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Microcrystalline cellulose-carboxymethyl cellulose sodium as an effective dispersant for drug nanocrystals: A case study

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ABSTRACT

This study is aimed at seeking an alternative dispersant for spray drying of drug nanosuspensions. The ideal dispersant is not only able to prevent the agglomeration of drug nanocrystals in the suspension state, but also it is able to preserve redispersibility of drug nanocrystals after drying. An active pharmaceutical ingredient (API) was used as a model drug. API nanosuspensions were prepared by homogenization and converted into nanocrystals powder (API-NP) with microcrystalline cellulose-carboxymethyl cellulose sodium (MCCS) via spray drying. It was found that MCCS was able to prevent the aggregation of API-NP in the suspension state and the agglomeration during spray-drying process, possibility due to its high Zeta potential and steric barrier from network structure, and reduction of API size at nanoscale and incorporation into MCCS network structure did not affect the solid state of API as evidenced by DSC and XRD analysis. The spray-dried API-NP/MCCS powders exhibited excellent sphere-shape performance, and could easily redispersed to API-NC suspensions state. Dissolution of the spray-dried API-NP was distinctly superior to those of the crude powder and physical mixture, respectively. Within 30 min, approximate 85.87% of API was dissolved from the API-NP/MCCS. MCCS was demonstrated to be an effective dispersant for spray-dried drug nanocrystals and preservation of the nanocrystals associated with excellent redispersibility.

1. Introduction

Nanocrystals suspensions (nanocrystals in suspension state), also named as nanosuspensions, is colloidal dispersion system for poorly soluble drug generally produced in liquid media in which drug particles size is less than 1 μm and stabilized by surfactants or polymers. Nanocrystals suspensions has a unique advantage that enhance the solubility and dissolution velocity of poorly soluble drugs due to their small particle size and high surface area (Müller, Gohla, & Keck, 2011; Muller, Jacobs, & Kayser, 2011; Shegokar & Müller, 2010), and strengthen the adhesion to biological membrane, prolong adhesion time and detention time (Ghosh, Bose, Vippagunta, & Harmon, 2011; Jacobs, Kayser, & Müller, 2000). However, nanocrystals in suspension state are essentially thermodynamically unstable systems, which would tend to generate flocculation, aggregation or crystal growth to decrease their free energy (Wang, Zheng, Zhang, Wang, & Zhang, 2013). The physical stability problems are crucial to be solved and recently have been widely investigated, which limits the industrialization and application of nanosuspensions. Therefore, in terms of the stability as well as the convenience for the patient, drug nanosuspensions are required to be converted into solid nanocrystals powders via solidification technology included spray-drying and freezing-drying (Chaubal & Popescu, 2008; Figueroa & Bose, 2013; Kim & Lee, 2010; Niwa & Danjo, 2013). During drying process, the water from nanosuspensions was removed via evaporation under high temperature. Reduction in the water volume can lead to a decrease in the solubility of the stabilizer, resulting in stabilizer precipitation and nanocrystals aggregation. Furthermore, this process can generate a series of stresses (e.g. heat intensity for spray drying) and induced irreversible agglomeration of individual nanocrystals particles, which can prevent nanocrystals from recovering to original nanosuspensions states followed by rehydration (redispersibility). It has been shown that the aggregation of nanocrystals during drying is dependent on the drug properties. During drying of nanosuspensions, it was found that the surface hydrophobicity and cohesive energy of drug were

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responsible for the redispersibility of nanocrystals (Yue, Li, Wan, Yang, et al., 2013; Yue, Li, Wan, Wang, et al., 2013).

To preserve the redispersibility of the nanocrystals particles after drying, some dispersants are frequently used to prevent agglomeration of nanocrystals during the drying process, e.g. lactose, sucrose, trehalose, manitol, etc. (Kumar, Gokhale, & Burgess, 2014). However, there were some inherent drawbacks associated with the sugar as dispersants. Sugars are incapable of preventing agglomeration of drug nanocrystals in the suspension state (Chaubal & Popescu, 2008), as the dissolved sugar molecules cannot form a permanent steric barrier against particle–particle aggregation (Hu, Ng, Dong, Shen, & Tan, 2011). And sugars, after the spray drying process, are generally amorphous and hygroscopic. If the stabilizers/dispersants, with amorphous state or low glass temperature, could be subjected to vitrification various due to heat or humidity during drying, the nanocrystals would be "mobile" and have opportunity to form some aggregates (Beirowski, Inghelbrecht, Arien, & Gieseler, 2012; Dong, Ng, Hu, Shen, & Tan, 2014).

