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Effective mucoadhesive water-soluble polymers for the solidification transformation of phospholipid-bile salts-mixed micelles

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Cucurbitacin B (Cu B), formulated in the phospholipid-bile salts-mixed micelles (PL-BS-MMs), was transformed into dry powders by solidification process. Solidification methods for this transformation included freeze-drying, spray-drying or vacuum-drying, and different grades of process parameters called conservative, moderate and aggressive have been used in each solidification method, respectively. Saccharides (mannose, trehalose and glucose), polyethylene glycol (PEG) and mucoadhesive water-soluble polymers (carrageenan, hydroxpropylmethylcellulose (HPMC) and gelatin) were selected as the stabilizer, respectively. The influence of different stabilizers on the redispersibility of solid Cu B-PL/SDC-MMs was systemically investigated, such as the redispersibility index (RDI). The results showed that there were significant differences in RDI from samples stabilized by different stabilizers. The solid Cu B-PL/SDC-MMs stabilized by mucoadhesive water-soluble polymers (carrageenan, HPMC and gelatin) have better redispersibility under different solidification approaches, compared with those samples stabilized by other stabilizers. The results indicated that the mucoadhesive water-soluble polymers could effectively counter various stresses from the solidification process and prevent the nanocrystal surface from agglomeration. The combined action between steric hindrance and increased viscosity appeared to effectively avoid irreversible particle aggregation.

1. Introduction

The most preferable route for drug administration is oral, due to high patient compliance and safety. But the solubility of an active pharmaceutical ingredient (API) has always been a concern for formulations because inadequate aqueous solubility may result in low oral bioavailability and poor absorption (Dressman et al. 2007). In order to solve this problem, many approaches have emerged to improve the solubility of API, such as crystal engineering (Blagden et al. 2007), salt formation (Serajuddin et al. 2007), nanosizing (Shen et al. 2013), prodrug strategies (Stella et al. 2007) and cyclodextrin complexation (Brewster et al. 2007). Among these applications, the use of nanoparticles which prepared by phospholipid (PL)-bile salts (BS)-mixed micelles (MMs) as a way to formulate poorly soluble drugs has matured rapidly in recent years due to its physiological compatibility and solubilizing capacity (Jin et al. 2012; Lv et al. 2014b). In the small intestine, particularly during lipid digestion, the PL-BS-MMs are stable and could enhance the transport of lipophilic drugs across biological membranes and thereby enhance oral bioavailability. In addition, such a MMs system is known to improve the solubility of extremely lipophilic drugs (Lv et al. 2014a). Moreover, from an economic or commercial perspective, this technique simplifies the process of manufacturing and allows for large-scale production.

Despite the advantages of PL-BS-MMs, it was produced in the liquid form. So stability is one of the crucial aspects in ensuring safety and efficacy of drug products. In order to obtain a long-term stable formulation and to benefit from the advantages associated with a solid dosage form from the perspective of physical stability and patient compliance, it is often essential to convert the liquid PL-BS-MMs into a dry powder form which can be subsequently filled into capsules or compressed into a tablet. The solid nanoparticles can be formed by evaporation of the solvent from the MMs solution in the solidification process (Lv et al. 2014a). This solid PL-BS-MMs drug delivery system (Fig. 1) is a novel drug delivery system to improve the physical and chemical stability of PL-BS-MMs, which is composed of drug, stabilizers or protectants, and can be reconstituted fine PL-BS-MMs instantaneously on mild agitation or peristalsis followed by dilution with aqueous media *in vitro* or gastrointestinal tract (Yue et al. 2012).

Common methods for the transformation of PL-BS-MMs include spray drying, freeze-drying and vacuum drying (Lv et al. 2014a; Yu et al. 2010). In general, the process of solidification consists of removing water from PL-BS-MMs by sublimation and evaporation. However, this process may negatively affect the size and dispersibility of nanoparticles. The generation of nanoparticles aggregation likely causes alteration of disintegration and dissolution, which may subsequently cause changes in bioavailability. Therefore, the redispersibility of solid PL-BS-MMs after solidification is a critical quality attribute. Besides the selection of the solidification method, the aggregation upon drying of PL-BS-MMs can be minimized by adding stabilizers

