inflammatory, analgesic, and immunomodulatory effects, and is used for the treatment of rheumatoid arthritis by oral tablet or intramuscular injection clinically. The current preparations have many defects, including low oral bioavailability, short biological half-life, severe gastrointestinal adverse reactions, serious damage to liver and kidney, and cardiotoxicity. In order to over these shortcomings, a sinomenine DNSPE injection was prepared using sinomenine nanocrystals as a stabilizer and medium-chain fatty acid triglycerides as an oil phase [10]. In contrast to the intragastric or intra-articular administration of the sinomenine suspension, intra-articular injection of the DNSPE could effectively reduce joint swelling and the inflammation index, improve synovial tissue lesions, and inhibit joint inflammation. The DNSPE also showed a superior therapeutic effect compared with the sinomenine suspension, because it could form a drug reservoir after injection into the joint cavity, thereby releasing the drug slowly and stably.

3. Topical Drug Delivery of DNSPEs

Catarina et al. [11] developed a Pickering emulsion with natural green *Quercus suber* bark (QSB) particles as the stabilizer. The QSB solid particles were dispersed first in caprylic/capric triglycerides and then mixed with pure water using a high-speed shearing machine to produce an emulsion with an approximate particle size of 90 μm.

Devoid of surfactants or additional solid particles, the emulsion comprised solely the oil phase, pure water, and QSB solid particles; thus, it was classified as a Pickering emulsion. QSB is a lightweight material obtained from the outer bark of *Quercus suber* L., consisting of suberin, lignin, cellulose, extractives, a small amount of fatty acids, terpenes, long-chain aliphatic compounds, and saccharides. This Pickering emulsion stabilized by QSB particles was a shear-thinning fluid, and was non-irritating to skin, which made it especially suitable for topical administration. QSB possesses specific antimicrobial, antioxidant, and anti-aging activities, which provided the Pickering emulsion with certain pharmacological effects, including protection against oxidative damage in the HaCaT cell line and inhibition of human neutrophil elastase.

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