Therefore, an alternative dispersant as matrix former is desired to circumvent the problems encountered using the sugars. In literature, some insoluble alternative dispersants, e.g. microcrystalline cellulose, SiO_2, clay, Avicel PH101, Fujicalin, Aerosol 200 and Intutec SP1, etc., have been reported to exhibit excellent performance to prevent nanocrystals aggregation after drying (Dong et al., 2014; Van Eerdenbrugh et al., 2008a,b; Van Eerdenbrugh, Froyen, et al., 2008).

The ideal dispersant is not only able to prevent the agglomeration of the drug nanocrystals in the suspension state, but also it is able to preserve redispersibility of drug nanocrytsals powder after drying. For this purpose, various cellulose derivatives such as hydroxypropyl methylcellulose, hydroxyethyl cellulose, microcrystalline cellulose as well as carboxymethylcellulose sodium have been used in the development of nanocrystals (Brinchi, Cotana, Fortunati, & Kenny, 2013; Charreau, Foresti, & Vazquez, 2013; Lavoine, Desloges, Dufresne, & Bras, 2012; Mishra, Sahoo, & Dixit, 2015). Microcrystalline cellulose-carboxymethyl cellulose sodium (MCCS) is a premixed and coprocessed mixture of microcrystalline cellulose (MCC) and carboxymethyl cellulose sodium (CCS) at ratio (mass basis) of 80: 20, which has more excellent dispersion performance (Zhao, Kapur, Carlin, Selinger, & Guthrie, 2011). Combinations of microcrystalline cellulose and sodium carboxymethyl cellulose are commonly used as stabilizing agents and suspending agents in pharmaceutical formulations (Zietsman, Kilian, Worthington, & Stubbs, 2007). Therefore, MCCS may be an alternative dispersant for spray drying of drug nanosuspensions. But MCCS has not been well characterized as a dispersant for drug nanocrystals during spray-drying.

In this work, an active pharmaceutical ingredient (API) was used as a model hydrophobic compound, which has very poor aqueous solubility, as well as poor oral absorption and low bioavailability. The objectives of this manuscript are as follows: (1) API nanocrystals suspension (API-NS) stabilized by MCCS were prepared by homogenization technology, which was processed into the dried nanocrystals particles (API-NP) via spray drying. And the comparative study on the dispersion efficiency between MCCS and microcrystalline cellulose, carboxymethyl cellulose sodium was investigated. (2) Morphology of the API-NS and the dried API-NP was visualized by transmitting electronic microscopy (TEM) and scanning electronic microscopy (SEM), respectively. Characteristic of API-NP was analyzed by Fourier transform infrared spectrophotometry (FT-IR), X-ray diffraction (XRD) and differential scanning calorimetry (DSC), respectively. (3) The redispersibility and dissolution evaluation were performed to investigate the success of MCCS as a dispersant for drug nanocrystals.

2. Materials and methods

2.1. Chemicals

API was obtained from Zelang Pharm. Co. (Nanjing, China). Hydroxypropylmethylcellulose (HPMC, Methocel E15LV Premium EP®, Colorcon, Dartford, UK). Microcrystalline cellulose and carboxymethyl cellulose sodium (MCCS, Ceolus™ RC-A591NF, Asahi KASEI, Japan) were commercially obtained. Microcrystalline cellulose (MCC) and Low substituted hydroxypropyl cellulose (L-HPC) were kindly donated by Beijing Fengli Jingqiu Commerce and Trade Co., Ltd. (Beijing, China). Carboxymethyl cellulose sodium (CCS, SHANHE, China) was commercially obtained.

2.2. API nanosuspensions (API-NS) production

API-NS was prepared by high pressure homogenization. Before producing API-NS, API coarse powder 1% (w/v) was dispersed in a different dispersant solution of HPC, HPMC and MCCS (0.5%, w/v). The obtained mixture was firstly disintegrated into coarse suspension by a high shear homogenizer (FLUKO® FA25, Essen, Germany) at 16,000 rpm for 5 min. and then the gained coarse suspension was homogenized at high pressure using a piston-gap high pressure homogenizer (AH-1000D, ATS Engineering Inc., Seeker, Canada). Firstly, 30 cycles at 100 bar, 20 cycles 500 bar were conducted as pre-milling step, and afterwards, 30 cycles at 800 bar were run to obtain the API-NS.