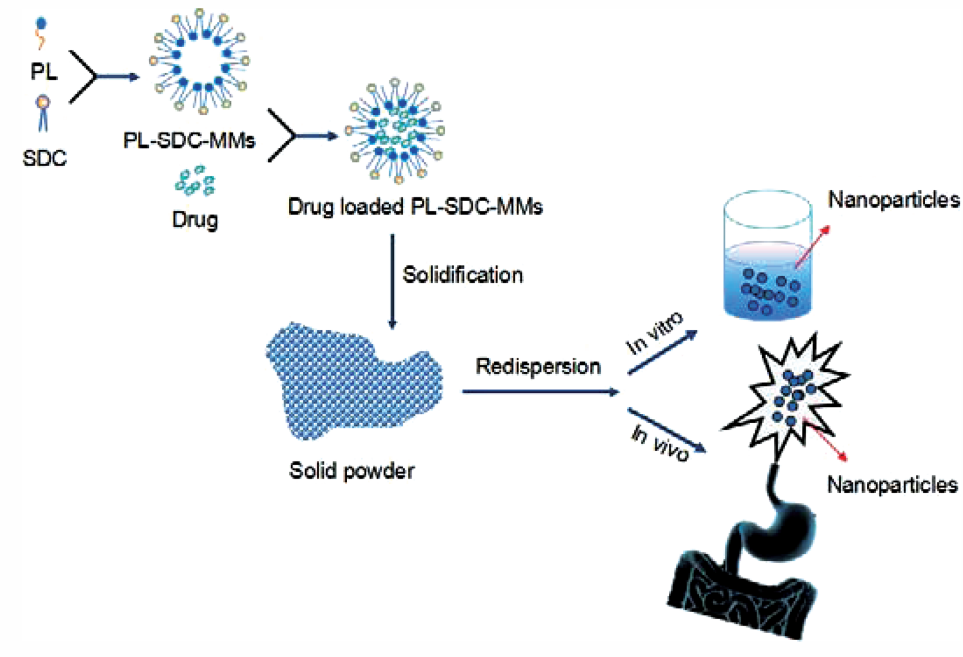

Fig. 1: Schematic diagram of solid PL-BS-MMs drug delivery system with redispersibility characterization.

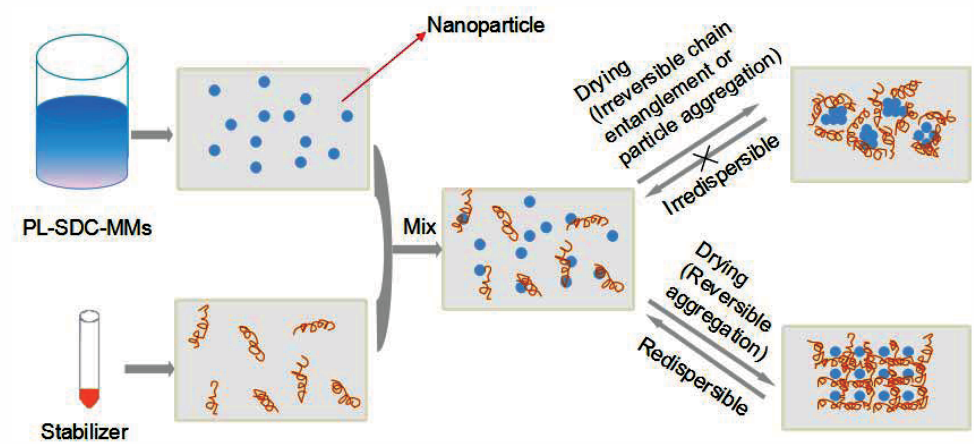

Fig. 2: Schematic diagram of protection mechanism of PL-BS-MMs after solidification.

to protect PL-BS-MMs from desiccation impairments (Lv et al. 2014a; Dong et al. 2013). However, whether the solid PL-BS-MMs can maintain good redispersibility (Fig. 2) remains an urgent scientific problem need to be solved. Although solidification technology has become particularly important, a review of the current literature shows only a few reports about the transformation of PL-BS-MMs into solid products (Lv et al. 2014a; Dong et al. 2013). Reports focusing on the maintenance of good redispersibility characteristics of the solid PL-BS-MMs obtained by different ways of solidification are even scarce.