2.3. Conversion API-NS into API-NP via spray-drying

The API-NP was obtained by spraying the API-NS through the nozzle of a Buchi mini spray dryer (model B290; Buchi Laboratoriums-Technik AG, Flawil, Switzerland). The process parameters were set as follows: inlet temperature was set as 140 °C; aspiration rate, 55%; and atomizing air flow, 50 mmHg. The dried nanocrystals were separated from the drying air in the cyclone (57–83 °C outlet temperature) and deposited at the bottom of the collector. They were collected and kept at room temperature for future testing and evaluation.

2.4. Particle size and zeta potential measurements

The determination of particles size was performed on a Mastersizer Micro Plus (Malvern Instruments Limited, Worcestershire, UK) which has a working range of 0.050–550 lm. Analysis of the diffraction patterns was done using the Mie model ("standard" presentation: dispersant refractive index = 1.33, real particle refractive index = 1.5295, imaginary particle refractive index = 0.1). From the resulting volume distributions, the median was calculated (=50% volume percentile, $d(v,0.5)$). All measurements were performed in triplicate. Zeta potential was estimated using the Zetasizer nano-ZS (Malvern Instruments, UK) by means of the M3-PALS (Phase Analysis Light Scattering) technique. Each sample was carried out in triplicate.

2.5. Redispersibility index (RDI) of API-NP

$$\mathrm{RDI} = \frac{D}{D_0} \times 100\%$$

where D_0 is the volume-weighed mean particle size of the redispersed nanosuspensions directly prior to drying and D is the corresponding value post-drying. An RDI of near 100% would therefore mean that spray-dried API-NP can be completely transformed to the original particle size after rehydration.

Table 1
The mean particles size, span and Zeta potential value of prepared API-NS dependent on different dispersants before and after spray-drying.

Dispersants		API-NS/MCC	API-NS/HPC	API-NS/CCS	API-NS/MCCS
Before spray-drying	D50 (μm)	1.885 ± 0.016	0.461 ± 0.001	0.621 ± 0.008	0.595 ± 0.011
	Span	1.135 ± 0.007	2.105 ± 0.015	2.237 ± 0.009	2.012 ± 0.008
After spray-drying	D50 (μm)	4.337 ± 0.022	9.075 ± 0.109	1.359 ± 0.017	0.771 ± 0.011
	RDI	2.301 ± 0.016	25.781 ± 0.024	2.188 ± 0.011	1.295 ± 0.008
Zeta (mV)		−88.2 ± 1.8	−18.6 ± 1.6	−97.4 ± 1.5	−96.7 ± 1.2

2.6. Analytical characterization

Thermo grams of the raw API, MCCS and the spray-dried API-NP were investigated using Diamond DSC Calorimeter (PerkinElmer). The sample was heated to 260 °C at 10 °C/min in N_2 atmosphere.

Fourier transform infrared spectrophotometry (FT-IR Spectrometer, BRUKER IFS-55, Switzerland) was used to study the interaction between API and MCCS. The IR spectra of API, MCCS, API-NP and a physical mixture of API and MCCS were obtained by the KBr method, respectively.

The XRD analyses of the MCCS, coarse API powder, API-NP powder and physical mixture were carried out by a powder X-ray diffractometer (D8ADVANCE, BRUKER AXS GMBH, German) with Cu source of radiation. Measurements were carried out at a voltage of 40 kV and 25 mA. The scanned angle was performed from $3^\circ \leq 2\theta \leq 60^\circ$ and the scanning rate was 2°/min. The measurement was carried out in triplicate.

2.7. Scanning electron microscope (SEM)

Morphological evaluation of the coarse API and representative samples of API-NP was performed and compared against each other under (SEM) (Nova Nano SEM45, FEI, USA). All samples were evaluated on a brass stub using carbon double-sided tape. The samples were gold coated (thickness ≈15–20 nm) with a sputter coater (Fison Instruments, UK) using an electrical potential of 2.0 kV at 25 mA for 10 min. An excitation voltage of 20 kV was used in the experiments.

2.8. Transmission electron microscopy (TEM)

Morphology of the redispersed AP-NS was visualized by using transmission electron microscopy (Tecnai 12, FEI, operating at 120 kV). To analyze morphology of nanosuspensions, a drop of API-NS were adsorbed on the surface of a copper grid and dried at room temperature for 24 h.

2.9. In vitro dissolution evaluation of API-NP

The dissolution characterization of API-NS, API-NP and physical mixture, containing the same amount of API (60 mg), was evaluated. According to the CP XC paddle method, a dissolution apparatus (RC-8, Tianjin Guoming Medicine and Equipment Co., Inc., China) was used. 900 ml of phosphate-buffered saline (PBS; pH 7.4) at 37 °C was used as a dissolution medium. The rotation speed of the paddles was set at 100 rpm. At pre-determined time intervals (5, 10, 20, 30, 45, 60 min), 2 ml samples were withdrawn and filtered through 0.22 μm filter membrane immediately. Simultaneously, equal blank medium was compensated immediately after the withdrawal. The amount of dissolved API in the sample solution was assayed by HPLC as described in Analytical method.

3. Results and discussions

3.1. Comparisons of API-NS stabilized by different cellulose as dispersants

API-NS was prepared by high pressure homogenization. The comparative study on the dispersion efficiency between MCCS, MCC, CCS and HPC was investigated. Average 50% volume percentiles (d_{50}) and the average span values for all the different dispersant are listed in Table 1. The mean particle size of the freshly prepared API-NS/HPC, API-NS/CCS, and API-NS/MCCS was on the range 500–600 nm, but the particle size of API-NS/MCC was larger than 1 μm. These results showed that the coarse API were completely disintegrated to nano-sized particles by means of high pressure homogenization technology, and could successfully form the API-NS in terms of different dispersants HPC, CCS and MCCS, respectively. The Zeta potential (ZP) of the API-NS/MCC, API-NS/HPC, API-NS/CCS, and API-NS/MCCS was −88.2, −18.6, −97.4 and −96.7 mV, respectively. It was demonstrated that the nanocrystals particle–particle interactions and the subsequent agglomeration in the API-NS could be alleviated during homogenization process, due to the electrostatic repulsion and steric barrier effect of stabilizers adsorbed onto surface of nanocrystals (Jiang & Hsieh, 2013). Furthermore, the rheological behavior of MCCS in API-NS also might have a marked influence on the dispersion of nanocrystals during homogenization process. It might be the reason that MCCS possessed more excellent rheological behavior compared with microcrystalline cellulose and carboxymethyl cellulose sodium (Zhao et al., 2011).

3.2. Comparisons of different cellulose as dispersants or matrix formers for spray-dried API-NP

The API-NS was transformed into API-NP via spray-drying. Spray-drying, a rapid process for generating particles in which a feed solution containing the drug nanosuspensions is atomized into droplets that rapidly dry due to their high surface area and intimate contact with drying air. However, this process can destabilize the nanocrystals and influence on the redispersibility of nanocrystals, due to water removal and thermal stresses. Therefore, the protection effects provided by different concentration of dispersants during spray-drying were investigated. Table 1 shows the particle size and redispersibility (RDI) of API-NS stabilized by MCC, HPC, CCS and MCCS, respectively. The RDI of spray-dried API-NP used MCCS as dispersant was 1.295, but RDI of spray-dried API-NP used MCC, HPC and CCS as dispersant was 2.301, 25.781 and 2.188, respectively. It has been recommended that, RDI < 1.5 of drug nanocrystals indicated that drug nanocrystals could recover back to the original nanosuspensions (Yue, Li, Wan, Yang, et al., 2013). It could be seen that the dispersant MCCS possessed a more excellent performance for RDI of API-NP, compared with MCC and CCS. But the performance of dispersant L-HPC was very bad (RDI 25.81), which indicated that API-NP had formed some irreversible aggregation after spray-drying.