In this study, we focused on the effect of different stabilizers for redispersibility of solid PL-BS-MMs during different solidification transformation. Cucurbitacin B (Cu B) was chosen as a model drug, which has potent pharmacological activity but poor water solubility (Lv et al. 2014b). We attempted to solidify the Cu B-PL/SDC-MMs using different transformation methods and the influence from different types of stabilizers on the solidification process was investigated. Three methods have been applied on the solidification for Cu B-PL/SDC-MMs in this study, including freeze-drying, spray drying and vacuum drying. Different grades of process parameters called conservative, moderate and aggressive have been used in each solidification method, respectively. Saccharides (mannose, trehalose and glucose), polyethylene glycol (PEG) and mucoadhesive water-soluble polymers (carrageenan, hydroxpropylmethylcellulose and gelatin) were selected as stabilizers. The redispersibility index (RDI) of solid Cu B-PL/SDC-MMs stabilized by different stabilizers was investigated by means of laser diffractometry and transmission electron microscopy.

2. Investigations and results

2.1. Preparation of Cu B-PL/SDC-MMs

Under mechanical force, Cu B was embedded into the hydrophobic core of the MMs, making it isolated from the medium. Average 50% volume percentile (D_{50}) and the average span values were 92.05 ± 8.92 nm and 0.146 ± 0.004. TEM imaging was performed and shown in Fig. 3. The Cu B-PL/SDC-MMs were spherical in shape with particle sizes around 100 nm. However, the coarse Cu B powder was irregular in shape with a broad particle size distribution (Fig. 4). This demonstrated that the coarse

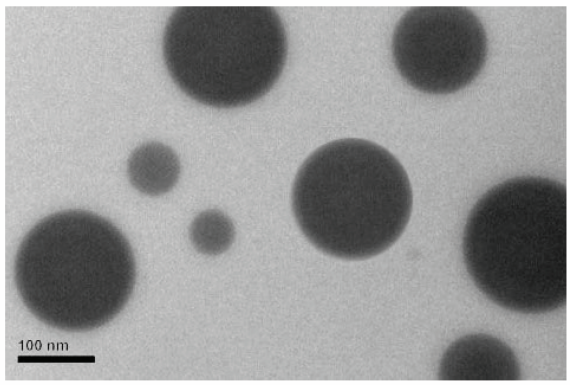

Fig. 3: Transmission electron micrograph of Cu B-PL/SDC-MMs. (scale bar = 100 nm).

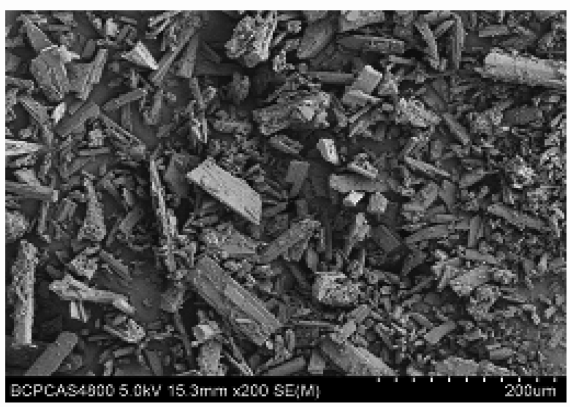

Fig. 4: Scanning electron microscopy micrograph of the coarse Cu B.

Cu B was completely transformed to nanoparticles by means of preparing PL-SDC-MMs.

2.2. Solidification transformation process of Cu B-PL/SDC-MMs

Additives are considered to be necessary during solidification transformation process (Ploehn et al. 1990). Thus, the influence and protection effect from different stabilizers on the redispersibility of solid Cu B-PL/SDC-MMs were investigated during different solidification processes.

2.2.1. Freeze-drying

Different process parameters have been applied in the freeze-drying process and RDI of the solid Cu B-PL/SDC-MMs after reconstitution are shown in Figure 3. After reconstitution, the RDI decreased as the grade of process parameters increased from conservative to aggressive for all solid Cu B-PL/SDC-MMs stabilized by either stabilizer. Under the aggressive process parameters (meant the highest freezing rates), the redispersibility of solid Cu B-PL/SDC-MMs became much better than with other grades of process parameters, while the nanoparticles in the MMs had sufficient time to form aggregations under the slower freezing rates (moderate or conservative). A reason might be that low freezing rates allowed water molecules to exclude foreign particles and eventually leads them to approach and aggregate, and then the stabilizers become no longer active due to the phase separation (Lee 2003). When the aggressive process parameters were used, the solid Cu B-PL/SDC-MMs stabilized