Fig. 1 displays the morphology of spray-dried API-NPs with different dispersants. It was seen that API-NP stabilized by MCCS

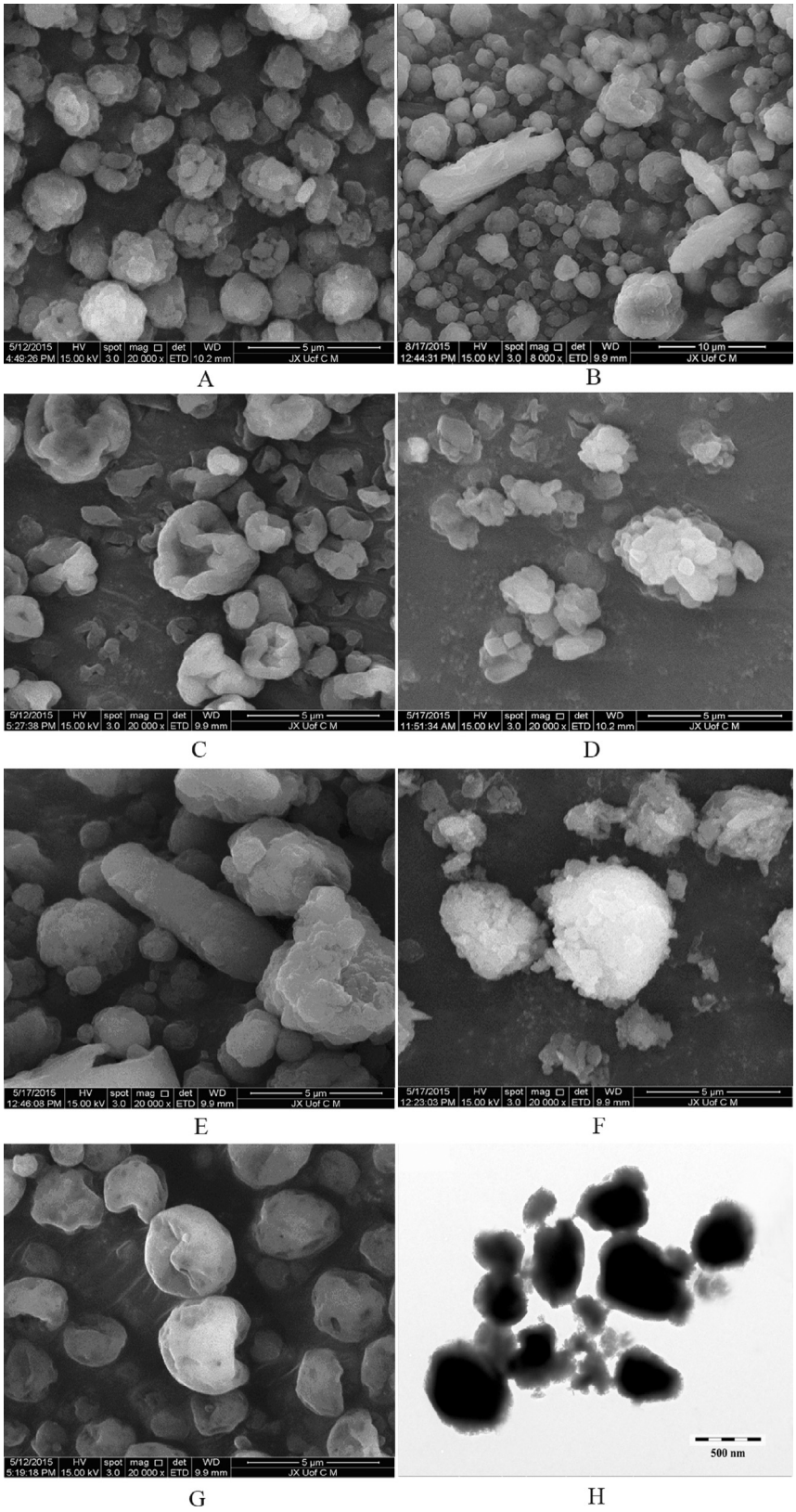

Fig. 1. SEM images of API-NP/MCCS (A), API-NP/MCC (B), API-NP/L-HPC (C), API-NP/CCS (D), API-NP/L-HPC/MCCS (E), API-NP/L-HPC/lactose (F), API-NP/L-HPC/trehalose (G), and TEM image of API-NS/MCCS (H).

had a rounding sphere-shape structure (Fig. 1A), but API-NP stabilized by MCC, L-HPC and CCS had an irregular structure (Fig. 1B–D), and the rounding of particles was very poor. But Fig. 1H displays the TEM morphology of API-NS/MCCS, which illustrated that API nanocrystals at suspension state was near-sphere in shape, with particle size of about 500 nm. It was also indicated that the API nanocrystals in API-NP had coated with the dispersant MCCS layer and formed composite particles. The

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