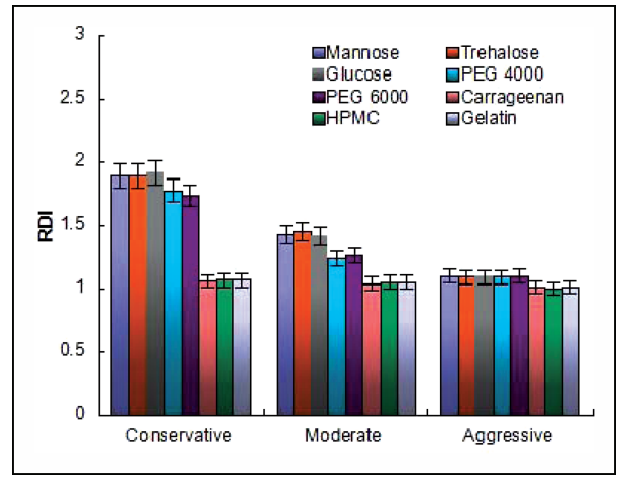

Fig. 5: The redispersibility index (RDI) of the solid Cu B-PL/SDC-MMs after freeze-drying under different grade of process parameters.

by all stabilizers were relatively stable, which indicated that solid Cu B-PL/SDC-MMs could be prevented from agglomerating if the solid phase was formed in a short time. As shown in Fig. 5, redispersibility seems not to be significantly affected by the different grades of process parameters for the solid Cu B-PL/SDC-MMs stabilized by carrageenan, HPMC and gelatin, with the values of RDI from them were all nearly equal to 1. The results demonstrated that the mucoadhesive water-soluble polymers, such as carrageenan, HPMC and gelatin, play a prominent role in preventing Cu B-PL/SDC-MMs from agglomeration. It was concluded that the redispersibility of solid Cu B-PL/SDC-MMs during freeze-drying was largely dependent on the process parameters and the nature of the stabilizer. Compared to other stabilizers, mucoadhesive water-soluble polymers were more effective under different grade of process parameters for the stabilization of Cu B-PL/SDC-MMs.

According to the crystal bridge theory, during the process of drying, capillary pressure enabled particles to approach each other and crystal bridges form and tighten (Wang et al. 2005). In the passage of time, these crystal bridges combine and large agglomerates are formed. However, this aggregation tendency can be counterbalanced by the protection effect of stabilizers (Yue et al. 2013). To characterize the agglomeration phenomenon of reconstituted Cu B-PL/SDC-MMs, TEM imaging for representative samples were performed and shown in Fig. 6. Figure 6A shows that the reconstituted Cu B-PL/SDC-MMs stabilized by carrageenan were spherical in shape with particle sizes around 100 nm. This demonstrated that solid Cu B-PL/SDC-MMs after freeze-drying could not form agglomerates under the conservative process parameters. But the reconstituted Cu B-PL/SDC-MMs stabilized by mannose after freeze-drying under the conservative process parameters had formed agglomerates, with some particle size about 150-250 nm (Fig. 6B). An explanation is that the stabilizer mannose might fail to prevent from forming irreversible agglomerates during freeze-drying.

2.2.2. Spray-drying

As shown in Fig. 7, a significant increase in the RDI of solid Cu B-PL/SDC-MMs after spray-drying could be observed under the moderate and aggressive process parameters. It indicated that the aggregation of nanoparticles has happened and the protection effect of stabilizers has been broken by the spray-drying process. No matter what type of stabilizer used in the solid Cu B-PL/SDC-MMs, the RDI increased with increasing the grade

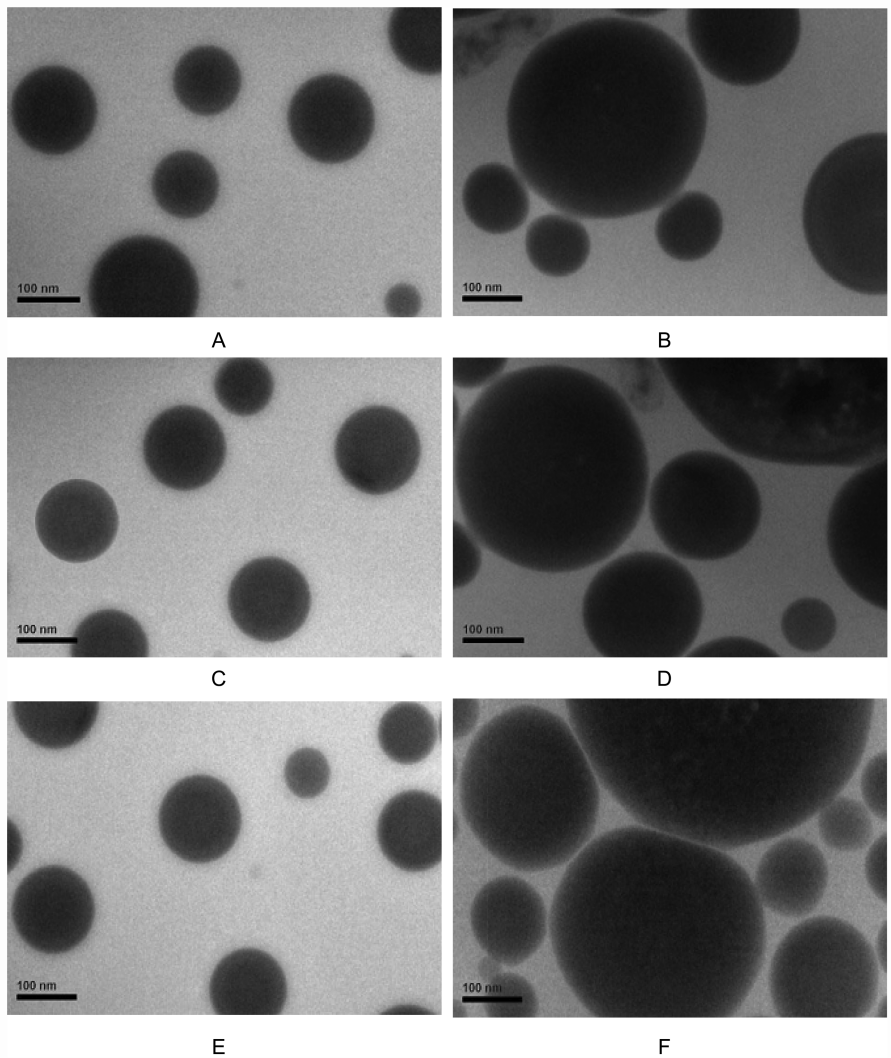

Fig. 6: TEM images of the reconstituted Cu B-PL/SDC-MMs after solidification under different grade of process parameters: (A) reconstituted Cu B-PL/SDC-MMs stabilized by carrageenan after freeze-drying under the conservative process parameters; (B) reconstituted Cu B-PL/SDC-MMs stabilized by mannose after freeze-drying under the conservative process parameters; (C) reconstituted Cu B-PL/SDC-MMs stabilized by HPMC after spray-drying under the aggressive process parameters; (D) reconstituted Cu B-PL/SDC-MMs stabilized by PEG 4000 after spray-drying under the aggressive process parameters; (E) reconstituted Cu B-PL/SDC-MMs stabilized by gelatin after vacuum-drying under the moderate process parameters; (F) reconstituted Cu B-PL/SDC-MMs stabilized by PEG 6000 after vacuum-drying under the moderate process parameters.

of process parameters, which indicated that under the aggressive process parameters (the highest drying rates), aggregation of Cu B-PL/SDC-MMs became more and more serious in the process of the spray-drying. A solid surface would be partially exposed when the water was evaporated during the spray-drying process. Owing to the existence of capillary pressure in water, the resulting surface tension might cause shrinkage of capillary walls (Iskandar et al. 2003). Damage of the porous capillary structure was the major reason for the poor redispersibility of solid Cu B-PL/SDC-MMs during spray-drying. However, under different grade of process parameters, the solid Cu B-PL/SDC-MMs stabilized by mucoadhesive water-soluble polymers, including carrageenan, HPMC and gelatin, have better redispersibility than those stabilized otherwise. The superiority of the mucoadhesive water-soluble polymers is highlighted. The TEM images also showed that the reconstituted Cu B-PL/SDC-MMs stabilized by HPMC after spray-drying could not form irreversible agglomerates, with particle sizes around 100 nm (Fig. 6C), but the reconstituted Cu B-PL/SDC-MMs stabilized by PEG 4000 after spray-drying had formed irreversible agglomerates, with some large size particles (Fig. 6D). As a result, the mucoadhesive water-soluble polymers could effectively keep surrounding nanoparticles surface to prevent their agglomeration during spray-drying.

2.2.3. Vacuum-drying

The values of RDI significantly increased after the vacuum-drying process as illustrated in Fig. 8 Most of the Cu B-PL/SDC-MMs stabilized by stabilizers have been broken by the vacuum-drying process. The RDI of Cu B-PL/SDC-MMs stabilized by either of these stabilizers increased with increasing the grade of process parameters, which indicated that at the aggressive dry temperature, the Cu B-PL/SDC-MMs became more and more aggregated. The TEM images in Fig. 6F demonstrated that the reconstituted Cu B-PL/SDC-MMs stabilized by PEG 6000 after vacuum-drying presented the particles with large diameter, due to forming dramatic agglomerates under the moderate condition. But the reconstituted Cu B-PL/SDC-MMs stabilized by gelatin after vacuum-drying could not form agglomerates (Fig. 6E). Furthermore, as shown in Fig. 8, all of the solid Cu B-PL/SDC-MMs stabilized by mucoadhesive water-soluble polymers (carrageenan, HPMC and gelatin) have better redispersibility under any grade of process parameters,

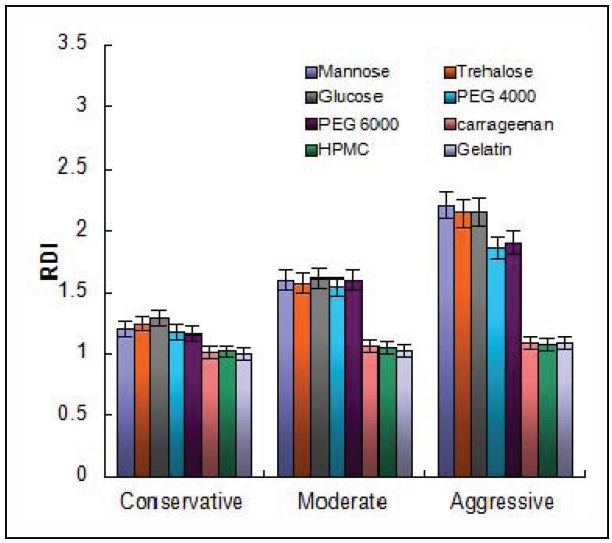

Fig. 7: The redispersibility index (RDI) of the solid Cu B-PL/SDC-MMs after spray-drying under different grade of process parameters.

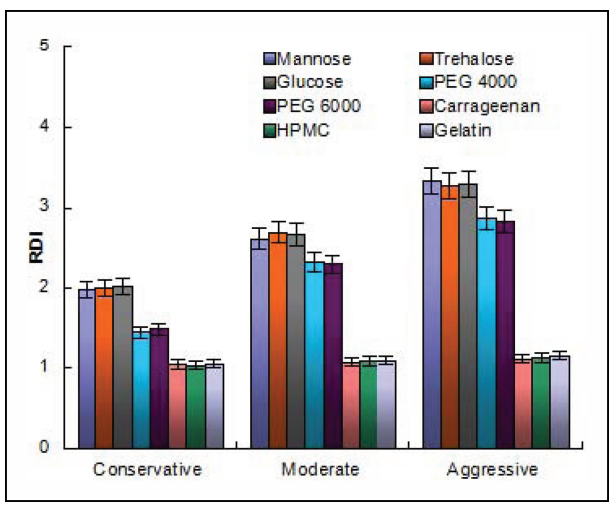

Fig. 8: The redispersibility index (RDI) of the solid Cu B-PL/SDC-MMs after Vacuum-drying under different grade of process parameters.

compared with those stabilized by other agents. This demonstrated that the mucoadhesive water-soluble polymers play an important role in maintaining good redispersibility of the solid Cu B-PL/SDC-MMs, which could effectively prevent nanoparticles from agglomeration during vacuum-drying.

3. Discussion

In order to produce solid Cu B-PL/SDC-MMs with better redispersion performance, mannose, trehalose, glucose, PEG 4000, PEG 6000, carrageenan, HPMC and gelatin were chosen as the stabilizers under different drying conditions. The results demonstrated that carrageenan, HPMC and gelatin, which all belong to mucoadhesive water-soluble polymers, are more effective than other stabilizers in stabilizing the solid Cu B-PL/SDC-MMs even when the drying conditions are more cruel. The results may be attributed to the different protective mechanisms of these stabilizers. Saccharides, such as mannose, trehalose and glucose, were widely used as stabilizer in the drying of liposomes and solid lipid nanoparticles by decreasing the osmotic activity of water crystallization and favor the glassy state of the frozen sample (Vemuri et al. 1991). However, the saccharides cannot act as steric stabilizers and form a coating layer on the surface of particles to prevent the nanoparticles from aggregation. Polyethylene glycols (eg. PEG 4000 and PEG 6000) are often used as steric stabilizers of nanoparticulate systems in pharmaceutical formulations (Dong et al. 2013; Armstrong et al. 2002). They were able to stabilize the nanoparticles by steric hindrance and by shielding the surface of the micellar particles, preventing the hydrophobic cores of micelles from aggregation in the drying process. But the results in this study showed that only this effect of steric hindrance could not meet the demand of favorite nanoparticles redispersion when the dry conditions became cruel. The additions of carrageenan, HPMC and gelatin were able to successfully protect drug nanoparticles from irreversible aggregation. These mucoadhesive water-soluble polymers not only acted as steric stabilizers, but also significantly increased the viscosity of the Cu B-PL/SDC-MMs. Their aqueous solutions can be physically gelled at a high concentration because of their strong interactions between polar functional groups. It was generally accepted that carrageenan undergones gelation through coil-helix transition followed by aggregation (Loret et al. 2009). Similar mechanisms will exist during drying and will restrict the motions of nanoparticles. The retarded motions of nanoparticles in the viscous solution can reduce the occurrence of particle aggregation. Thus, for the development of the solid Cu B-PL/SDC-MMs formulations, mucoadhesive water-soluble polymers seems to be the best choices.

The solid PL-BS-MMs with redispersibility is a novel drug delivery system to improve the physical and chemical stability of PL-BS-MMs. In this study, the Cu B-PL/SDC-MMs were investigated for the influence of different stabilizers on the redispersibility of nanoparticles under different solidification transformation methods. The results showed that there was significant difference in RDI from samples stabilized by different stabilizers. The solid Cu B-PL/SDC-MMs stabilized by mucoadhesive water-soluble polymers (carrageenan, HPMC and gelatin) have better redispersibility under different solidification approaches, which indicated that the mucoadhesive water-soluble polymers could effectively counter various stresses from solidification process and keep surrounding the nanocrystal surface to prevent agglomeration.

4. Experimental

4.1. Materials

Cucurbitacin B (98%) was from Nantong Feiyu Biological Technology Co. Ltd. (Nantong, China); phospholipid (PC > 95%) was obtained from Shanghai TaiWei Pharmaceutical Industry Co. Ltd. (Shanghai, China); sodium deoxycholate (SDC) was from Beijing Hotaibio Science and Technology Co. Ltd. (Beijing, China); D-(+)-trehalose, D-(+)-anhydrous glucose, mannose, λ-Carrageenan, PEG 4000 and PEG 6000 were purchased from Sigma-Aldrich (St. Louis, MO, USA); Hydroxpropyl methyl cellulose (HPMC) 5mPa.s was obtained from Colorcon Inc. (West Point, PA, USA); gelatin was purchased from Geltech (South Korea); methanol of HPLC-grade was purchased from Promptar Ltd. (Elk Grove, CA, USA). All other solvents and reagents were of HPLC or analytical grade.

4.2. Preparation of Cu B-PL/SDC-MMs

The preparation of Cu B-PL/SDC-MMs was carried out by film dispersion method based on our previous researches (Lv et al. 2014b). In the optimized formulation, the total concentration of PL/SDC was 54 mg/mL and the mass concentration ratio was 1:0.8. Briefly, PL and SDC were dissolved by anhydrous ethanol in round-bottom flask. A thin film was formed after evaporation of organic solvent by rotary evaporator (Laborota 4000, Heidolph Instruments Ltd., Germany). The film was rehydrated in a given amount of distilled water to give clear solution. Cu B (the mass concentration was 5 mg/mL) was added to this solution, nitrogen sealed and mixed 24 h on a magnetic stirrer (85-2, Guohua Instrument Co. Ltd., China) at room temperature to form clarified Cu B-PL/SDC-MMs.

Table 1: Process parameters applied in the freeze-drying process

Grade	Temperature (F°C)	Duration (h)
Conservative	−20	12
Moderate	−80	6
Aggressive	−196	2

Table 2: Process parameters applied in the spray-drying process

Grade	Inlet temperature (F°C)	Feed flow rate (mL/min)	Atomizing air flow (bars)
Conservative	50	5	2
Moderate	80	5	2
Aggressive	100	5	2

Table 3: Process parameter applied in the vacuum-drying process.

Grade	Inlet temperature (°C)
Conservative	40
Moderate	50
Aggressive	60

4.3. Solidification transformation process

4.4. Freeze-drying of Cu B-PL/SDC-MMs

The Cu B-PL/SDC-MMs was transferred into a 100 mL vial. The stabilizer was also added to the vial with a mass concentration of 10 mg/mL. Then, the samples were frozen by immersing the vials in liquid nitrogen. Freeze-drying was performed with a freeze-dryer (FD5 series; Gold SIM, Beijing, People's Republic of China). The process parameters used in freeze-drying are listed in Table 1. Measurements were made in triplicate for the following measurements.

4.5. Spray-drying of Cu B-PL/SDC-MMs

Buchi mini spray dryer (model B290, Buchi Laboratoriums-Technik AG, Flawil, Switzerland) has been used in the spray-drying process. The mass concentration of stabilizer was set as 10 mg/mL. The process parameters used in spray-drying are listed in Table 2. At the end of the spraying process, samples were allowed to cool down to room temperature and kept for future testing and evaluation.

4.6. Vacuum-drying of Cu B-PL/SDC-MMs

The stabilizer was added to the Cu B-PL/SDC-MMs with a mass concentration of 10 mg/mL. The solutions underwent vacuum drying at room temperature for 12 h (chamber 64 L, 76 cm Hg), drying in a convection oven for 12 h. The process temperature was set as shown in Table 3.

4.7. Reconstitution of the solid Cu B-PL/SDC-MMs

The solid Cu B-PL/SDC-MMs were reconstituted by adding water to obtain a colloidal system. Reconstitution was tested both by simple shaking and stirring for 30 min.

4.8. Laser diffractometry

Laser diffractometry was performed on a Mastersizer Micro Plus (Malvern Instruments Limited, Worcestershire, UK). Analysis of the diffraction patterns was taken using the Mie model ("standard" presentation: imaginary particle refractive index = 0.1, dispersant refractive index = 1.33, real particle refractive index = 1.53). From the resulting volume distributions, D_{50} (equal to 50% volume percentile) was calculated. All measurements were performed in triplicate.

4.9. Surface analysis using scanning electron microscopy

Morphological evaluation of the coarse Cu B was performed under a scanning electron microscope (SEM) (S-4800, Hitachi Technologies Corporation, Japan). Samples were gold coated at 10 mA for 20 s in vacuum by a sputter coater (SBC-12, KYKY technology Co., Ltd., China) before analysis.

4.10. Transmission electron microscopy

The morphology of Cu B-PL/SDC-MMs and reconstituted Cu B-PL/SDC-MMs from some representative samples subjected to different solidification conditions were observed with the transmission electron microscope (TEM) (Tecnai G 2 F30, FEI, Eindhoven, The Netherlands). The samples were placed on copper grids. After being air dried, the films were observed by TEM.

4.11. Redispersibility index

The stability of Cu B-PL/SDC-MMs after solidification was evaluated by the redispersibility index (RI) according to the follow equation:

$$RI = \frac{D}{D_0} \times 100\% \quad (1)$$

in which D_0 represents the volume-weighed mean particle size of the Cu B-PL/SDC-MMs prior to solidification and D represents the corresponding value after solidification. The value of RI of near 100% would therefore mean that the solid Cu B-PL/SDC-MMs obtained by solidification transformation can be completely reconstituted to the original particle size after rehydration.

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